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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sweeney CJ, Martin AJ, Stockler MR, et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023; **24:** 323–34.

Sweeney CJ et al: Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial

Supplementary Appendix

Contents

Supplementary Table S1: ENZAMET sites, investigators, key sponsor and coordinating centre staff

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United Kingdom:
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USA:
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Ireland and United Kingdom (Cancer Trials Ireland): Olwyn Deignan, Eibhlín Mulroe, Kathleen Scott
United States of America: Paul Nguyen
ANZUP Independent Data & Safety Monitoring Committee: Ian Olver (to 2021), Richard Bell (to date), Peta Forder, David Goldstein, Jonathan Cebon

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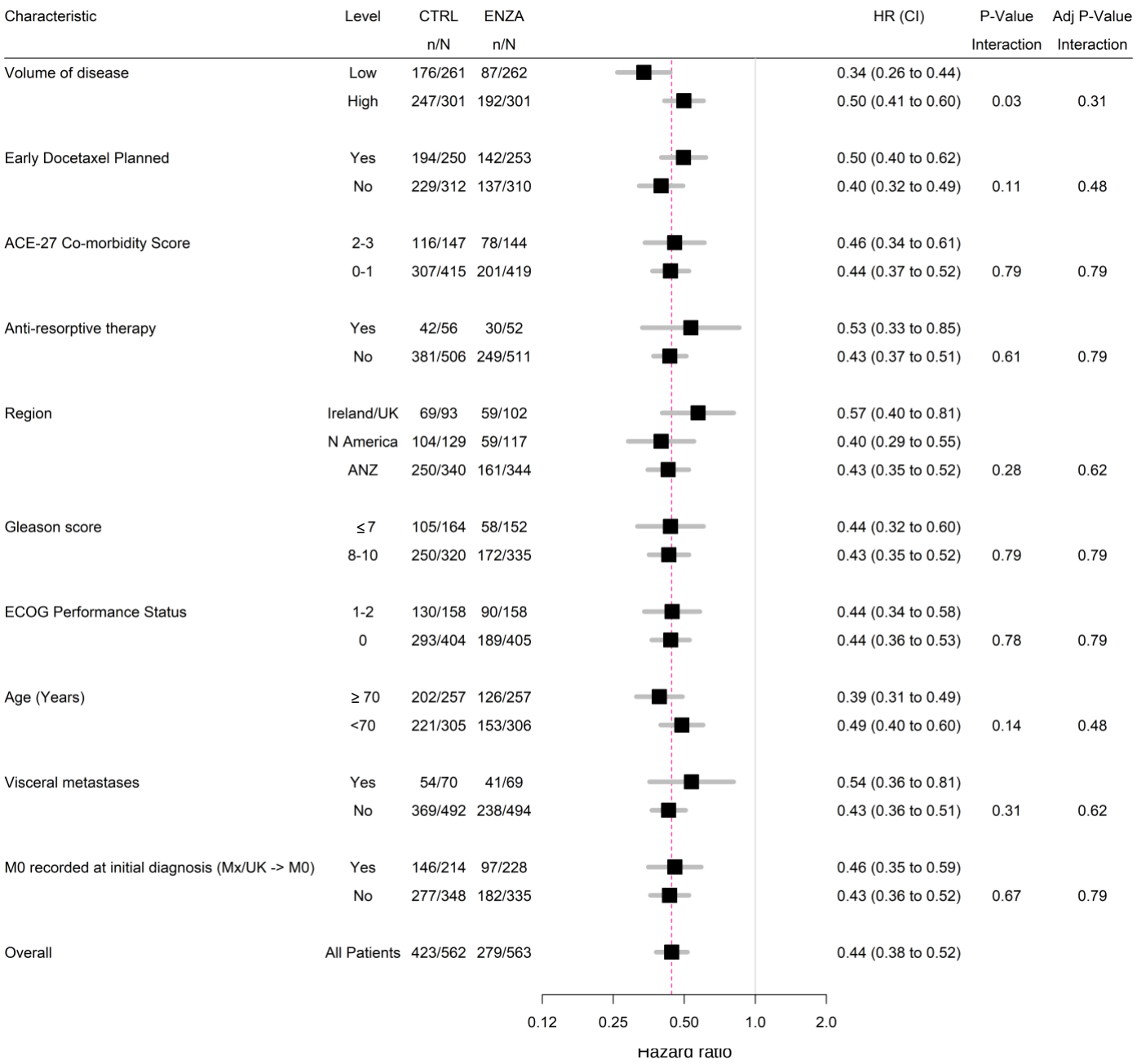
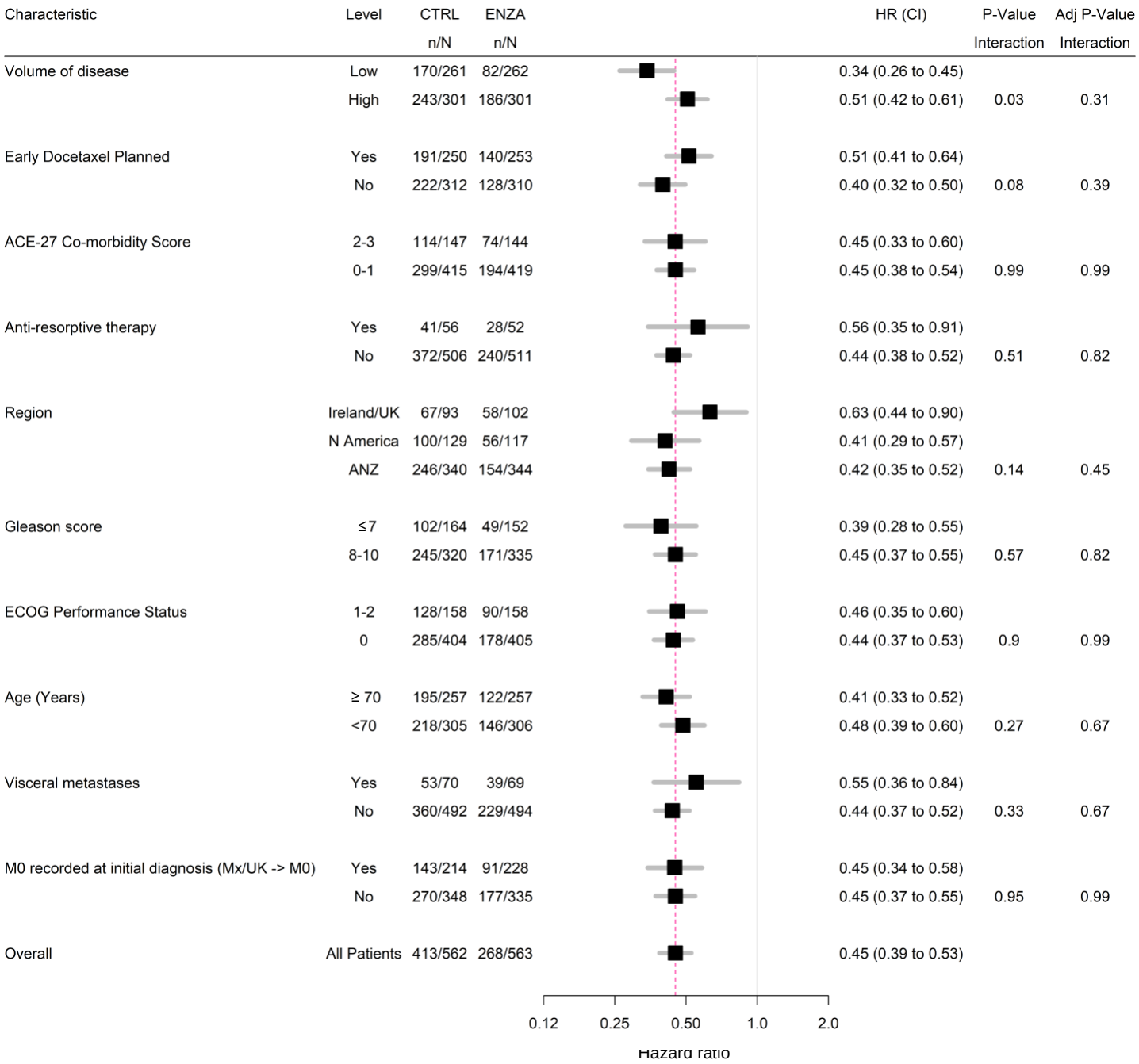
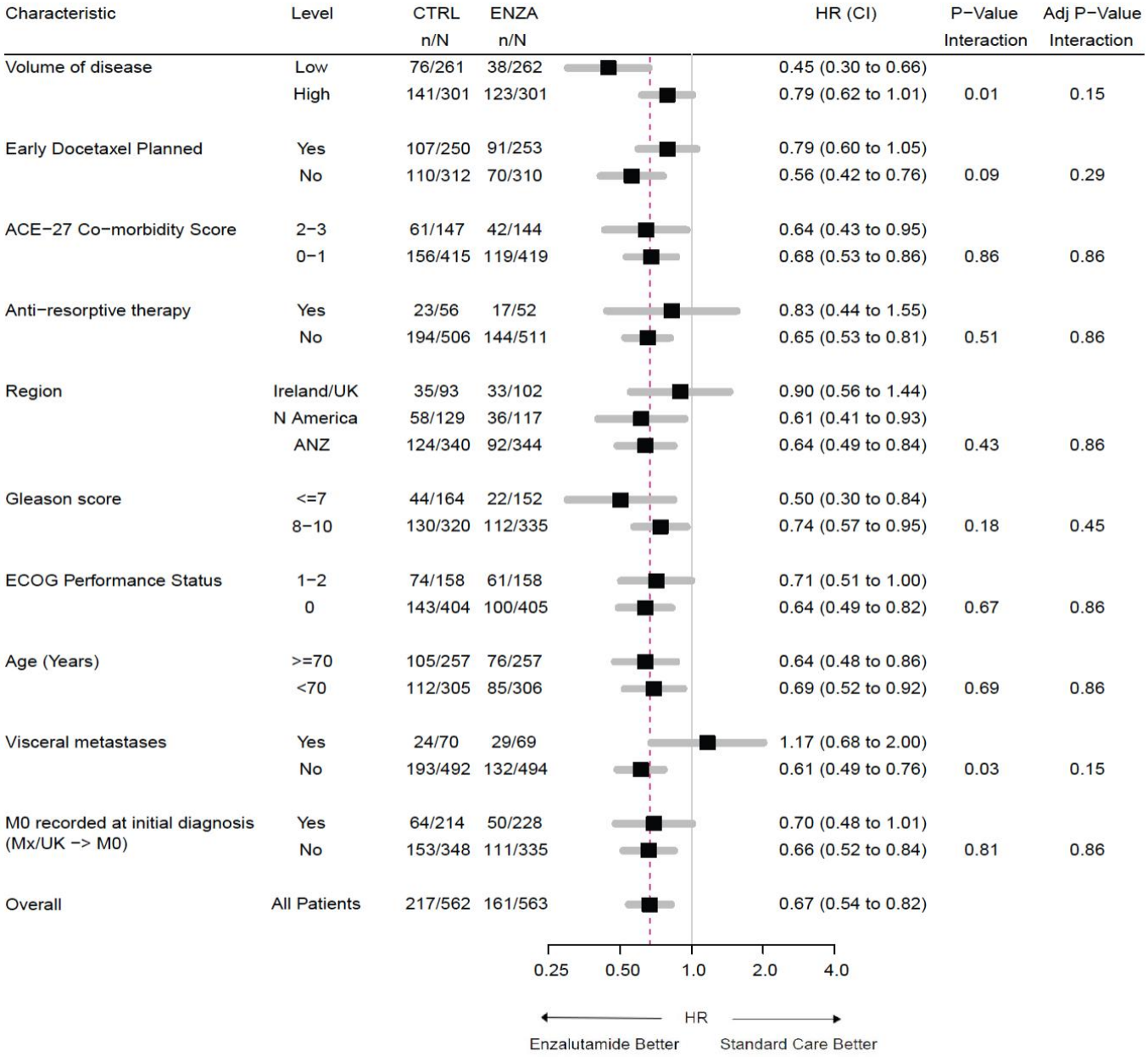
Supplementary Figure S1A: Forest Plot of PSA Progression-Free Survival



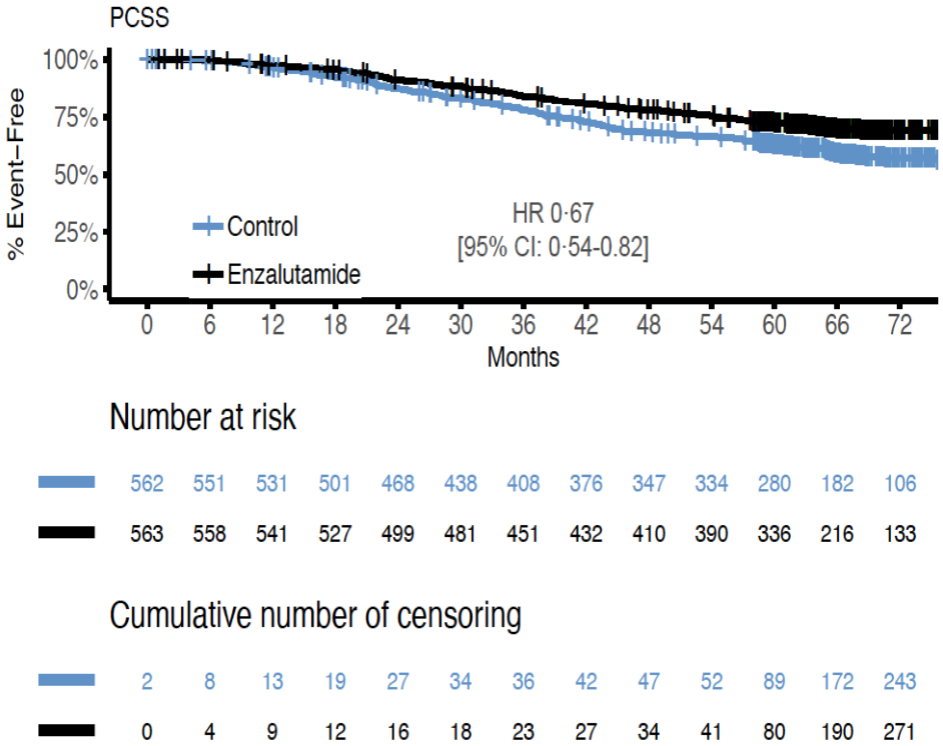
Supplementary Figure S1B: Forest Plot of Clinical Progression-Free Survival



Supplementary Figure S1C: Forest Plot of Prostate Cancer-Specific Survival

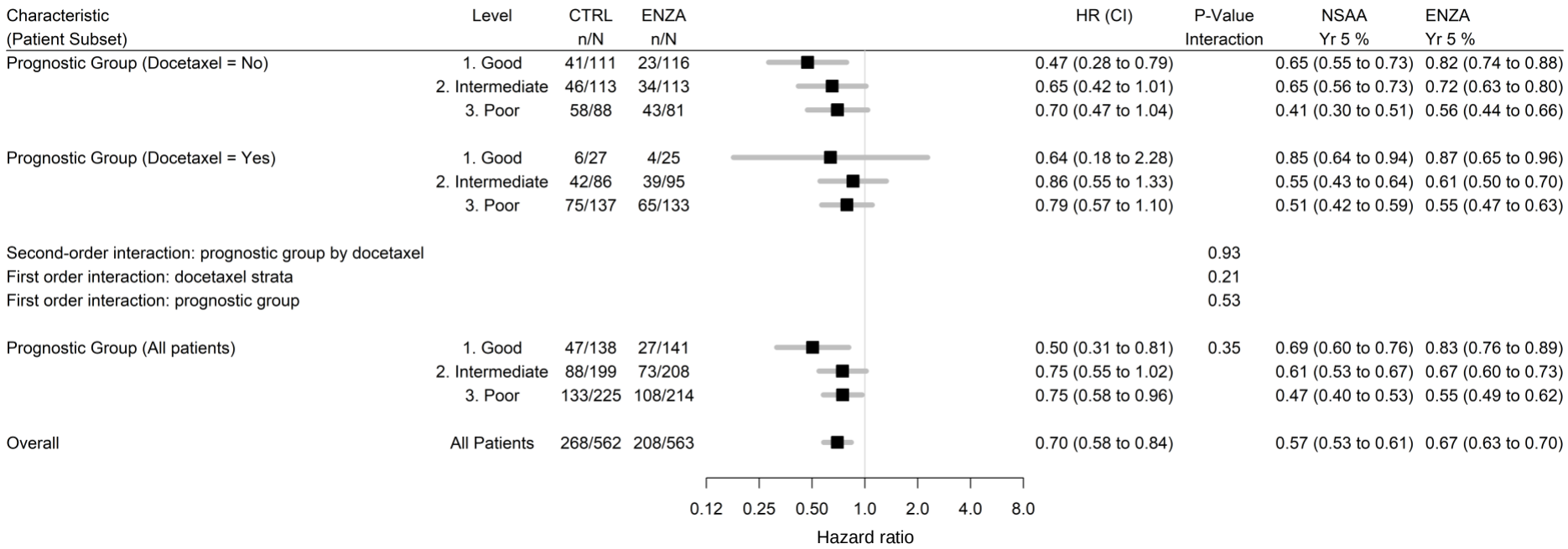


Supplementary Figure S1D Prostate Cancer Specific Survival



Legend for Supplementary Figure S1A-D: Shown are the results of subgroup analysis of Overall Survival (Panel A) and Clinical Progression Free Survival (Panel B) and Prostate Cancer Specific Survival in 10 key subgroups of patients in the enzalutamide group and the control group treated with non-steroidal anti-androgen (NSAA). Hazard ratios and 95% confidence intervals are provided. The dashed vertical line indicates the overall hazard ratio in all the patients. Scores on the Eastern Cooperative Oncology Group (ECOG) performance-status scale range from 0 (no disability) to 5 (death). Scores on the Adult Comorbidity Evaluation 27 (ACE-27) are 0 (none) or 1 (mild) vs. 2 (moderate) or 3 (severe). M0: Metachronous: First presentation of prostate cancer with non-metastatic disease, M0; 127 participants were recorded as Mx or UK (Unknown) and analysed as part of M0 subgroup given patients with intermediate and low risk localised prostate cancer are recorded as Nx, Mx when no staging scans are required; 30 of the 127 patients had prior radiation therapy and remaining 97 presumably were managed with watchful waiting or prostatectomy. The CRF collected prior surgery as prostatectomy; biopsy or TURP and did not collect prostatectomy as unique field to be able to detail how many of the 85 had a prior prostatectomy. Among the patients who received enzalutamide and those who received standard nonsteroidal antiandrogen therapy (control group), shown are Kaplan–Meier curves for prostate cancer specific survival – PCSS (Panel D)

Supplementary Figure S2: Overall Survival by Planned Pre-Defined Prognostic Subgroups without and with docetaxel



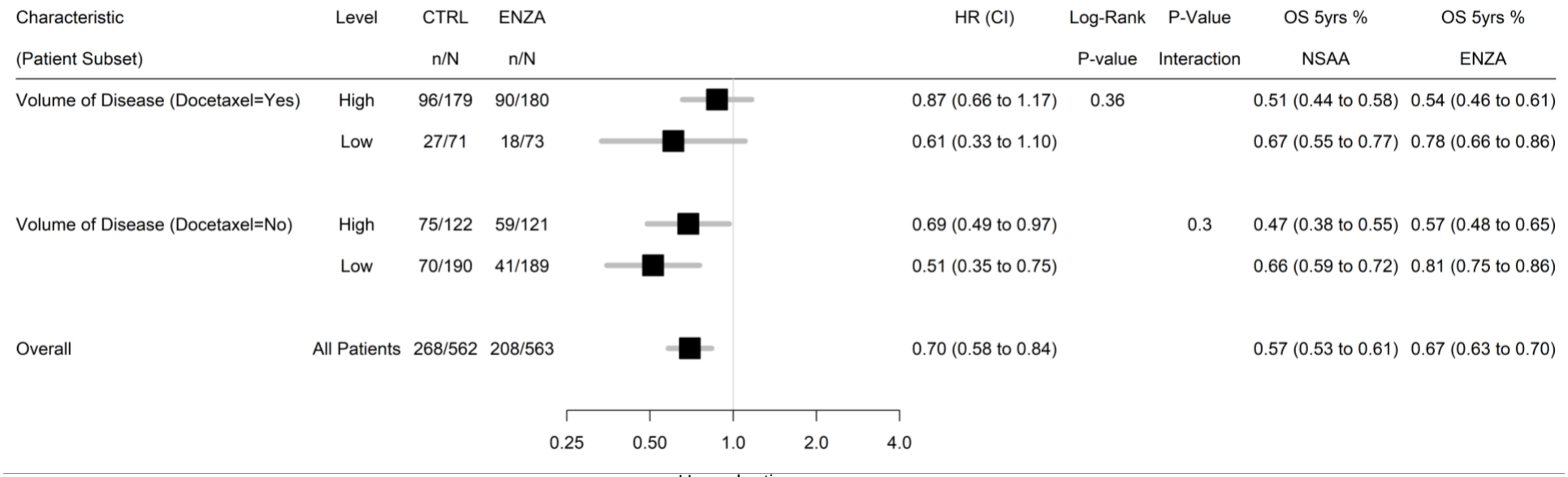
Legend for Supplementary Figure S2: Shown are the results of subgroup analysis of Overall Survival in planned pre-defined good, intermediate and poor prognostic subgroups without (Docetaxel = No) and with docetaxel (Docetaxel = Yes) in the enzalutamide group and the control group treated with non-steroidal anti-androgen (NSAA). Hazard ratios and 95% confidence intervals are provided. Good prognosis: metachronous low-volume with a median OS of about 8 years with testosterone suppression alone; Intermediate prognosis: synchronous low-volume and metachronous high-volume with median OS of about 5 years with testosterone suppression alone. Poor prognosis: synchronous high-volume with median OS of about 3 years with testosterone suppression alone. (Prognostic groups defined from References 1, 2, and 3 in main manuscript).

The hypotheses of specific interest in the pre-defined analyses:

Hypothesis 1: Whether there is an effect of enzalutamide within the subset of patients with high volume disease in the early docetaxel stratum. Hypothesis 1 is tested using the log-rank p-value for the subset of patients with high volume disease in the early docetaxel stratum.

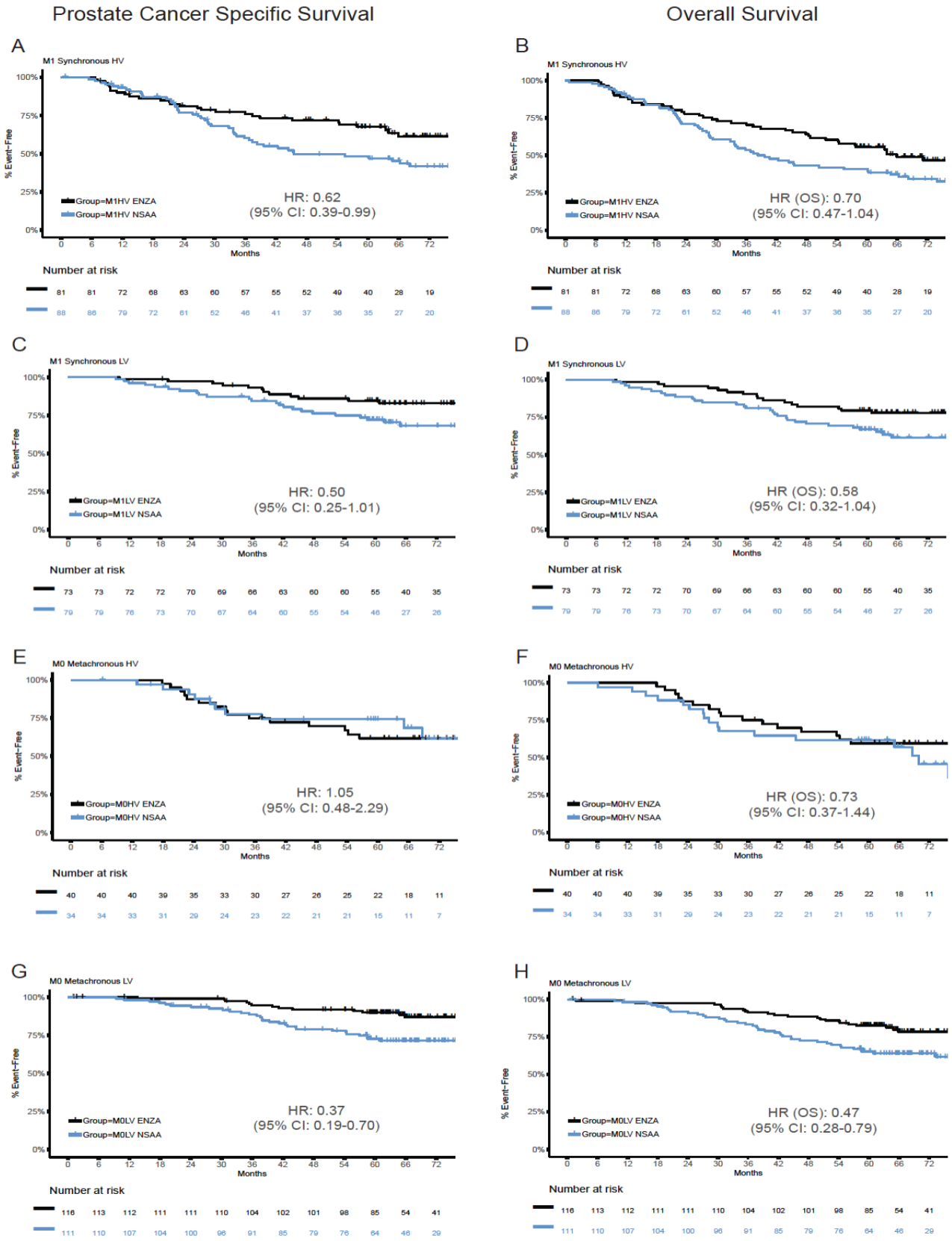
Hypothesis 2: Whether the effect of enzalutamide is homogeneous across the volume of disease subgroups (high versus low) for those NOT in the early docetaxel stratum. Hypothesis 2 is tested using the test of interaction (i.e. heterogeneity) for the comparison between the volume of disease subgroups (high versus low) for those in NOT in the early docetaxel stratum.

Supplementary Figure S3: Overall Survival by Disease Volume and Docetaxel (All Patients)



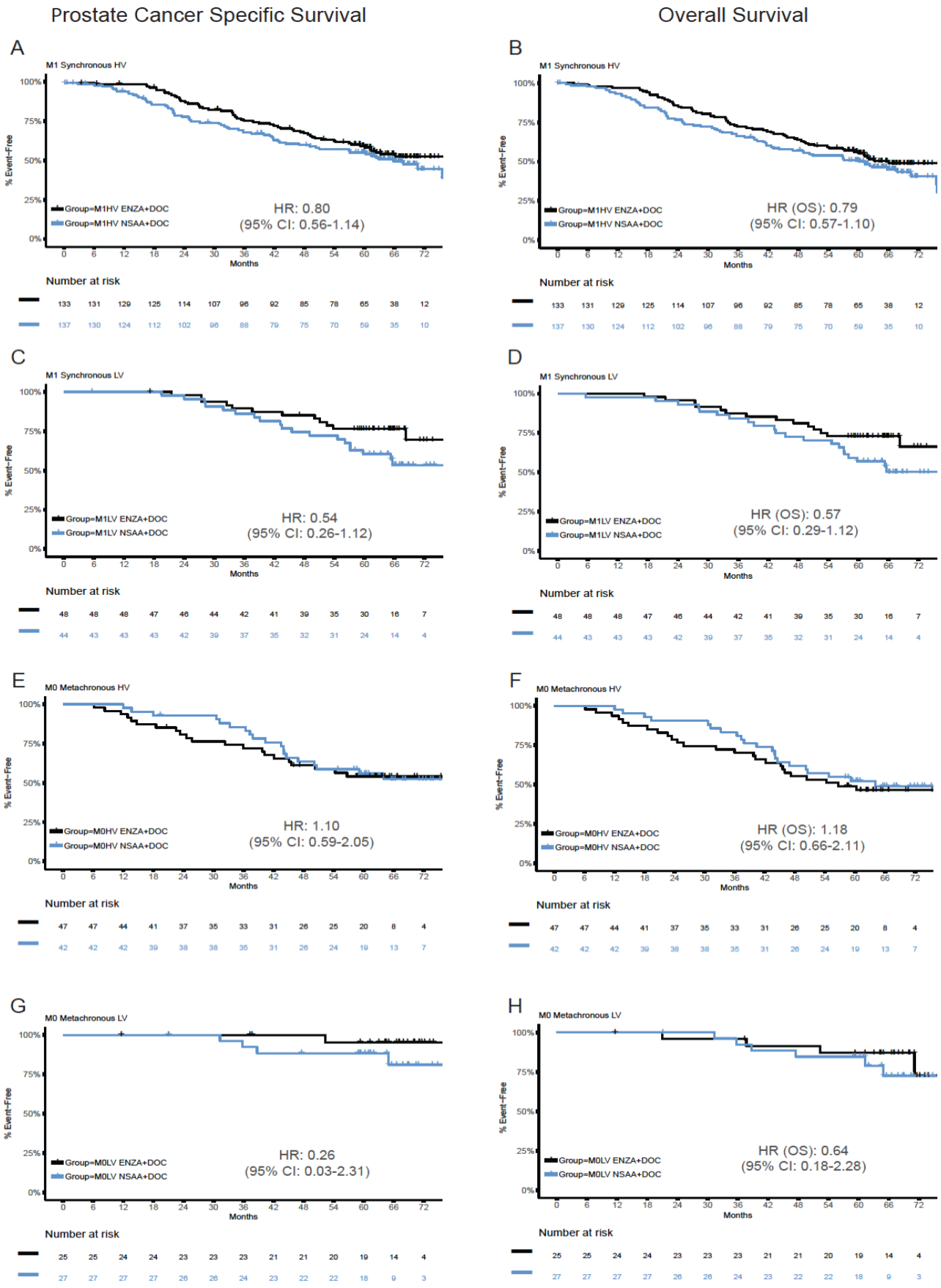
Legend for Supplementary Figure S3: Shown are the results of subgroup analysis of Overall Survival in the prospectively captured prognostic subgroups of all patients (synchronous and metachronous metastatic disease) and analysed by presence of high- and low-volume per the CHAARTED criteria without (Docetaxel = No) and with docetaxel (Docetaxel = Yes) in the enzalutamide group and the control group treated with non-steroidal anti-androgen (NSAA). Hazard ratios and 95% confidence intervals are provided.

Supplementary Figure S4 Prostate Cancer Specific Survival and Overall Survival by Prognostic Groups (No Docetaxel Subset)



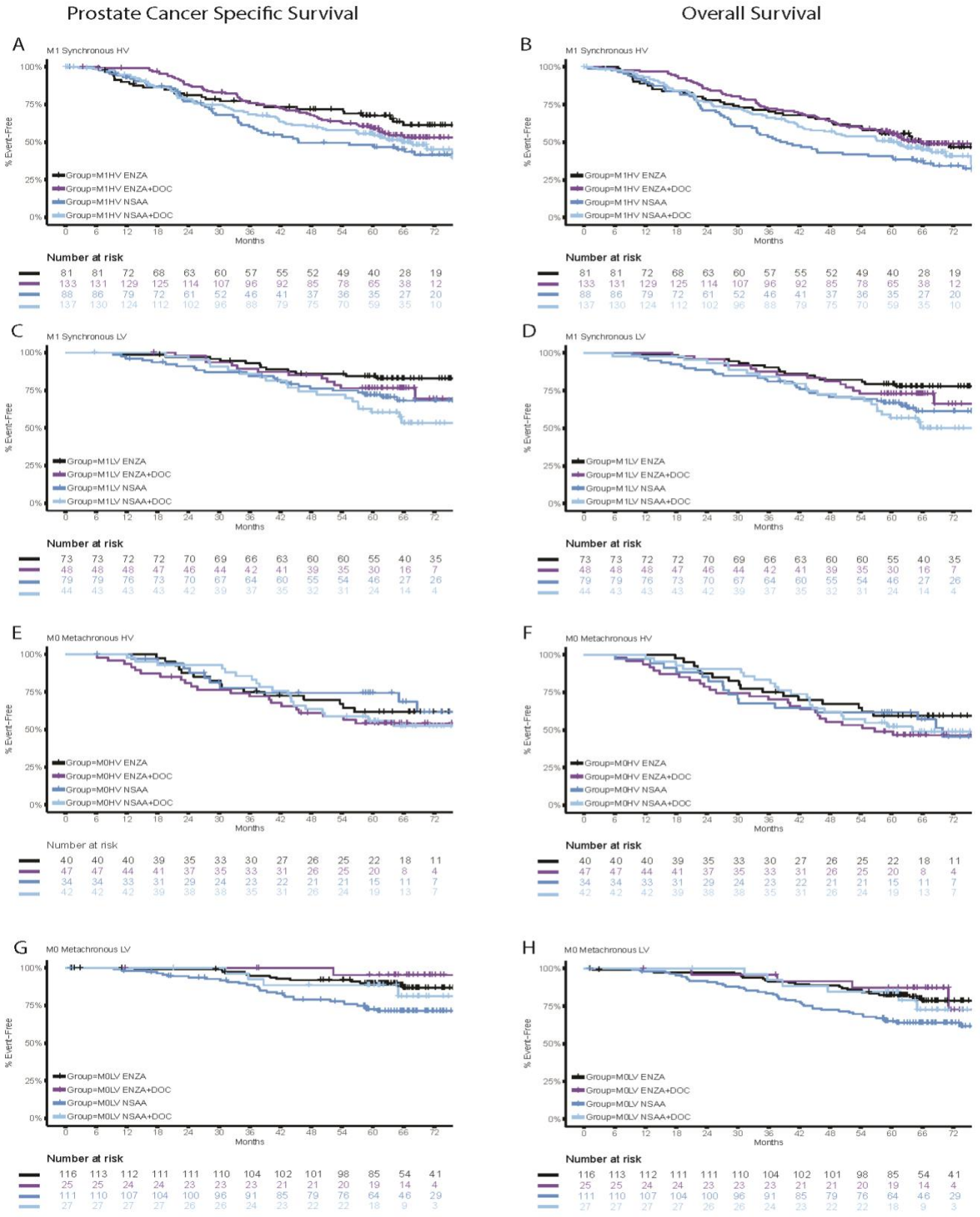
Legend for Supplementary Figure S4: Prostate Cancer Specific Survival and Overall Survival by Prognostic Groups, without docetaxel.
Among the patients not selected for docetaxel and who also received enzalutamide and those who also received standard nonsteroidal antiandrogen therapy (NSAA), shown are Kaplan–Meier curves for Prostate Cancer Specific Survival - PCSS – (Panels A, C, E, G) and Overall Survival – OS (Panels B, D, F, H). M1 Synchronous: Patients present with metastatic disease at first diagnosis; M0 Metachronous: Patients present with localised disease at first diagnosis and relapse with metastatic disease after primary treatment or initial observation. HV: high-volume metastatic disease per CHAARTED criteria; LV low-volume disease per CHAARTED criteria. NSAA: non-steroidal anti-androgen; ENZA: enzalutamide; DOC: docetaxel

Supplementary Figure S5 Prostate Cancer Specific Survival and Overall Survival by Prognostic Groups (Docetaxel Subset)



Legend for Supplementary Figure S5
Among the patients selected for docetaxel and who also received enzalutamide and those who also received standard nonsteroidal antiandrogen therapy (NSAA), shown are Kaplan–Meier curves for Prostate Cancer Specific Survival - PCSS – (Panels A, C, E, G) and Overall Survival – OS (Panels B, D, F, H). M1 Synchronous: Patients present with metastatic disease at first diagnosis; M0 Metachronous: Patients present with localised disease at first diagnosis and relapse with metastatic disease after primary treatment or initial observation. HV: high-volume metastatic disease per CHAARTED criteria; LV low-volume disease per CHAARTED criteria. NSAA: non-steroidal anti-androgen; ENZA: enzalutamide; DOC: docetaxel

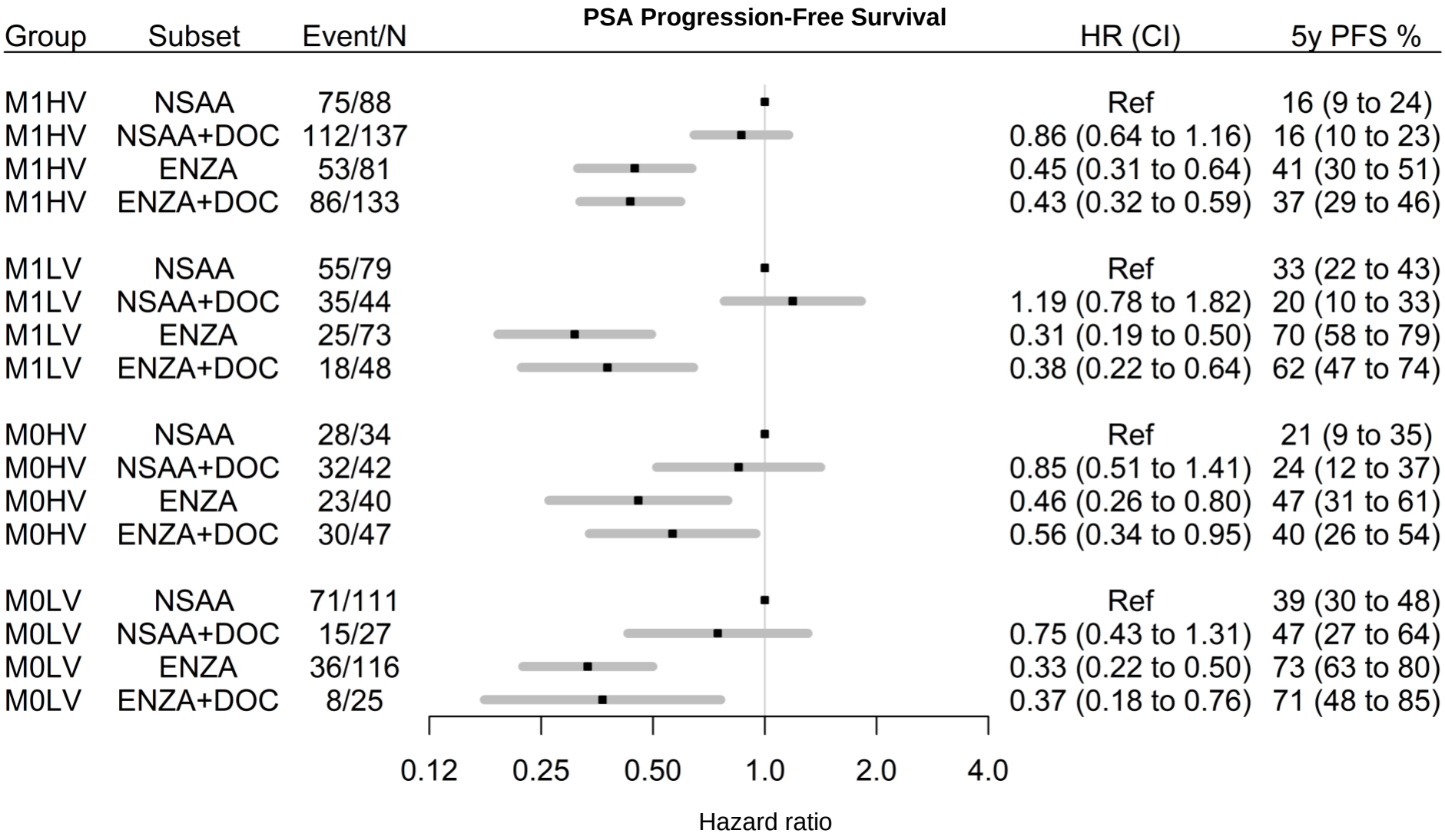
Supplementary Figure S6: Exploratory Analysis: Prostate Cancer Specific and Overall Survival by Disease Volume and M-Stage at Presentation with and without Docetaxel



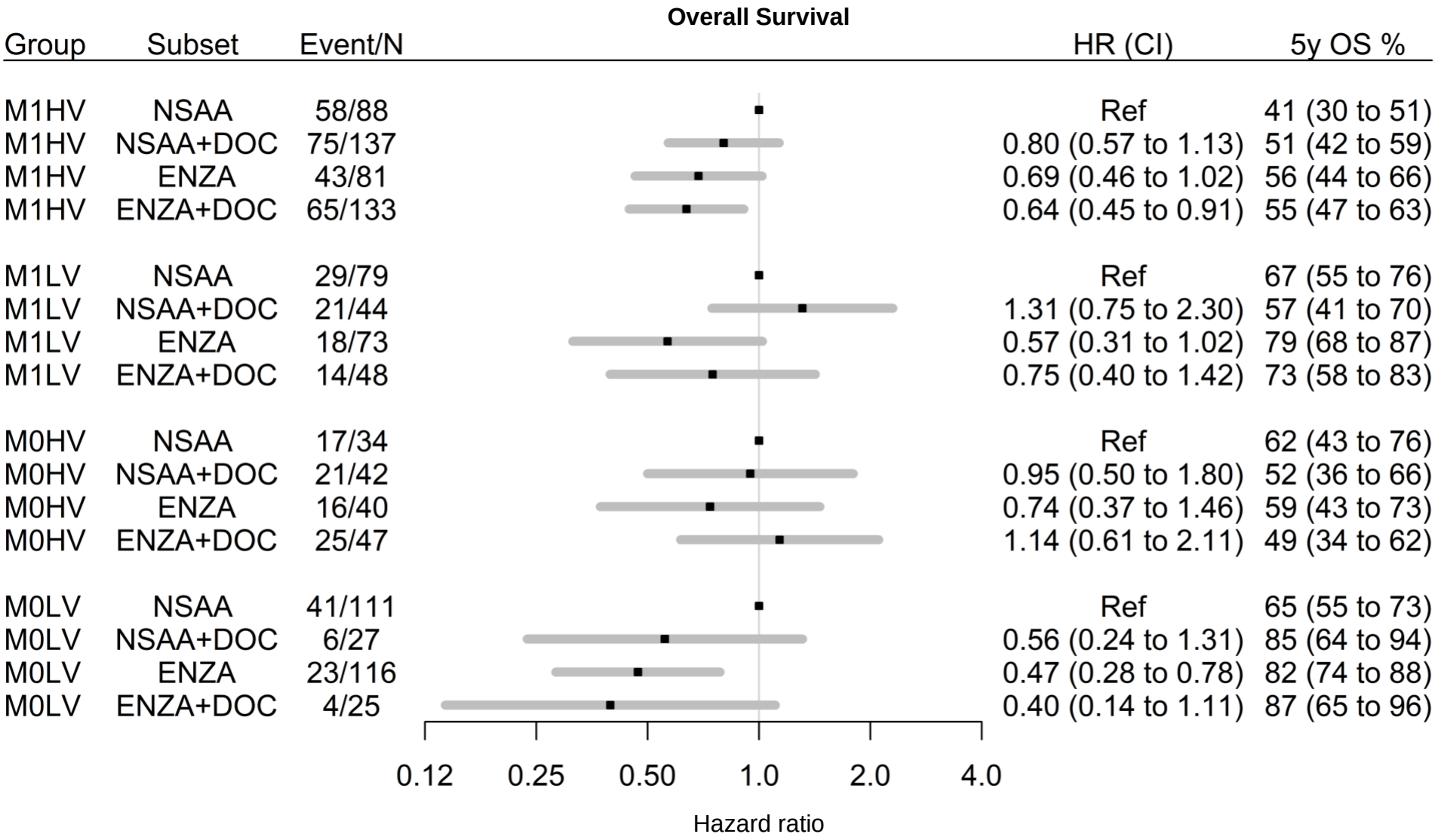
Legend for Supplementary Figure S6: Exploratory Analysis:Prostate Cancer Specific and Overall Survival by Disease Volume and M-Stage at Presentation with and without Docetaxel: A composite presentation of the data from Figures S4 and S5 of the patients selected for docetaxel and not selected for docetaxel and who also received enzalutamide and those who also received standard nonsteroidal antiandrogen therapy (NSAA). Shown are Kaplan–Meier curves for Prostate Cancer Specific Survival - PCSS – (Panels A, C, E, G) and Overall Survival – OS (Panels B, D, F, H) and detail the outcomes of each contemporaneously enrolled group. M1 Synchronous: Patients present with metastatic disease at first diagnosis; M0 Metachronous: Patients present with localised disease at first diagnosis and relapse with metastatic disease after primary treatment or initial observation. HV: high-volume metastatic disease per CHAARTED criteria; LV low-volume disease per CHAARTED criteria. NSAA: non-steroidal anti-androgen; ENZA: enzalutamide; DOC: docetaxel

Supplementary Figure S7: Exploratory Analysis - Forest Plots for PSA progression-free survival; overall survival; prostate cancer-specific survival

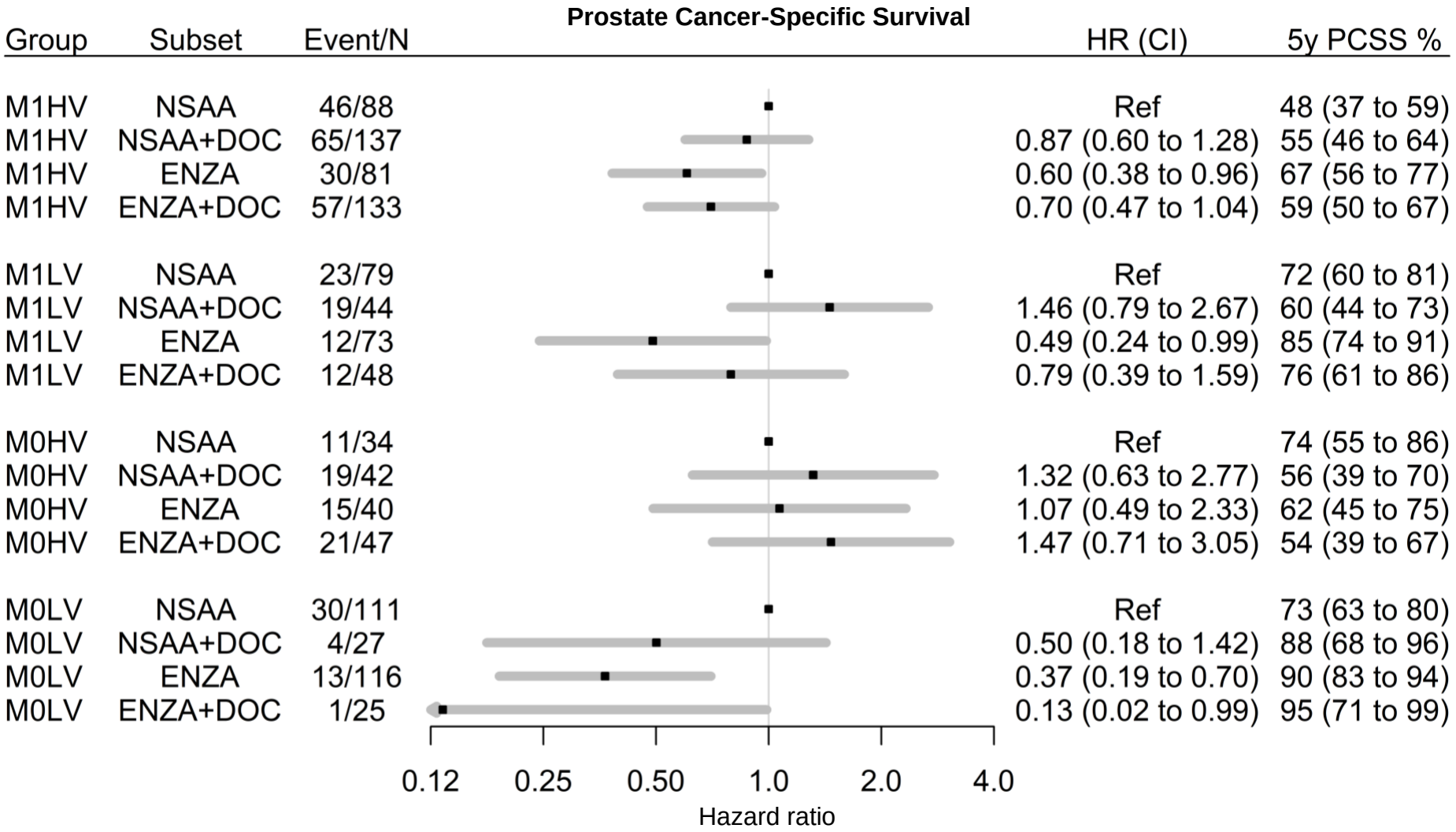
(Supplementary Figure S7A)



(Supplementary Figure S7B)

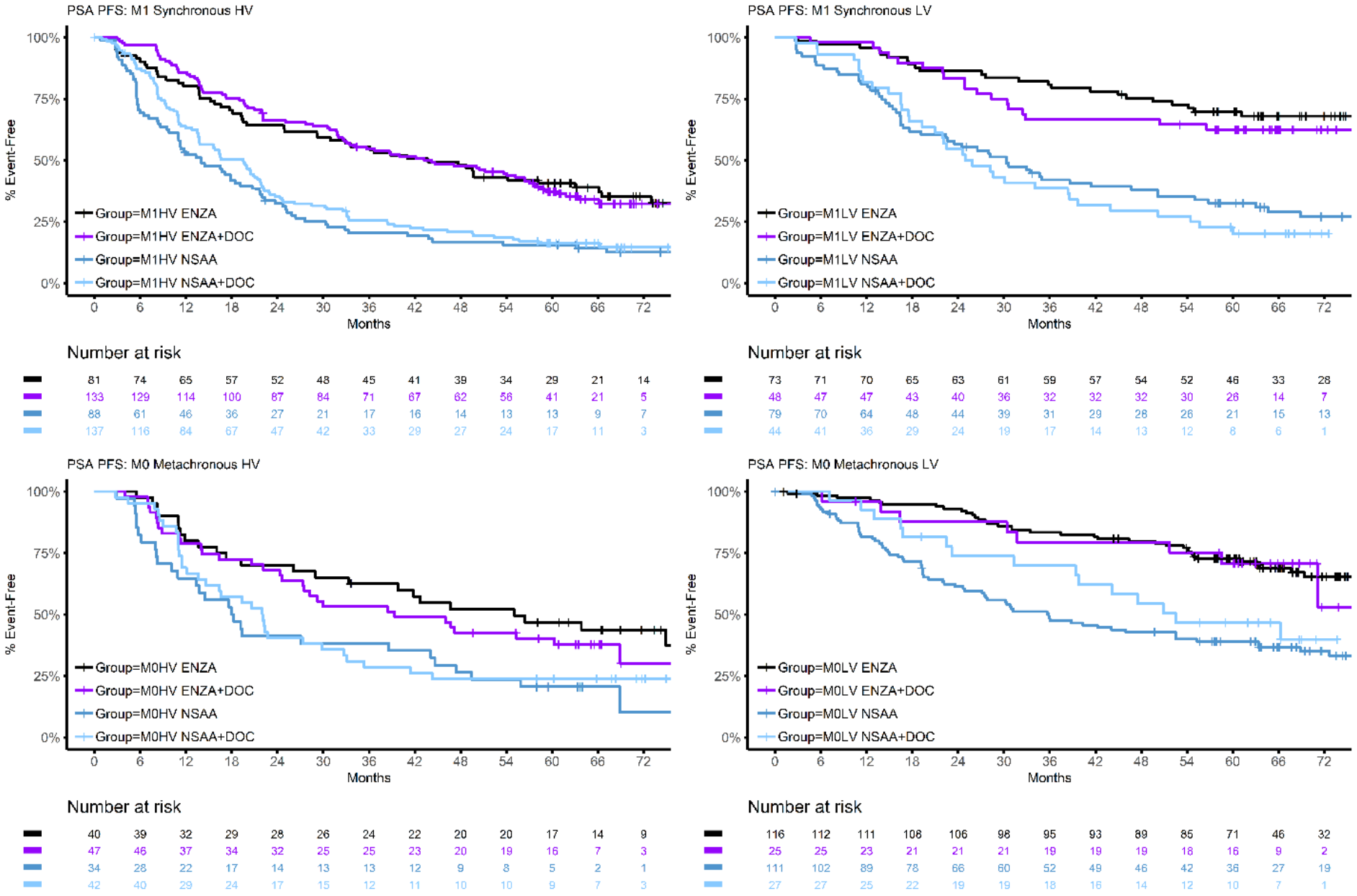


(Supplementary Figure S7C)



Legend for Supplementary Figure S7: Shown are the results of subgroup analysis of PSA Progression-Free Survival (S6A), Overall Survival (S6B), and Prostate Cancer-Specific Survival (S6C) in planned pre-defined prognostic subgroups, without and with docetaxel (DOC) in the enzalutamide (ENZA) group and the control group treated with non-steroidal anti-androgen (NSAA). Hazard ratios and 95% confidence intervals are provided. M1: Patients present with metastatic disease at first diagnosis (synchronous); M0: Patients present with localised disease at first diagnosis and relapse with metastatic disease after primary treatment or initial observation (metachronous). HV: high-volume metastatic disease per CHAARTED criteria; LV low-volume disease per CHAARTED criteria.

Supplementary Figure S8: Exploratory Analysis of PSA progression-free survival Kaplan-Meier curves by prognostic group without and with docetaxel



Legend for Supplementary Figure S8: Among the patients who received enzalutamide and those who received standard nonsteroidal antiandrogen therapy (NSAA), shown are Kaplan–Meier curves for PSA Progression-free Survival. The curves detail the outcomes of each contemporaneously enrolled group.; M1 Synchronous: Patients present with metastatic disease at first diagnosis; M0 Metachronous: Patients present with localised disease at first diagnosis and relapse with metastatic disease after primary treatment or initial observation. HV: high-volume metastatic disease per CHAARTED criteria; LV low-volume disease per CHAARTED criteria. NSAA: non-steroidal anti-androgen; ENZA: enzalutamide; DOC: docetaxel. PSA-PFS is a more direct evaluation of disease control than clinical PFS as the latter is influenced by treatment switch which was most likely triggered by a PSA rise prior to definition of PSA progression and/or radiographic progression. We have therefore highlighted the PSA-PFS data, given the high rate of treatment switch in the NSAA arm qualifying as clinical-progression, and noting that data are similar for PSA-PFS and clinical PFS for those randomized to NSAA or enzalutamide.

Supplementary Table S2: Baseline Characteristics by Docetaxel Stratum: M1HV Subset

	Chosen for Docetaxel	
Characteristic	**No**, N = 169[1]	**Yes**, N = 270[1]
Age (Years)		
Mean (SD)	73 (8)	66 (8)
Median (25% to 75%)	74 (67 to 79)	66 (60 to 72)
ACE-27 strata		
0-1	120 (71%)	212 (79%)
2-3	49 (29%)	58 (21%)
ACE-27 co-morbidity score		
0	43 (25%)	98 (36%)
1	77 (46%)	114 (42%)
2	28 (17%)	42 (16%)
3	21 (12%)	16 (6%)

[1]n(%)

Supplementary Table S3: Total Number of Discontinuations and Reasons for Discontinuation for Each Group

Characteristic		Control	Enzalutamide
Discontinued Therapy		450 (80.6%)	309 (54.9%)
Reason for permanently ceasing anti-androgen treatment*	Clinical Progression (Imaging)	173 (38.4%^)	121 (39.2%^)
	Clinical Progression (Symptoms)	72 (16.0%)	46 (14.9%)
	Clinical Progression (Anti-cancer Rx)	41 (9.1%)	12 (3.9%)
	Clinical Progression OTHER	1 (0.2%)	
	Adverse event	25 (5.6%)	63 (20.4%)
	Clinician preference	90 (20.0%)	23 (7.4%)
	Death	9 (2.0%)	15 (4.9%)
	Other	6 (1.3%)	9 (2.9%)
	Patient preference	33 (7.3%)	20 (6.5%)

*Investigators allowed to select more than one criterion for clinical progression, however only one criterion is shown in the table with sequence for attribution being: (1) imaging, (2) symptoms, (3) anti-cancer Rx, (4) Other; ^Denominator for percentages is number who have discontinued.

Supplementary Table S4: Subsequent and Total Therapy for Patients Who Had Progressed

Therapy	NSAA N=413	Enzalutamide N=268
All	N (%)	N (%)
Enzalutamide	205 (49.6)	0 (0)
Abiraterone	148 (35.8)	70 (26.1)
Other NHT*	2 (0.5)	1 (0.4)
At least one NHT for CRPC	313 (75.8)	70 (26.1)
At least one NHT for mHSPC or mCRPC	313 (75.8)	268 (100)
Docetaxel post cessation of study treatment	79 (19.1)	47 (17.5)
Cabazitaxel	104 (25.2)	57 (21.3)
Other chemo	38 (9.2)	37 (13.8)
Immune checkpoint inhibitor	11 (2.7)	11 (4.1)
LuPSMA	12 (2.9)	9 (3.4)
PARP-inhibitor	21 (5.1)	7 (2.6)
Radium-223	28 (6.8)	26 (9.7)
Sipuleucel-T	3 (0.7)	1 (0.4)
No Treatment	60 (14.5)	104 (38.8)
Planned Early Docetaxel	N=191	N=140
Enzalutamide	103 (53.9)	0 (0)
Abiraterone	80 (41.9)	38 (27.1)
Other NHT	1 (0.5)	0 (0)
At least one NHT for CRPC	160 (83.8)	38 (27.1)
Docetaxel post cessation of study treatment	2 (1.0%)	3 (2.1%)
Cabazitaxel	69 (36.1)	36 (25.7)
Other Treatment	34 (17.8)	32 (22.9)
No Treatment	16 (8.4)	49 (35.0)
No Planned Early Docetaxel	N=222	N=128
Enzalutamide	102 (45.9)	0 (0)
Abiraterone	68 (30.6)	32 (25.0)
Other NHT	1 (0.5)	1 (0.8)
At least one NHT for CRPC	153 (68.9)	32 (25.0)
Docetaxel post cessation of study treatment	77 (34.7)	44 (34.4)
Cabazitaxel	35 (15.8)	21 (16.4)
Other treatment	27 (12.2)	20 (15.6)
No other treatment	44 (19.8)	55 (43.0)

Treatment given subsequent (with 21-day window) to study treatment discontinuation
***Other NHT: novel hormonal therapy: apalutamide or galeterone**

Supplementary Table S5: Participants with Serious Adverse Events Judged by Investigator to be Related to NSAA or ENZA (by Term, Class, and Worst Grade; Not normalized for time on therapy)

	Conventional NSAA, N = 558					**Enzalutamide**, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Acute coronary syndrome	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Myocardial infarction	—	1 (0.2)	—	—	1 (0.2)	—	1 (0.2)	1 (0.2)	—	2 (0.4)
Nausea	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Fatigue	—	—	—	—	—	—	2 (0.4)	—	—	2 (0.4)
Sepsis	—	—	—	—	—	—	—	1 (0.2)	—	1 (0.2)
Fracture	—	1 (0.2)	—	—	1 (0.2)	—	—	—	—	—
Spinal fracture	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)
Alanine aminotransferase increased	—	1 (0.2)	—	—	1 (0.2)	—	—	—	—	—
Pancreatic enzymes decreased	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Lethargy	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Memory impairment	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Seizure	—	—	—	—	—	3 (0.5)	1 (0.2)	—	—	4 (0.7)
Syncope	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)
Mania	—	—	—	—	—	—	—	1 (0.2)	—	1 (0.2)
Pneumonitis	—	1 (0.2)	—	1 (0.2)	2 (0.4)	—	—	—	—	—
Hypertension	—	—	—	—	—	2 (0.4)	2 (0.4)	—	—	4 (0.7)
Any AE	1 (0.2)	4 (0.7)	—	1 (0.2)	6 (1.1)	8 (1.4)	8 (1.4)	3 (0.5)	—	19 (3.4)

Supplementary Table S6: Number of Patients Experiencing Selected Adverse Events Per 100,000 Person-Years

	NSAA N=558						Enzalutamide N=563					
Grade	1	2	3	4	5	Total	1	2	3	4	5	Total
Fatigue	20018	5957	277	_	_	26252	12760	7519	1504	_	_	21784
Cognitive disturbance	139	139	_	_	_	277	501	182	46	_	_	729
Concentration impairment	485	_	_	_	_	485	1185	137	_	_	_	1322
Seizure	_	_	_	_	_	_	91	182	46	_	_	319
Peripheral sensory neuropathy	6788	1455	69	_	_	8312	5605	1823	182	_	_	7611
Fall	900	762	139	_	_	1801	1777	1868	410	_	_	4056
Fracture	69	554	485	_	_	1108	410	638	911	46	_	2005
Generalised muscle weakness	900	346	_	_	_	1247	1413	91	91	_	_	1595
Any Cardiac disorder	1178	1662	1870	277	69	5056	1823	1686	1641	273	137	5560
Hypertension	1178	2632	2078	69	_	5957	820	3281	2689	_	_	6790
Myocardial infarction	_	_	346	69	_	416	_	46	319	_	91	456
Heart failure	_	208	208	69	_	485	46	91	410	_	_	547
Aspartate aminotransferase increased	2216	416	69	_	_	2701	501	182	46	_	_	729
Alanine aminotransferase increased	2355	554	208	_	_	3117	1094	182	182	_	_	1458

*AE rate normalisation for time on protocol therapy per 100,000 person-years of exposure time (calculated by dividing the patient counts by the cumulative treatment exposure durations for each treatment group and scaling this to 100,000 person-years of exposure time; ^see initial report and relationship to docetaxel

Supplementary Table S7: Participants with All Adverse Events by Term, Class, and Worst Grade (Not normalized for time on treatment)

	Conventional NSAA, N = 558					**Enzalutamide**, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Blood and lymphatic system disorders	98 (18)	30 (5.4)	10 (1.8)	—	138 (25)	107 (19)	39 (6.9)	7 (1.2)	—	153 (27)
Anemia	88 (16)	8 (1.4)	1 (0.2)	—	97 (17)	95 (17)	7 (1.2)	—	—	102 (18)
Blood and lymphatic system disorders - Other	28 (5.0)	—	—	—	28 (5.0)	32 (5.7)	2 (0.4)	—	—	34 (6.0)
Bone marrow hypocellular	—	—	—	—	—	2 (0.4)	—	—	—	2 (0.4)
Febrile neutropenia	—	24 (4.3)	9 (1.6)	—	33 (5.9)	—	30 (5.3)	7 (1.2)	—	37 (6.6)
Leukocytosis	—	1 (0.2)	—	—	1 (0.2)	—	—	—	—	—
Lymph node pain	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Thrombotic thrombocytopenic purpura	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Cardiac disorders	41 (7.3)	27 (4.8)	4 (0.7)	1 (0.2)	73 (13)	77 (14)	36 (6.4)	6 (1.1)	3 (0.5)	122 (22)
Acute coronary syndrome	2 (0.4)	4 (0.7)	—	—	6 (1.1)	3 (0.5)	3 (0.5)	1 (0.2)	—	7 (1.2)
Aortic valve disease	2 (0.4)	3 (0.5)	1 (0.2)	—	6 (1.1)	—	2 (0.4)	2 (0.4)	—	4 (0.7)
Atrial fibrillation	7 (1.3)	3 (0.5)	—	—	10 (1.8)	5 (0.9)	8 (1.4)	1 (0.2)	—	14 (2.5)
Atrial flutter	1 (0.2)	3 (0.5)	—	—	4 (0.7)	2 (0.4)	3 (0.5)	1 (0.2)	—	6 (1.1)
Atrioventricular block complete	—	1 (0.2)	—	—	1 (0.2)	—	1 (0.2)	—	—	1 (0.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Atrioventricular block first degree	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Cardiac arrest	—	—	—	1 (0.2)	1 (0.2)	—	—	—	—	—
Cardiac disorders - Other	24 (4.3)	3 (0.5)	—	—	27 (4.8)	42 (7.5)	5 (0.9)	1 (0.2)	1 (0.2)	49 (8.7)
Chest pain - cardiac	7 (1.3)	4 (0.7)	—	—	11 (2.0)	24 (4.3)	5 (0.9)	—	—	29 (5.2)
Heart failure	3 (0.5)	3 (0.5)	1 (0.2)	—	7 (1.3)	3 (0.5)	9 (1.6)	—	—	12 (2.1)
Left ventricular systolic dysfunction	—	2 (0.4)	—	—	2 (0.4)	—	—	—	—	—
Mitral valve disease	—	—	1 (0.2)	—	1 (0.2)	2 (0.4)	1 (0.2)	—	—	3 (0.5)
Mobitz (type) II atrioventricular block	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Myocardial infarction	—	5 (0.9)	1 (0.2)	—	6 (1.1)	1 (0.2)	7 (1.2)	—	2 (0.4)	10 (1.8)
Palpitations	5 (0.9)	—	—	—	5 (0.9)	12 (2.1)	—	—	—	12 (2.1)
Paroxysmal atrial tachycardia	1 (0.2)	1 (0.2)	—	—	2 (0.4)	—	—	—	—	—
Pericardial effusion	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Pericarditis	1 (0.2)	—	—	—	1 (0.2)	2 (0.4)	—	—	—	2 (0.4)
Sick sinus syndrome	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Sinus bradycardia	5 (0.9)	1 (0.2)	—	—	6 (1.1)	13 (2.3)	—	—	—	13 (2.3)
Sinus tachycardia	3 (0.5)	—	—	—	3 (0.5)	9 (1.6)	—	—	—	9 (1.6)
Supraventricular tachycardia	3 (0.5)	2 (0.4)	—	—	5 (0.9)	—	1 (0.2)	—	—	1 (0.2)
Ventricular arrhythmia	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—
Ventricular tachycardia	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Ear and labyrinth disorders	26 (4.7)	2 (0.4)	—	—	28 (5.0)	57 (10)	4 (0.7)	—	—	61 (11)
Ear and labyrinth disorders - Other	11 (2.0)	—	—	—	11 (2.0)	22 (3.9)	—	—	—	22 (3.9)
Ear pain	1 (0.2)	—	—	—	1 (0.2)	4 (0.7)	—	—	—	4 (0.7)
External ear inflammation	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Hearing impaired	—	1 (0.2)	—	—	1 (0.2)	9 (1.6)	3 (0.5)	—	—	12 (2.1)
Middle ear inflammation	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Tinnitus	6 (1.1)	—	—	—	6 (1.1)	20 (3.6)	—	—	—	20 (3.6)
Vertigo	7 (1.3)	—	—	—	7 (1.3)	18 (3.2)	1 (0.2)	—	—	19 (3.4)
Vestibular disorder	1 (0.2)	1 (0.2)	—	—	2 (0.4)	2 (0.4)	—	—	—	2 (0.4)
Endocrine disorders	24 (4.3)	1 (0.2)	—	—	25 (4.5)	34 (6.0)	—	—	—	34 (6.0)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Cushingoid	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—
Endocrine disorders - Other	19 (3.4)	1 (0.2)	—	—	20 (3.6)	27 (4.8)	—	—	—	27 (4.8)
Hyperparathyroidism	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Hyperthyroidism	1 (0.2)	—	—	—	1 (0.2)	3 (0.5)	—	—	—	3 (0.5)
Hypoparathyroidism	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Hypothyroidism	2 (0.4)	—	—	—	2 (0.4)	3 (0.5)	—	—	—	3 (0.5)
Virilization	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Eye disorders	61 (11)	12 (2.2)	1 (0.2)	—	74 (13)	128 (23)	18 (3.2)	1 (0.2)	—	147 (26)
Blurred vision	9 (1.6)	1 (0.2)	—	—	10 (1.8)	13 (2.3)	—	—	—	13 (2.3)
Cataract	3 (0.5)	10 (1.8)	—	—	13 (2.3)	4 (0.7)	13 (2.3)	—	—	17 (3.0)
Conjunctivitis	5 (0.9)	—	—	—	5 (0.9)	13 (2.3)	—	—	—	13 (2.3)
Corneal ulcer	—	1 (0.2)	—	—	1 (0.2)	—	—	—	—	—
Dry eye	13 (2.3)	—	—	—	13 (2.3)	19 (3.4)	—	—	—	19 (3.4)
Eye disorders - Other	26 (4.7)	1 (0.2)	1 (0.2)	—	28 (5.0)	48 (8.5)	2 (0.4)	—	—	50 (8.9)
Eye pain	2 (0.4)	—	—	—	2 (0.4)	8 (1.4)	—	—	—	8 (1.4)
Eyelid function disorder	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Floaters	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Glaucoma	2 (0.4)	—	—	—	2 (0.4)	4 (0.7)	—	1 (0.2)	—	5 (0.9)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Keratitis	1 (0.2)	—	—	—	1 (0.2)	—	1 (0.2)	—	—	1 (0.2)
Optic nerve disorder	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Photophobia	4 (0.7)	—	—	—	4 (0.7)	3 (0.5)	—	—	—	3 (0.5)
Retinal detachment	—	1 (0.2)	—	—	1 (0.2)	1 (0.2)	2 (0.4)	—	—	3 (0.5)
Vitreous hemorrhage	3 (0.5)	—	—	—	3 (0.5)	1 (0.2)	—	—	—	1 (0.2)
Watering eyes	18 (3.2)	—	—	—	18 (3.2)	63 (11)	1 (0.2)	—	—	64 (11)
Gastrointestinal disorders	291 (52)	34 (6.1)	—	2 (0.4)	327 (59)	351 (62)	30 (5.3)	1 (0.2)	—	382 (68)
Abdominal distension	1 (0.2)	—	—	—	1 (0.2)	5 (0.9)	—	—	—	5 (0.9)
Abdominal pain	33 (5.9)	6 (1.1)	—	—	39 (7.0)	50 (8.9)	3 (0.5)	—	—	53 (9.4)
Anal fistula	—	—	—	—	—	—	2 (0.4)	—	—	2 (0.4)
Anal hemorrhage	3 (0.5)	—	—	—	3 (0.5)	3 (0.5)	—	—	—	3 (0.5)
Anal pain	3 (0.5)	—	—	—	3 (0.5)	3 (0.5)	—	—	—	3 (0.5)
Ascites	1 (0.2)	1 (0.2)	—	—	2 (0.4)	—	—	—	—	—
Bloating	4 (0.7)	—	—	—	4 (0.7)	17 (3.0)	—	—	—	17 (3.0)
Colitis	—	2 (0.4)	—	—	2 (0.4)	1 (0.2)	2 (0.4)	—	—	3 (0.5)
Colonic hemorrhage	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Constipation	115 (21)	5 (0.9)	—	—	120 (22)	148 (26)	—	—	—	148 (26)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Dental caries	4 (0.7)	—	—	—	4 (0.7)	2 (0.4)	—	—	—	2 (0.4)
Diarrhea	101 (18)	6 (1.1)	—	—	107 (19)	131 (23)	5 (0.9)	—	—	136 (24)
Dry mouth	9 (1.6)	—	—	—	9 (1.6)	14 (2.5)	—	—	—	14 (2.5)
Dyspepsia	19 (3.4)	—	—	—	19 (3.4)	28 (5.0)	—	—	—	28 (5.0)
Dysphagia	5 (0.9)	2 (0.4)	—	—	7 (1.3)	6 (1.1)	—	—	—	6 (1.1)
Enterocolitis	2 (0.4)	1 (0.2)	—	—	3 (0.5)	—	1 (0.2)	—	—	1 (0.2)
Esophageal obstruction	—	1 (0.2)	—	—	1 (0.2)	—	1 (0.2)	—	—	1 (0.2)
Esophageal pain	—	—	—	—	—	4 (0.7)	—	—	—	4 (0.7)
Esophageal stenosis	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—
Esophageal ulcer	—	—	—	—	—	1 (0.2)	1 (0.2)	—	—	2 (0.4)
Esophagitis	—	—	—	—	—	2 (0.4)	—	—	—	2 (0.4)
Fecal incontinence	3 (0.5)	—	—	—	3 (0.5)	5 (0.9)	—	—	—	5 (0.9)
Flatulence	7 (1.3)	—	—	—	7 (1.3)	14 (2.5)	—	—	—	14 (2.5)
Gastric hemorrhage	2 (0.4)	1 (0.2)	—	1 (0.2)	4 (0.7)	—	—	—	—	—
Gastric ulcer	—	1 (0.2)	—	—	1 (0.2)	5 (0.9)	—	—	—	5 (0.9)
Gastritis	1 (0.2)	2 (0.4)	—	—	3 (0.5)	5 (0.9)	1 (0.2)	—	—	6 (1.1)
Gastroesophageal reflux disease	27 (4.8)	—	—	—	27 (4.8)	24 (4.3)	—	—	—	24 (4.3)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Gastrointestinal disorders - Other	85 (15)	1 (0.2)	—	1 (0.2)	87 (16)	120 (21)	3 (0.5)	—	—	123 (22)
Gastrointestinal pain	3 (0.5)	—	—	—	3 (0.5)	3 (0.5)	—	—	—	3 (0.5)
Gingival pain	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Hemorrhoidal hemorrhage	4 (0.7)	1 (0.2)	—	—	5 (0.9)	1 (0.2)	—	—	—	1 (0.2)
Hemorrhoids	13 (2.3)	—	—	—	13 (2.3)	7 (1.2)	—	—	—	7 (1.2)
Intra-abdominal hemorrhage	—	2 (0.4)	—	—	2 (0.4)	—	—	—	—	—
Lower gastrointestinal hemorrhage	—	1 (0.2)	—	—	1 (0.2)	—	2 (0.4)	—	—	2 (0.4)
Mucositis oral	21 (3.8)	3 (0.5)	—	—	24 (4.3)	32 (5.7)	2 (0.4)	—	—	34 (6.0)
Nausea	88 (16)	—	—	—	88 (16)	146 (26)	3 (0.5)	—	—	149 (26)
Oral dysesthesia	—	—	—	—	—	3 (0.5)	—	—	—	3 (0.5)
Oral pain	5 (0.9)	—	—	—	5 (0.9)	1 (0.2)	—	—	—	1 (0.2)
Pancreatitis	—	1 (0.2)	—	—	1 (0.2)	—	2 (0.4)	—	—	2 (0.4)
Periodontal disease	2 (0.4)	—	—	—	2 (0.4)	1 (0.2)	—	—	—	1 (0.2)
Proctitis	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—
Rectal hemorrhage	8 (1.4)	1 (0.2)	—	—	9 (1.6)	20 (3.6)	3 (0.5)	—	—	23 (4.1)
Rectal mucositis	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Rectal pain	2 (0.4)	—	—	—	2 (0.4)	3 (0.5)	1 (0.2)	—	—	4 (0.7)
Salivary duct inflammation	5 (0.9)	—	—	—	5 (0.9)	3 (0.5)	—	—	—	3 (0.5)
Small intestinal obstruction	—	2 (0.4)	—	—	2 (0.4)	—	1 (0.2)	1 (0.2)	—	2 (0.4)
Small intestinal perforation	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)
Stomach pain	3 (0.5)	—	—	—	3 (0.5)	5 (0.9)	—	—	—	5 (0.9)
Toothache	7 (1.3)	—	—	—	7 (1.3)	4 (0.7)	—	—	—	4 (0.7)
Vomiting	32 (5.7)	—	—	—	32 (5.7)	36 (6.4)	1 (0.2)	—	—	37 (6.6)
General disorders and administration site conditions	442 (79)	13 (2.3)	—	2 (0.4)	457 (82)	459 (82)	55 (9.8)	—	5 (0.9)	519 (92)
Chills	5 (0.9)	—	—	—	5 (0.9)	10 (1.8)	—	—	—	10 (1.8)
Death NOS	—	—	—	—	—	—	—	—	3 (0.5)	3 (0.5)
Edema face	1 (0.2)	—	—	—	1 (0.2)	2 (0.4)	—	—	—	2 (0.4)
Edema limbs	96 (17)	—	—	—	96 (17)	105 (19)	—	—	—	105 (19)
Edema trunk	—	1 (0.2)	—	—	1 (0.2)	4 (0.7)	—	—	—	4 (0.7)
Facial pain	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Fatigue	375 (67)	4 (0.7)	—	—	379 (68)	445 (79)	33 (5.9)	—	—	478 (85)
Fever	24 (4.3)	1 (0.2)	—	—	25 (4.5)	21 (3.7)	2 (0.4)	—	—	23 (4.1)
Flu like symptoms	37 (6.6)	—	—	—	37 (6.6)	43 (7.6)	2 (0.4)	—	—	45 (8.0)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Gait disturbance	3 (0.5)	1 (0.2)	—	—	4 (0.7)	14 (2.5)	1 (0.2)	—	—	15 (2.7)
General disorders and administration site conditions - Other	122 (22)	2 (0.4)	—	1 (0.2)	125 (22)	182 (32)	4 (0.7)	—	1 (0.2)	187 (33)
Infusion related reaction	12 (2.2)	—	—	—	12 (2.2)	4 (0.7)	—	—	—	4 (0.7)
Infusion site extravasation	1 (0.2)	—	—	—	1 (0.2)	3 (0.5)	—	—	—	3 (0.5)
Injection site reaction	8 (1.4)	—	—	—	8 (1.4)	8 (1.4)	—	—	—	8 (1.4)
Irritability	6 (1.1)	—	—	—	6 (1.1)	9 (1.6)	—	—	—	9 (1.6)
Localized edema	5 (0.9)	1 (0.2)	—	—	6 (1.1)	11 (2.0)	1 (0.2)	—	—	12 (2.1)
Malaise	5 (0.9)	—	—	—	5 (0.9)	4 (0.7)	—	—	—	4 (0.7)
Neck edema	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Non-cardiac chest pain	8 (1.4)	—	—	—	8 (1.4)	12 (2.1)	1 (0.2)	—	—	13 (2.3)
Pain	108 (19)	5 (0.9)	—	—	113 (20)	139 (25)	14 (2.5)	—	—	153 (27)
Sudden death NOS	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)
Hepatobiliary disorders	6 (1.1)	5 (0.9)	1 (0.2)	—	12 (2.2)	5 (0.9)	6 (1.1)	—	—	11 (2.0)
Cholecystitis	1 (0.2)	3 (0.5)	1 (0.2)	—	5 (0.9)	1 (0.2)	5 (0.9)	—	—	6 (1.1)
Gallbladder obstruction	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Hepatic hemorrhage	—	1 (0.2)	—	—	1 (0.2)	—	—	—	—	—
Hepatobiliary disorders - Other	5 (0.9)	1 (0.2)	—	—	6 (1.1)	3 (0.5)	—	—	—	3 (0.5)
Portal hypertension	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Immune system disorders	11 (2.0)	4 (0.7)	—	—	15 (2.7)	18 (3.2)	3 (0.5)	—	—	21 (3.7)
Allergic reaction	6 (1.1)	2 (0.4)	—	—	8 (1.4)	14 (2.5)	2 (0.4)	—	—	16 (2.8)
Anaphylaxis	—	2 (0.4)	—	—	2 (0.4)	—	1 (0.2)	—	—	1 (0.2)
Immune system disorders - Other	5 (0.9)	—	—	—	5 (0.9)	5 (0.9)	—	—	—	5 (0.9)
Infections and infestations	165 (30)	37 (6.6)	12 (2.2)	4 (0.7)	218 (39)	199 (35)	46 (8.2)	9 (1.6)	—	254 (45)
Abdominal infection	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)
Anorectal infection	1 (0.2)	—	—	—	1 (0.2)	—	2 (0.4)	—	—	2 (0.4)
Appendicitis	—	1 (0.2)	—	—	1 (0.2)	—	—	—	—	—
Bladder infection	9 (1.6)	1 (0.2)	—	—	10 (1.8)	2 (0.4)	1 (0.2)	—	—	3 (0.5)
Bone infection	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)
Bronchial infection	9 (1.6)	1 (0.2)	—	—	10 (1.8)	10 (1.8)	1 (0.2)	—	—	11 (2.0)
Catheter related infection	1 (0.2)	—	—	—	1 (0.2)	—	1 (0.2)	1 (0.2)	—	2 (0.4)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Conjunctivitis infective	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Corneal infection	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Endocarditis infective	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)
Enterocolitis infectious	—	1 (0.2)	—	—	1 (0.2)	1 (0.2)	3 (0.5)	—	—	4 (0.7)
Esophageal infection	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Eye infection	3 (0.5)	—	—	—	3 (0.5)	4 (0.7)	—	—	—	4 (0.7)
Gallbladder infection	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)
Gum infection	1 (0.2)	—	—	—	1 (0.2)	5 (0.9)	2 (0.4)	—	—	7 (1.2)
Infections and infestations - Other	61 (11)	3 (0.5)	1 (0.2)	1 (0.2)	66 (12)	103 (18)	3 (0.5)	—	—	106 (19)
Joint infection	—	1 (0.2)	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Kidney infection	—	1 (0.2)	—	—	1 (0.2)	1 (0.2)	2 (0.4)	—	—	3 (0.5)
Laryngitis	—	—	—	—	—	2 (0.4)	—	—	—	2 (0.4)
Lip infection	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Lung infection	13 (2.3)	11 (2.0)	1 (0.2)	1 (0.2)	26 (4.7)	10 (1.8)	13 (2.3)	2 (0.4)	—	25 (4.4)
Mucosal infection	9 (1.6)	1 (0.2)	—	—	10 (1.8)	8 (1.4)	—	—	—	8 (1.4)
Nail infection	7 (1.3)	—	—	—	7 (1.3)	11 (2.0)	1 (0.2)	—	—	12 (2.1)
Otitis externa	1 (0.2)	—	—	—	1 (0.2)	2 (0.4)	—	—	—	2 (0.4)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Otitis media	2 (0.4)	—	—	—	2 (0.4)	3 (0.5)	—	—	—	3 (0.5)
Papulopustular rash	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Paronychia	1 (0.2)	1 (0.2)	—	—	2 (0.4)	3 (0.5)	1 (0.2)	—	—	4 (0.7)
Penile infection	1 (0.2)	—	—	—	1 (0.2)	2 (0.4)	—	—	—	2 (0.4)
Pharyngitis	—	1 (0.2)	—	—	1 (0.2)	2 (0.4)	—	—	—	2 (0.4)
Phlebitis infective	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)
Rash pustular	1 (0.2)	—	—	—	1 (0.2)	2 (0.4)	—	—	—	2 (0.4)
Rhinitis infective	2 (0.4)	—	—	—	2 (0.4)	1 (0.2)	—	—	—	1 (0.2)
Salivary gland infection	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Scrotal infection	2 (0.4)	—	—	—	2 (0.4)	5 (0.9)	—	—	—	5 (0.9)
Sepsis	—	—	11 (2.0)	1 (0.2)	12 (2.2)	—	—	6 (1.1)	—	6 (1.1)
Sinusitis	9 (1.6)	—	—	—	9 (1.6)	16 (2.8)	—	—	—	16 (2.8)
Skin infection	22 (3.9)	10 (1.8)	—	—	32 (5.7)	25 (4.4)	9 (1.6)	—	—	34 (6.0)
Soft tissue infection	—	1 (0.2)	—	—	1 (0.2)	1 (0.2)	2 (0.4)	—	—	3 (0.5)
Tooth infection	9 (1.6)	1 (0.2)	—	—	10 (1.8)	13 (2.3)	—	—	—	13 (2.3)
Upper respiratory infection	47 (8.4)	3 (0.5)	—	—	50 (9.0)	62 (11)	2 (0.4)	—	—	64 (11)
Urinary tract infection	25 (4.5)	8 (1.4)	—	1 (0.2)	34 (6.1)	28 (5.0)	10 (1.8)	—	—	38 (6.7)
Wound infection	6 (1.1)	—	—	—	6 (1.1)	5 (0.9)	—	—	—	5 (0.9)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Injury, poisoning and procedural complications	54 (9.7)	14 (2.5)	—	—	68 (12)	115 (20)	40 (7.1)	3 (0.5)	—	158 (28)
Ankle fracture	1 (0.2)	—	—	—	1 (0.2)	3 (0.5)	2 (0.4)	—	—	5 (0.9)
Bruising	5 (0.9)	—	—	—	5 (0.9)	12 (2.1)	—	—	—	12 (2.1)
Burn	—	—	—	—	—	2 (0.4)	1 (0.2)	—	—	3 (0.5)
Dermatitis radiation	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Fall	24 (4.3)	2 (0.4)	—	—	26 (4.7)	80 (14)	9 (1.6)	—	—	89 (16)
Fallopian tube anastomotic leak	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Fracture	9 (1.6)	7 (1.3)	—	—	16 (2.9)	23 (4.1)	20 (3.6)	1 (0.2)	—	44 (7.8)
Hip fracture	—	1 (0.2)	—	—	1 (0.2)	1 (0.2)	3 (0.5)	—	—	4 (0.7)
Injury, poisoning and procedural complications - Other	29 (5.2)	2 (0.4)	—	—	31 (5.6)	36 (6.4)	5 (0.9)	—	—	41 (7.3)
Intestinal stoma site bleeding	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Intraoperative gastrointestinal injury	—	—	—	—	—	—	—	1 (0.2)	—	1 (0.2)
Postoperative hemorrhage	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Spinal fracture	—	—	—	—	—	3 (0.5)	6 (1.1)	1 (0.2)	—	10 (1.8)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Wound complication	—	—	—	—	—	—	1 (0.2)	—	—	1 (0.2)
Wound dehiscence	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Wrist fracture	1 (0.2)	2 (0.4)	—	—	3 (0.5)	7 (1.2)	—	—	—	7 (1.2)
Investigations	158 (28)	20 (3.6)	14 (2.5)	—	192 (34)	168 (30)	29 (5.2)	14 (2.5)	—	211 (37)
Alanine aminotransferase increased	42 (7.5)	3 (0.5)	—	—	45 (8.1)	28 (5.0)	4 (0.7)	—	—	32 (5.7)
Alkaline phosphatase increased	35 (6.3)	1 (0.2)	—	—	36 (6.5)	34 (6.0)	4 (0.7)	—	—	38 (6.7)
Aspartate aminotransferase increased	38 (6.8)	1 (0.2)	—	—	39 (7.0)	15 (2.7)	1 (0.2)	—	—	16 (2.8)
Blood bilirubin increased	4 (0.7)	—	1 (0.2)	—	5 (0.9)	4 (0.7)	1 (0.2)	—	—	5 (0.9)
Cholesterol high	32 (5.7)	—	1 (0.2)	—	33 (5.9)	42 (7.5)	—	—	—	42 (7.5)
Creatinine increased	30 (5.4)	1 (0.2)	—	—	31 (5.6)	41 (7.3)	—	—	—	41 (7.3)
Electrocardiogram QT corrected interval prolonged	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Forced expiratory volume decreased	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
GGT increased	16 (2.9)	4 (0.7)	2 (0.4)	—	22 (3.9)	11 (2.0)	4 (0.7)	—	—	15 (2.7)
Hemoglobin increased	—	—	—	—	—	2 (0.4)	—	—	—	2 (0.4)
Investigations - Other	37 (6.6)	—	—	—	37 (6.6)	39 (6.9)	2 (0.4)	—	—	41 (7.3)
Lymphocyte count decreased	9 (1.6)	—	—	—	9 (1.6)	10 (1.8)	1 (0.2)	—	—	11 (2.0)
Lymphocyte count increased	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Neutrophil count decreased	13 (2.3)	8 (1.4)	10 (1.8)	—	31 (5.6)	19 (3.4)	17 (3.0)	14 (2.5)	—	50 (8.9)
Pancreatic enzymes decreased	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Platelet count decreased	7 (1.3)	—	—	—	7 (1.3)	8 (1.4)	1 (0.2)	—	—	9 (1.6)
Weight gain	38 (6.8)	3 (0.5)	—	—	41 (7.3)	36 (6.4)	3 (0.5)	—	—	39 (6.9)
Weight loss	15 (2.7)	—	—	—	15 (2.7)	34 (6.0)	—	—	—	34 (6.0)
White blood cell decreased	6 (1.1)	1 (0.2)	1 (0.2)	—	8 (1.4)	9 (1.6)	2 (0.4)	—	—	11 (2.0)
Metabolism and nutrition disorders	126 (23)	13 (2.3)	3 (0.5)	—	142 (25)	177 (31)	14 (2.5)	2 (0.4)	1 (0.2)	194 (34)
Acidosis	—	—	—	—	—	—	—	—	1 (0.2)	1 (0.2)
Alcohol intolerance	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Anorexia	50 (9.0)	—	—	—	50 (9.0)	97 (17)	1 (0.2)	—	—	98 (17)
Dehydration	4 (0.7)	2 (0.4)	—	—	6 (1.1)	3 (0.5)	3 (0.5)	—	—	6 (1.1)
Glucose intolerance	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—
Hypercalcemia	9 (1.6)	1 (0.2)	—	—	10 (1.8)	18 (3.2)	1 (0.2)	—	—	19 (3.4)
Hyperglycemia	21 (3.8)	5 (0.9)	2 (0.4)	—	28 (5.0)	20 (3.6)	6 (1.1)	—	—	26 (4.6)
Hyperkalemia	6 (1.1)	2 (0.4)	—	—	8 (1.4)	12 (2.1)	—	—	—	12 (2.1)
Hypermagnesemia	2 (0.4)	—	—	—	2 (0.4)	1 (0.2)	—	—	—	1 (0.2)
Hypernatremia	1 (0.2)	—	—	—	1 (0.2)	4 (0.7)	1 (0.2)	—	—	5 (0.9)
Hypertriglyceridemia	13 (2.3)	1 (0.2)	1 (0.2)	—	15 (2.7)	15 (2.7)	1 (0.2)	—	—	16 (2.8)
Hyperuricemia	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Hypoalbuminemia	3 (0.5)	—	—	—	3 (0.5)	2 (0.4)	—	—	—	2 (0.4)
Hypocalcemia	5 (0.9)	—	—	—	5 (0.9)	5 (0.9)	—	—	—	5 (0.9)
Hypoglycemia	8 (1.4)	—	—	—	8 (1.4)	3 (0.5)	—	—	—	3 (0.5)
Hypokalemia	9 (1.6)	1 (0.2)	—	—	10 (1.8)	8 (1.4)	—	—	—	8 (1.4)
Hypomagnesemia	4 (0.7)	—	—	—	4 (0.7)	3 (0.5)	1 (0.2)	—	—	4 (0.7)
Hyponatremia	3 (0.5)	—	—	—	3 (0.5)	3 (0.5)	1 (0.2)	2 (0.4)	—	6 (1.1)
Hypophosphatemia	3 (0.5)	—	—	—	3 (0.5)	1 (0.2)	—	—	—	1 (0.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Metabolism and nutrition disorders - Other	45 (8.1)	1 (0.2)	—	—	46 (8.2)	53 (9.4)	—	—	—	53 (9.4)
Obesity	3 (0.5)	—	—	—	3 (0.5)	2 (0.4)	1 (0.2)	—	—	3 (0.5)
Musculoskeletal and connective tissue disorders	358 (64)	43 (7.7)	—	—	401 (72)	380 (67)	58 (10)	—	—	438 (78)
Arthralgia	79 (14)	2 (0.4)	—	—	81 (15)	96 (17)	4 (0.7)	—	—	100 (18)
Arthritis	36 (6.5)	15 (2.7)	—	—	51 (9.1)	37 (6.6)	14 (2.5)	—	—	51 (9.1)
Avascular necrosis	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Back pain	152 (27)	12 (2.2)	—	—	164 (29)	189 (34)	17 (3.0)	—	—	206 (37)
Bone pain	59 (11)	2 (0.4)	—	—	61 (11)	58 (10)	4 (0.7)	—	—	62 (11)
Buttock pain	8 (1.4)	1 (0.2)	—	—	9 (1.6)	10 (1.8)	—	—	—	10 (1.8)
Chest wall pain	18 (3.2)	—	—	—	18 (3.2)	22 (3.9)	—	—	—	22 (3.9)
Flank pain	13 (2.3)	1 (0.2)	—	—	14 (2.5)	14 (2.5)	—	—	—	14 (2.5)
Generalized muscle weakness	18 (3.2)	—	—	—	18 (3.2)	33 (5.9)	2 (0.4)	—	—	35 (6.2)
Joint effusion	2 (0.4)	—	—	—	2 (0.4)	2 (0.4)	—	—	—	2 (0.4)
Joint range of motion decreased	5 (0.9)	—	—	—	5 (0.9)	6 (1.1)	—	—	—	6 (1.1)
Muscle weakness left-sided	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Muscle weakness lower limb	15 (2.7)	—	—	—	15 (2.7)	31 (5.5)	2 (0.4)	—	—	33 (5.9)
Muscle weakness right-sided	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Muscle weakness trunk	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Muscle weakness upper limb	5 (0.9)	—	—	—	5 (0.9)	13 (2.3)	—	—	—	13 (2.3)
Musculoskeletal and connective tissue disorder - Other	239 (43)	9 (1.6)	—	—	248 (44)	252 (45)	16 (2.8)	—	—	268 (48)
Musculoskeletal deformity	1 (0.2)	—	—	—	1 (0.2)	—	1 (0.2)	—	—	1 (0.2)
Myalgia	59 (11)	—	—	—	59 (11)	72 (13)	2 (0.4)	—	—	74 (13)
Neck pain	17 (3.0)	1 (0.2)	—	—	18 (3.2)	44 (7.8)	3 (0.5)	—	—	47 (8.3)
Osteonecrosis of jaw	5 (0.9)	—	—	—	5 (0.9)	2 (0.4)	—	—	—	2 (0.4)
Osteoporosis	8 (1.4)	1 (0.2)	—	—	9 (1.6)	24 (4.3)	—	—	—	24 (4.3)
Pain in extremity	73 (13)	4 (0.7)	—	—	77 (14)	78 (14)	2 (0.4)	—	—	80 (14)
Scoliosis	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Soft tissue necrosis lower limb	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (4.3)	18 (3.2)	4 (0.7)	—	46 (8.2)	48 (8.5)	22 (3.9)	4 (0.7)	—	74 (13)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, spe	23 (4.1)	18 (3.2)	4 (0.7)	—	45 (8.1)	48 (8.5)	21 (3.7)	4 (0.7)	—	73 (13)
Tumor pain	1 (0.2)	—	—	—	1 (0.2)	2 (0.4)	1 (0.2)	—	—	3 (0.5)
Nervous system disorders	234 (42)	30 (5.4)	—	—	264 (47)	337 (60)	48 (8.5)	2 (0.4)	2 (0.4)	389 (69)
Akathisia	1 (0.2)	—	—	—	1 (0.2)	2 (0.4)	—	—	—	2 (0.4)
Amnesia	5 (0.9)	—	—	—	5 (0.9)	15 (2.7)	1 (0.2)	—	—	16 (2.8)
Ataxia	3 (0.5)	2 (0.4)	—	—	5 (0.9)	5 (0.9)	—	—	—	5 (0.9)
Cognitive disturbance	4 (0.7)	—	—	—	4 (0.7)	15 (2.7)	1 (0.2)	—	—	16 (2.8)
Concentration impairment	7 (1.3)	—	—	—	7 (1.3)	29 (5.2)	—	—	—	29 (5.2)
Dizziness	44 (7.9)	—	—	—	44 (7.9)	87 (15)	2 (0.4)	—	—	89 (16)
Dysarthria	3 (0.5)	—	—	—	3 (0.5)	1 (0.2)	—	—	—	1 (0.2)
Dysesthesia	2 (0.4)	—	—	—	2 (0.4)	2 (0.4)	—	—	—	2 (0.4)
Dysgeusia	26 (4.7)	—	—	—	26 (4.7)	52 (9.2)	—	—	—	52 (9.2)
Dysphasia	1 (0.2)	—	—	—	1 (0.2)	4 (0.7)	—	—	—	4 (0.7)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Extrapyramidal disorder	—	—	—	—	—	3 (0.5)	—	—	—	3 (0.5)
Facial muscle weakness	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—
Facial nerve disorder	1 (0.2)	1 (0.2)	—	—	2 (0.4)	1 (0.2)	1 (0.2)	—	—	2 (0.4)
Headache	54 (9.7)	2 (0.4)	—	—	56 (10)	91 (16)	2 (0.4)	—	—	93 (17)
Hypersomnia	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Intracranial hemorrhage	1 (0.2)	—	—	—	1 (0.2)	—	2 (0.4)	1 (0.2)	—	3 (0.5)
Ischemia cerebrovascular	2 (0.4)	—	—	—	2 (0.4)	—	1 (0.2)	—	—	1 (0.2)
Lethargy	9 (1.6)	—	—	—	9 (1.6)	13 (2.3)	—	—	—	13 (2.3)
Memory impairment	24 (4.3)	1 (0.2)	—	—	25 (4.5)	74 (13)	1 (0.2)	—	—	75 (13)
Meningismus	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Movements involuntary	1 (0.2)	—	—	—	1 (0.2)	6 (1.1)	—	—	—	6 (1.1)
Nervous system disorders - Other	44 (7.9)	3 (0.5)	—	—	47 (8.4)	87 (15)	7 (1.2)	—	—	94 (17)
Neuralgia	7 (1.3)	1 (0.2)	—	—	8 (1.4)	5 (0.9)	—	—	—	5 (0.9)
Oculomotor nerve disorder	1 (0.2)	1 (0.2)	—	—	2 (0.4)	—	—	—	—	—
Paresthesia	27 (4.8)	—	—	—	27 (4.8)	44 (7.8)	—	—	—	44 (7.8)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Peripheral motor neuropathy	5 (0.9)	—	—	—	5 (0.9)	22 (3.9)	1 (0.2)	—	—	23 (4.1)
Peripheral sensory neuropathy	119 (21)	1 (0.2)	—	—	120 (22)	163 (29)	4 (0.7)	—	—	167 (30)
Presyncope	4 (0.7)	—	—	—	4 (0.7)	12 (2.1)	—	—	—	12 (2.1)
Pyramidal tract syndrome	—	5 (0.9)	—	—	5 (0.9)	1 (0.2)	3 (0.5)	—	—	4 (0.7)
Radiculitis	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	1 (0.2)	—	—	2 (0.4)
Seizure	—	—	—	—	—	6 (1.1)	1 (0.2)	—	—	7 (1.2)
Sinus pain	—	—	—	—	—	2 (0.4)	—	—	—	2 (0.4)
Somnolence	—	—	—	—	—	2 (0.4)	—	—	—	2 (0.4)
Spasticity	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Stroke	—	2 (0.4)	—	—	2 (0.4)	5 (0.9)	—	2 (0.4)	2 (0.4)	9 (1.6)
Syncope	1 (0.2)	9 (1.6)	—	—	10 (1.8)	1 (0.2)	24 (4.3)	—	—	25 (4.4)
Transient ischemic attacks	3 (0.5)	—	—	—	3 (0.5)	8 (1.4)	—	—	—	8 (1.4)
Tremor	2 (0.4)	—	—	—	2 (0.4)	13 (2.3)	—	—	—	13 (2.3)
Vasovagal reaction	—	5 (0.9)	—	—	5 (0.9)	—	3 (0.5)	—	—	3 (0.5)
Psychiatric disorders	175 (31)	4 (0.7)	—	—	179 (32)	228 (40)	11 (2.0)	5 (0.9)	—	244 (43)
Agitation	7 (1.3)	—	—	—	7 (1.3)	10 (1.8)	—	1 (0.2)	—	11 (2.0)
Anxiety	34 (6.1)	1 (0.2)	—	—	35 (6.3)	54 (9.6)	—	—	—	54 (9.6)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Confusion	10 (1.8)	—	—	—	10 (1.8)	14 (2.5)	—	—	—	14 (2.5)
Delirium	4 (0.7)	1 (0.2)	—	—	5 (0.9)	2 (0.4)	5 (0.9)	—	—	7 (1.2)
Depression	47 (8.4)	—	—	—	47 (8.4)	66 (12)	2 (0.4)	2 (0.4)	—	70 (12)
Hallucinations	—	—	—	—	—	2 (0.4)	—	—	—	2 (0.4)
Insomnia	88 (16)	1 (0.2)	—	—	89 (16)	122 (22)	4 (0.7)	—	—	126 (22)
Libido decreased	15 (2.7)	—	—	—	15 (2.7)	22 (3.9)	—	—	—	22 (3.9)
Libido increased	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Mania	—	—	—	—	—	—	—	1 (0.2)	—	1 (0.2)
Personality change	2 (0.4)	—	—	—	2 (0.4)	1 (0.2)	—	—	—	1 (0.2)
Psychiatric disorders - Other	38 (6.8)	1 (0.2)	—	—	39 (7.0)	68 (12)	—	—	—	68 (12)
Psychosis	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Restlessness	2 (0.4)	—	—	—	2 (0.4)	7 (1.2)	—	—	—	7 (1.2)
Suicidal ideation	—	—	—	—	—	2 (0.4)	—	—	—	2 (0.4)
Suicide attempt	—	—	—	—	—	—	1 (0.2)	1 (0.2)	—	2 (0.4)
Renal and urinary disorders	210 (38)	25 (4.5)	2 (0.4)	—	237 (42)	222 (39)	53 (9.4)	2 (0.4)	—	277 (49)
Acute kidney injury	5 (0.9)	1 (0.2)	—	—	6 (1.1)	2 (0.4)	6 (1.1)	—	—	8 (1.4)
Bladder spasm	3 (0.5)	—	—	—	3 (0.5)	4 (0.7)	—	—	—	4 (0.7)
Chronic kidney disease	2 (0.4)	—	—	—	2 (0.4)	1 (0.2)	—	—	—	1 (0.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Cystitis noninfective	8 (1.4)	—	—	—	8 (1.4)	6 (1.1)	5 (0.9)	—	—	11 (2.0)
Hematuria	32 (5.7)	6 (1.1)	—	—	38 (6.8)	43 (7.6)	13 (2.3)	2 (0.4)	—	58 (10)
Proteinuria	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Renal and urinary disorders - Other	84 (15)	1 (0.2)	—	—	85 (15)	112 (20)	5 (0.9)	—	—	117 (21)
Renal calculi	6 (1.1)	5 (0.9)	1 (0.2)	—	12 (2.2)	9 (1.6)	6 (1.1)	—	—	15 (2.7)
Renal colic	—	1 (0.2)	—	—	1 (0.2)	—	1 (0.2)	—	—	1 (0.2)
Renal hemorrhage	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Urinary fistula	—	—	—	—	—	1 (0.2)	1 (0.2)	—	—	2 (0.4)
Urinary frequency	115 (21)	—	—	—	115 (21)	135 (24)	1 (0.2)	—	—	136 (24)
Urinary incontinence	40 (7.2)	2 (0.4)	—	—	42 (7.5)	43 (7.6)	3 (0.5)	—	—	46 (8.2)
Urinary retention	22 (3.9)	5 (0.9)	—	—	27 (4.8)	12 (2.1)	10 (1.8)	—	—	22 (3.9)
Urinary tract obstruction	4 (0.7)	8 (1.4)	1 (0.2)	—	13 (2.3)	6 (1.1)	12 (2.1)	—	—	18 (3.2)
Urinary tract pain	11 (2.0)	—	—	—	11 (2.0)	9 (1.6)	1 (0.2)	—	—	10 (1.8)
Urinary urgency	19 (3.4)	—	—	—	19 (3.4)	35 (6.2)	—	—	—	35 (6.2)
Urine discoloration	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Reproductive system and breast disorders	102 (18)	13 (2.3)	—	—	115 (21)	130 (23)	15 (2.7)	—	—	145 (26)
Breast atrophy	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Breast pain	8 (1.4)	—	—	—	8 (1.4)	9 (1.6)	—	—	—	9 (1.6)
Erectile dysfunction	32 (5.7)	12 (2.2)	—	—	44 (7.9)	30 (5.3)	14 (2.5)	—	—	44 (7.8)
Gynecomastia	35 (6.3)	—	—	—	35 (6.3)	51 (9.1)	—	—	—	51 (9.1)
Pelvic pain	2 (0.4)	—	—	—	2 (0.4)	4 (0.7)	—	—	—	4 (0.7)
Penile pain	3 (0.5)	—	—	—	3 (0.5)	3 (0.5)	—	—	—	3 (0.5)
Perineal pain	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Prostatic obstruction	—	1 (0.2)	—	—	1 (0.2)	—	1 (0.2)	—	—	1 (0.2)
Prostatic pain	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Reproductive system and breast disorders - Other	31 (5.6)	—	—	—	31 (5.6)	42 (7.5)	—	—	—	42 (7.5)
Scrotal pain	1 (0.2)	—	—	—	1 (0.2)	3 (0.5)	—	—	—	3 (0.5)
Testicular disorder	1 (0.2)	—	—	—	1 (0.2)	3 (0.5)	—	—	—	3 (0.5)
Testicular pain	7 (1.3)	—	—	—	7 (1.3)	28 (5.0)	—	—	—	28 (5.0)
Respiratory, thoracic and mediastinal disorders	183 (33)	4 (0.7)	1 (0.2)	1 (0.2)	189 (34)	245 (44)	17 (3.0)	—	2 (0.4)	264 (47)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Allergic rhinitis	7 (1.3)	—	—	—	7 (1.3)	11 (2.0)	—	—	—	11 (2.0)
Apnea	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Aspiration	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Atelectasis	—	—	—	—	—	3 (0.5)	—	—	—	3 (0.5)
Bronchopulmonary hemorrhage	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—
Bronchospasm	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Cough	78 (14)	—	—	—	78 (14)	101 (18)	—	—	—	101 (18)
Dyspnea	66 (12)	1 (0.2)	1 (0.2)	—	68 (12)	123 (22)	9 (1.6)	—	—	132 (23)
Epistaxis	17 (3.0)	—	—	—	17 (3.0)	29 (5.2)	—	—	—	29 (5.2)
Hiccups	7 (1.3)	—	—	—	7 (1.3)	—	—	—	—	—
Hoarseness	2 (0.4)	—	—	—	2 (0.4)	9 (1.6)	—	—	—	9 (1.6)
Hypoxia	1 (0.2)	1 (0.2)	—	—	2 (0.4)	—	—	—	—	—
Laryngeal fistula	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Laryngeal mucositis	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Laryngopharyngeal dysesthesia	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Nasal congestion	5 (0.9)	—	—	—	5 (0.9)	12 (2.1)	—	—	—	12 (2.1)
Pleural effusion	4 (0.7)	—	—	—	4 (0.7)	2 (0.4)	2 (0.4)	—	—	4 (0.7)
Pleuritic pain	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Pneumonitis	1 (0.2)	1 (0.2)	—	1 (0.2)	3 (0.5)	4 (0.7)	1 (0.2)	—	—	5 (0.9)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Pneumothorax	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Postnasal drip	2 (0.4)	—	—	—	2 (0.4)	11 (2.0)	—	—	—	11 (2.0)
Productive cough	4 (0.7)	—	—	—	4 (0.7)	13 (2.3)	—	—	—	13 (2.3)
Pulmonary edema	—	—	—	—	—	2 (0.4)	2 (0.4)	—	—	4 (0.7)
Pulmonary fibrosis	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Pulmonary hypertension	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Respiratory failure	—	—	—	—	—	—	—	—	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders - Other	62 (11)	—	—	—	62 (11)	103 (18)	2 (0.4)	—	1 (0.2)	106 (19)
Retinoic acid syndrome	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Sinus disorder	3 (0.5)	—	—	—	3 (0.5)	6 (1.1)	—	—	—	6 (1.1)
Sleep apnea	3 (0.5)	1 (0.2)	—	—	4 (0.7)	5 (0.9)	2 (0.4)	—	—	7 (1.2)
Sneezing	—	—	—	—	—	5 (0.9)	—	—	—	5 (0.9)
Sore throat	10 (1.8)	—	—	—	10 (1.8)	13 (2.3)	—	—	—	13 (2.3)
Voice alteration	2 (0.4)	—	—	—	2 (0.4)	1 (0.2)	—	—	—	1 (0.2)
Wheezing	5 (0.9)	—	—	—	5 (0.9)	7 (1.2)	—	—	—	7 (1.2)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Skin and subcutaneous tissue disorders	228 (41)	6 (1.1)	—	—	234 (42)	273 (48)	8 (1.4)	—	—	281 (50)
Alopecia	66 (12)	—	—	—	66 (12)	88 (16)	—	—	—	88 (16)
Bullous dermatitis	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Dry skin	35 (6.3)	—	—	—	35 (6.3)	51 (9.1)	—	—	—	51 (9.1)
Erythema multiforme	4 (0.7)	—	—	—	4 (0.7)	4 (0.7)	—	—	—	4 (0.7)
Erythroderma	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Hyperhidrosis	8 (1.4)	—	—	—	8 (1.4)	2 (0.4)	—	—	—	2 (0.4)
Nail discoloration	16 (2.9)	—	—	—	16 (2.9)	32 (5.7)	—	—	—	32 (5.7)
Nail loss	8 (1.4)	—	—	—	8 (1.4)	6 (1.1)	—	—	—	6 (1.1)
Nail ridging	17 (3.0)	—	—	—	17 (3.0)	15 (2.7)	—	—	—	15 (2.7)
Pain of skin	1 (0.2)	—	—	—	1 (0.2)	3 (0.5)	—	—	—	3 (0.5)
Palmar-plantar erythrodysesthesia syndrome	7 (1.3)	1 (0.2)	—	—	8 (1.4)	14 (2.5)	—	—	—	14 (2.5)
Periorbital edema	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Photosensitivity	2 (0.4)	—	—	—	2 (0.4)	3 (0.5)	—	—	—	3 (0.5)
Pruritus	20 (3.6)	—	—	—	20 (3.6)	28 (5.0)	—	—	—	28 (5.0)
Purpura	2 (0.4)	—	—	—	2 (0.4)	—	—	—	—	—
Rash acneiform	8 (1.4)	—	—	—	8 (1.4)	6 (1.1)	—	—	—	6 (1.1)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Rash maculo-papular	18 (3.2)	1 (0.2)	—	—	19 (3.4)	39 (6.9)	3 (0.5)	—	—	42 (7.5)
Scalp pain	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Skin and subcutaneous tissue disorders - Other	120 (22)	3 (0.5)	—	—	123 (22)	157 (28)	3 (0.5)	—	—	160 (28)
Skin atrophy	—	—	—	—	—	2 (0.4)	—	—	—	2 (0.4)
Skin hyperpigmentation	2 (0.4)	—	—	—	2 (0.4)	4 (0.7)	—	—	—	4 (0.7)
Skin hypopigmentation	1 (0.2)	—	—	—	1 (0.2)	2 (0.4)	—	—	—	2 (0.4)
Skin ulceration	4 (0.7)	1 (0.2)	—	—	5 (0.9)	10 (1.8)	1 (0.2)	—	—	11 (2.0)
Urticaria	4 (0.7)	—	—	—	4 (0.7)	8 (1.4)	1 (0.2)	—	—	9 (1.6)
Social circumstances	5 (0.9)	—	—	—	5 (0.9)	3 (0.5)	1 (0.2)	—	—	4 (0.7)
Social circumstances - Other	5 (0.9)	—	—	—	5 (0.9)	3 (0.5)	1 (0.2)	—	—	4 (0.7)
Surgical and medical procedures	27 (4.8)	12 (2.2)	—	—	39 (7.0)	41 (7.3)	14 (2.5)	1 (0.2)	—	56 (9.9)
Surgical and medical procedures - Other	27 (4.8)	12 (2.2)	—	—	39 (7.0)	41 (7.3)	14 (2.5)	1 (0.2)	—	56 (9.9)

	Conventional NSAA, N = 558					Enzalutamide, N = 563				
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Overall**
Vascular disorders	349 (63)	45 (8.1)	1 (0.2)	—	395 (71)	367 (65)	77 (14)	1 (0.2)	—	445 (79)
Flushing	41 (7.3)	—	—	—	41 (7.3)	46 (8.2)	—	—	—	46 (8.2)
Hematoma	4 (0.7)	1 (0.2)	—	—	5 (0.9)	5 (0.9)	—	—	—	5 (0.9)
Hot flashes	355 (64)	1 (0.2)	—	—	356 (64)	388 (69)	5 (0.9)	—	—	393 (70)
Hypertension	55 (9.9)	30 (5.4)	1 (0.2)	—	86 (15)	90 (16)	59 (10)	—	—	149 (26)
Hypotension	14 (2.5)	4 (0.7)	—	—	18 (3.2)	18 (3.2)	6 (1.1)	—	—	24 (4.3)
Lymph leakage	1 (0.2)	—	—	—	1 (0.2)	—	—	—	—	—
Lymphedema	11 (2.0)	1 (0.2)	—	—	12 (2.2)	7 (1.2)	—	—	—	7 (1.2)
Peripheral ischemia	2 (0.4)	2 (0.4)	—	—	4 (0.7)	—	2 (0.4)	—	—	2 (0.4)
Phlebitis	2 (0.4)	—	—	—	2 (0.4)	1 (0.2)	—	—	—	1 (0.2)
Superficial thrombophlebitis	1 (0.2)	—	—	—	1 (0.2)	1 (0.2)	—	—	—	1 (0.2)
Superior vena cava syndrome	—	—	—	—	—	1 (0.2)	—	—	—	1 (0.2)
Thromboembolic event	4 (0.7)	5 (0.9)	—	—	9 (1.6)	5 (0.9)	6 (1.1)	1 (0.2)	—	12 (2.1)
Vascular disorders - Other	43 (7.7)	3 (0.5)	—	—	46 (8.2)	50 (8.9)	3 (0.5)	—	—	53 (9.4)
Visceral arterial ischemia	—	—	—	—	—	—	2 (0.4)	—	—	2 (0.4)

Protocol and Statistical Analysis Plan: Original and Final Versions and Summary of Changes

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: ENZAMET. Protocol number: ANZUP 1304.

The following pages of this appendix contains the following items:

1. Original protocol, final protocol, summary of changes.

2. Original statistical analysis plan, final statistical analysis plan, summary of change

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: ENZAMET

Protocol number: ANZUP 1304
Protocol version: Version 1, 11 November, 2013

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ABBREVIATIONS

ADT	Androgen deprivation therapy
AR	Androgen receptor
CT	Computed tomography (scan)
CRF	Case report form
CTC	NHMRC Clinical Trials Centre, University of Sydney
DRG	Diagnosis Related Groups
EBRT	External beam radiation therapy
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	Euroqol 5 item preference-based measure of health (5L)
FDHT	Fluoro dihydrotestosterone
GSA	Group Specific Appendix
HRQL	Health-Related Quality of Life
IC_{50}	50% maximal inhibitory concentration
ICER	Incremental cost effectiveness ratio
ICORG	All Ireland Cooperative Oncology Research Group
LHRHA	Luteinizing Hormone Releasing Hormone Analogue
MBS	Medicare Benefits Scheme (Australia)
NCIC CTG	Canadian NCIC Clinical Trials Group
NSAA	Non-steroidal anti androgen
OS	Overall survival
PBS	Pharmaceutical Benefits Scheme (Australia)
PCWG2	Prostate Cancer Working Group 2 (see Appendix 3)
PFS	Progression free survival
PR-25	EORTC Quality of Life Questionnaire for Prostate Cancer (25 items)
PSA	Prostate Specific Antigen
QLQ-C30	EORTC Core Quality of Life Questionnaire (30 items)
RECIST	Response Evaluation Criteria in Solid Tumours
ULN	Upper limit of normal range
USYD	University of Sydney
WBBS	Whole Body Bone Scan

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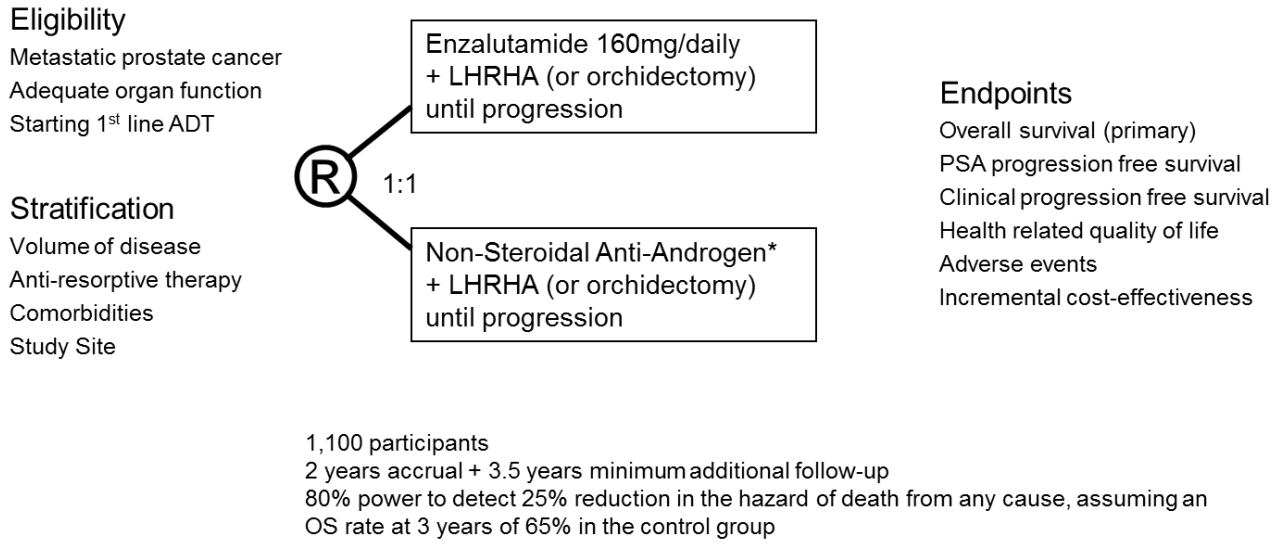
SYNOPSIS

Background	Combined androgen deprivation therapy (ADT) with a luteinising hormone releasing hormone analogue (LHRHA) or surgical castration, plus a conventional non-steroidal anti-androgen (NSAA: bicalutamide, nilutamide, or flutamide), is widely used as initial treatment for hormone-sensitive prostate cancer. Meta-analysis of RCTs showed a 3% absolute improvement in 5 year survival rates with the addition of a conventional NSAA to a LHRHA or surgical castration (1). Residual, low level androgen receptor AR signalling, or agonist activity from conventional NSAA, may provide a stimulatory signal to hormone-sensitive prostate cancer cells. We hypothesize that early use of enzalutamide, a more potent and effective androgen receptor blocker, will reduce residual androgen receptor signalling, and thereby improve outcomes.
General aim	To determine the effectiveness of enzalutamide, versus a conventional NSAA, when combined with a LHRHA or surgical castration, as first line androgen deprivation therapy (ADT).
Primary objective (endpoint)	To determine effects on: 1) Overall survival (death from any cause)
Secondary objectives (endpoints)	To determine effects on: 2) Prostate specific antigen progression free survival (PCGW2) 3) Clinical progression free survival (imaging, symptoms, signs) 4) Adverse events (CTCAE v4.03) 5) Health related quality of life (EORTC QLQ C-30, PR-25 and EQ-5D-5L) 6) Health outcomes relative to costs (incremental cost effectiveness ratio)
Tertiary/Correlative objectives	7) To identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes)
Design	Open label, randomised, stratified, 2-arm, multicentre, phase 3 clinical trial
Population	The target population is men with metastatic prostate cancer commencing androgen deprivation therapy. Key eligibility criteria include metastatic prostate cancer, adequate organ function and ECOG performance status 0-2.
Study treatments	Participants randomised to: • Enzalutamide 160mg daily, by mouth, until disease progression or prohibitive toxicity (experimental group). OR • Conventional NSAA, by mouth, until disease progression or prohibitive toxicity (control group). All participants are treated with a LHRHA or surgical castration.
Assessments	Assessments at baseline, day 29, week 12, and then every 12 weeks from randomisation until evidence of clinical progression. Imaging with CT scan and whole body bone scan at baseline and at evidence of PSA or clinical progression

	(whichever occurs first). Blood tests for translational studies at baseline, day 29, week 25, and end of study treatment.
Statistical considerations	A trial of 1,100 participants followed until approximately 470 deaths are observed (e.g. 2 year recruitment plus 3.5 years follow-up) provides at least 80% power to detect a 25% reduction in the hazard of death with a logrank test evaluated at the 2-sided 5% level of significance assuming a 3-year survival rate of 65% amongst controls.

SCHEMA



1,100 participants
2 years accrual + 3.5 years minimum additional follow-up
80% power to detect 25% reduction in the hazard of death from any cause, assuming an OS rate at 3 years of 65% in the control group

*Non-Steroidal Anti-Androgens: bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg tid

1 BACKGROUND

Prostate cancer is often diagnosed when apparently localized to the prostate gland. However, metastatic disease can occur after surgery or radiation therapy given with curative intent or present as de novo metastatic disease. For cancer that has spread beyond the prostate, androgen suppression for hormone sensitive disease and then subsequent new generation hormonal therapies (enzalutamide, abiraterone), cytotoxic therapy and vaccine therapy for castration resistant prostate cancer (CRPC) can delay and/or cause cancer regression and increase the chance a man will live longer but are not able to cure metastatic prostate cancer. This protocol is based on the hypothesis that earlier use of a therapy shown to be effective in the more advanced state of castration resistant prostate cancer will prevent or delay the emergence of castration resistant disease and will prolong overall survival. As such this protocol aims to determine whether the potent second generation androgen receptor inhibitor, enzalutamide can enhance the ability of androgen suppression to increase the longevity of men commencing androgen suppression for newly metastatic prostate cancer.

The current treatment for patients commencing hormonal therapy for metastatic prostate cancer is androgen suppression either by LHRH analogue therapy or orchidectomy as monotherapy or in combination with an anti-androgen, also known as combined androgen deprivation therapy. Survival varies depending on the extent of disease at commencement of therapy. With the advent of the PSA test many patients are commenced on hormonal therapy at a very early stage (biochemical recurrence) and subjected to the long-term effects of androgen deprivation including osteoporosis. However, if patients with an asymptomatic rising PSA after definitive local therapy are observed until they develop overt metastatic disease (i.e. evident by imaging techniques), the median time from PSA relapse to clinical progression is approximately 8 years. In the pre-PSA era, studies relied upon bone scan and CT scans to document the presence of metastatic disease.

The median overall survival for men commencing androgen deprivation therapy with clinically evident metastatic disease (i.e. not PSA only disease) is about 30 months(1). This information is derived from a meta-analysis including 8,275 men in 27 randomized trials comparing castration alone (medical or surgical) versus combined androgen deprivation therapy including an oral, peripheral anti-androgen (previously known as maximal or combined androgen blockade). This individually updated patient-data meta-analysis showed that overall survival was not improved by the addition of a peripheral anti-androgen when all trials were analysed together. However, a planned subgroup analysis showed that overall survival at 5 years was approximately 3% higher (2p=0.005) in patients assigned combined androgen blockade including a Non-Steroidal Anti-Androgen (NSAA, nilutamide or flutamide) than control patients, and approximately 3% lower (2p=0.04) in patients assigned cyproterone compared with control patients.

The treatment of patients with newly diagnosed metastatic disease is heterogeneous. Some clinicians start treatment with castration alone, and only add a peripheral anti-androgen on progression, while others start treatment with combined androgen deprivation therapy. Both approaches are considered within the range of standard practice. Progression on combined androgen deprivation therapy eventually occurs in most patients, and is thought to be related to either residual low level AR signalling or to agonist activity from older anti-androgens. These may provide a survival signal or escape mechanism to metastatic hormone-sensitive prostate cancer cells. It is possible that a more effective and profound AR blockade with a more potent androgen receptor blocker like enzalutamide might therefore eliminate any such survival signal and improve progression free survival.

Phase 3 studies are ongoing or have recently been performed with the goal of improving the efficacy or tolerability of therapy for metastatic disease. Specifically, intermittent versus continuous dosing LHRH analogue suppression of testosterone in men who responded to therapy has been reported in a large randomized phase 3 SWOG trial (2). Specifically, in this study of 3040 men, 1535 achieved a PSA of < 4 in the induction phase and were randomized. The Hazard Ratio for death with intermittent dosing was 1.10; 90% CI - 0.99 to 1.23 and exceeded the upper boundary for non-inferiority (i.e. cannot rule out a 20% greater risk of death with intermittent versus continuous therapy). However, there were too few events to rule out

significant inferiority of intermittent therapy. A number of studies are comparing ADT plus docetaxel versus ADT alone in men commencing therapy for newly metastatic prostate cancer. The French study of 385 patients reported improvements in times to PSA and clinical progression but not overall survival (3). The US based ECOG E3805 CHAARTED study with 780 patients and the UK STAMPEDE study had not reported their outcomes by July of 2013. Studies of ADT with or without cytochrome P450 inhibitors (abiraterone and TAK700) with activity in CRPC were commenced in 2012 and 2013.

Once progression is documented with a testosterone less than 50ng/dL, the disease is referred to as castration resistant prostate cancer. Recent advances in our understanding of the molecular basis of CRPC have led to a growing number of innovative therapies that target these resistance mechanisms. Moreover, six agents prolong the longevity of a man with CRPC. These include two cytotoxic agents (docetaxel (4) and cabazitaxel (5)), two hormonal therapies (abiraterone(6) and enzalutamide(7)), an alpha-emitting radiopharmaceutical (radium-223 chloride(8)) and an immune therapy (sipuleucel-T(9)). Denosumab, a RANK-ligand inhibitor blocking NFκB mediated effects in the bone micro-environment, delays bone events, such as pathological fractures, more effectively than the bisphosphonate, zoledronic acid. (10) Unfortunately, none of these therapies cure CRPC.

A rational strategy to improve the efficacy of testosterone suppression for patients commencing therapy for metastatic prostate cancer would be to take agents which are proven to be effective in the metastatic setting and attempt to use them when starting therapy for metastatic disease. Enzalutamide has proven highly effective at reducing overall mortality in men with castrate-resistant metastatic prostate cancer and has a tolerable side-effect profile, making it an attractive candidate for testing in the up-front metastatic setting (11). Enzalutamide is a rationally-designed second generation androgen receptor (AR) inhibitor which competitively binds the AR with great potency. Additionally, enzalutamide inhibits nuclear translocation of activated AR and inhibits the association of activated AR with DNA (12).

Preclinical Data with Enzalutamide

Using the non-steroidal agonist RU59603 as the parent scaffold compound, Sawyers and colleagues identified two oral diarylthiohydantoins, RD162 and enzalutamide, from a screen of non-steroidal anti-androgens that retain anti-androgen activity in the setting of increased AR expression (12). Both compounds have enhanced affinity for the AR (5-8 fold) compared to the anti-androgen bicalutamide. Enzalutamide competitively binds the AR with an $\mathbf{IC_{50}}$ of 36 nM compared to 160 nM for bicalutamide. Additionally, enzalutamide inhibits nuclear translocation of activated AR, inhibits DNA binding to androgen response elements, and inhibits recruitment of co-activators, even in the setting of AR over expression and in prostate cancer cells resistant to anti-androgens. By contrast with bicalutamide, enzalutamide is a pure antagonist with no detectable agonist effects in LNCaP/AR prostate cells, which over express AR. The drug also induces regression of established LNCaP/AR xenograft tumours growing in castrated male mice, a model in which bicalutamide treatment only slows tumour growth.

Clinical Data with Enzalutamide

A phase I/II first in man study in patients with progressive, metastatic CRPC was initiated in July 2007 to assess safety, pharmacokinetics, tolerability, and antitumor activity (13). After administration of one dose, the drug was rapidly absorbed, and median time to Cmax was one hour (range 0.42 minutes – 4 hours). The t1/2 was about 1 week (range 3 – 10 days) and was not affected by dose. Full pharmacokinetic profiles were linear and consistent over the dose range study. Plasma concentrations reached steady state after one month of treatment. Once achievement of steady state, the Cmin in individual patients remained constant for several months, suggesting time-linear pharmacokinetics. Due to slow clearance from plasma, the daily fluctuation in steady-state enzalutamide concentrations was low. The mean Cmax/Cmin was 1.2 (range 1.14-1.3) indicating that the average difference between the peak and trough concentrations was ≤ 30%. AR binding was assessed in 22 patients at doses from 60-480 mg daily with FHDT-PET. All patients showed clear reduction of FDHT uptake (range 20-100%).

Fatigue was the most frequently reported adverse event, with dose-dependent increases of grade 3 fatigue (0% at 150 mg/day, 9% at 240 mg/day, 15% at 360 mg/day, and 20% at 480

mg/day). The dose of 240 mg/day was defined as the maximum tolerated dose. At doses of 240 mg and above, an increasing proportion of patients needed dose reductions for fatigue. Dose reductions were needed in 1 of 29 patients (3%) that received 240 mg/day, 3 of 28 patients (11%) that received 360 mg/day, and 5 of 22 patients (23%) that received 480 mg/day, and 0 of 58 patients that received 30, 60, or 150 mg/day. After dose reductions, the symptoms resolved. Only 1 patient discontinued treatment due to fatigue with an onset coinciding with PSA rise. Overall, the most common mild (grade 2) adverse events were fatigue (n = 38, 27.1%), nausea (n = 12, 8.6%), dyspnoea (n = 11, 7.9%), anorexia (n = 8, 5.7%), and back pain (n = 8, 5.7%). Fatigue, nausea, and anorexia were the only mild adverse events with an increasing incidence as the dose of enzalutamide was increased. None of the grade 2 events required dose modification or the discontinuation of treatment, apart from 1 patient treated at 480 mg/day who had nausea at baseline and stopped therapy after 7 weeks.

Two witnessed seizures occurred in patients receiving doses of 600 and 360 mg/day, and 1 possible seizure occurred at 480 mg/day. Both patients also had complicated medical problems that could have contributed to their seizures. Other causes of treatment discontinuation included rash in 1 patient that received 480 mg/day after 10 days and in 1 patient that received 600 mg/day after 3 days, and a myocardial infarction after 15 weeks of therapy in a patient with a history of diabetes, hypertension, and hypercholesterolemia that received 360 mg/day. All patients recovered without sequelae. No deaths and no other drug-related SAEs were reported.

In regard to efficacy, antitumor effects were noted at all doses including >50% declines in PSA in 78 (56%) patients, response in soft tissue in 13 (22%) of 59 patients, stabilized bone disease in 61 (56%) of 109 patients, and conversion from unfavourable to favourable circulating tumour cell (CTC) counts in 25 (49%) of 51 patients. Disease regression was dose dependent between daily doses of 30 mg and 150 mg, however no additional benefit was noted above this threshold.

Based on these results, two placebo-controlled, randomized phase 3 studies (AFFIRM and PREVAIL) were initiated to evaluate the efficacy and safety of enzalutamide in patient with advanced prostate cancer. The AFFIRM study evaluated the safety and efficacy of enzalutamide in 1,199 patients with CRPC after chemotherapy with docetaxel (11). Patients were randomized in a 2:1 ratio to receive oral enzalutamide at a dose of 160 mg per day or placebo. The primary endpoint was OS. The study was stopped after a planned interim analysis at the time of 520 deaths. The median OS was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR 0.63, 95% CI 0.53-0.75, p<0.001). The superiority of enzalutamide over placebo was shown with respect to all secondary endpoints: ≥50% PSA reduction (54% vs. 2%, p<0.001), soft-tissue response rate (29% vs. 4%, p<0.001), the quality-of-life response rate (43% vs. 18%, p<0.001), time to PSA progression (8.3 vs. 3.0 months, p<0.001), time to first SRE (16.7 vs. 13.3 months, p<0.001).

The rates of AEs between the enzalutamide and placebo group were similar. The enzalutamide group had a lower incidence of adverse events of grade 3 or above (45.3% vs. 53.1%). The median time to first AE was 12.6 months in the enzalutamide group compared to 4.2 months in the placebo group. There was a higher incidence of all grades of fatigue, diarrhoea, hot flushes, musculoskeletal pain, and headache in the enzalutamide group compared to placebo. Cardiac disorders were noted in 6% of patients receiving enzalutamide and in 8% of patients receiving placebo. Hypertension was observed in 6.6% of patients in the enzalutamide group compared to 3.3% in the placebo group. LFT abnormalities were reported as adverse events in 1% and 2% of the enzalutamide and placebo group, respectively. Five of the 800 patients in the enzalutamide group (0.6%) were reported to have seizures and no seizures were reported in the placebo group. One case of status epilepticus required medical intervention while the other four seizures were self-limited. There were potentially predisposing factors in several patients, including two patients who had brain metastases, one patient who had inadvertently been administered lidocaine intravenously, and one patient with brain atrophy in the context of heavy alcohol use and initiation of haloperidol. Based on the results of this trial, the FDA approved enzalutamide August 2012 for the treatment of patients with metastatic CRPC who have previously received docetaxel.

Results were recently released from the second interim analysis of PREVAIL, a double-blinded, randomized, placebo-controlled trial, investigating the effectiveness of 160mg daily enzalutamide in patients with metastatic CRPC who had not yet received chemotherapy. The trial was stopped early and unblinded at the recommendation of the independent data and safety monitoring committee because of a substantial benefit in OS that met the pre-specified stopping rule: hazard ratio for overall survival 0.70; 95% confidence interval, 0.59-0.83, p<0.0001, median survival 32 versus 30 months) and radiological PFS (hazard ratio for radiological PFS 0.19; 95% confidence interval, 0.15-0.23, p < 0.0001). [Medivation Press Release, dated 22 October 2013. (http://www.astellas.com/en/corporate/news/pdf/131022_1_Eg.pdf)

The purpose of this study is to determine whether enzalutamide in combination with androgen suppression can increase the longevity of men commencing androgen suppression for newly diagnosed metastatic prostate cancer.

2 AIM AND OBJECTIVES

General aim	To determine the effectiveness of enzalutamide versus a conventional NSAA, when combined with a LHRHA or surgical castration, as first line androgen deprivation therapy (ADT).
Primary objective (endpoint)	To determine effects on: 1) Overall survival (death from any cause)
Secondary objectives (endpoints)	To determine effects on: 2) Prostate specific antigen progression free survival (PCGW2) 3) Clinical progression free survival (imaging, symptoms, signs) 4) Adverse events (CTCAE v4.03) 5) Health related quality of life (EORTC QLQ C-30, PR-25 and EQ-5D-5L) 6) Health outcomes relative to costs (incremental cost effectiveness ratio)
Tertiary/Correlative objectives	7) To identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes)

3 DESIGN

This is a multicentre, open label, randomised, phase 3 trial.

Participants will be allocated to treatment via a central randomisation system that stratifies for:

1. High volume disease (yes versus no), characterised as:
   - 4 or more bone metastases, one of which is outside the vertebral column and pelvis AND/OR
   - Visceral metastases (e.g. lung, pleura, liver, adrenal and others)

   Lymph node involvement or bladder invasion do NOT qualify as visceral disease.
2. Study site
3. Concomitant “anti-resorptive” therapy to delay skeletal related events when commencing ADT (denosumab, zoledronic acid or any other therapy at doses proven to prevent SRE. This does not include the use of these drugs at lower doses or frequencies for the treatment or prevention of osteoporosis).
4. Co-morbidities according to the Adult Co-morbidity Evaluation (ACE-27: 0-1 vs 2-3)

4 STUDY POPULATION

Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of randomisation. All enquiries about eligibility should be addressed by contacting the CTC prior to randomisation.

4.1 *Target Population*

Men starting first line androgen deprivation therapy for metastatic prostate cancer.

4.2 *Inclusion criteria*

1. Male aged 18 or older with metastatic adenocarcinoma of the prostate defined by
   - Documented histopathology or cytopathology of prostate adenocarcinoma from a biopsy of a metastatic site

     OR
   - Documented histopathology of prostate adenocarcinoma from a TRUS biopsy, radical prostatectomy, or TURP and metastatic disease consistent with prostate cancer.

     OR
   - Metastatic disease typical of prostate cancer (i.e. involving bone or pelvic lymph nodes or para-aortic lymph nodes) AND a serum concentration of PSA that is rising and >20ng/mL
2. Target or non-target lesions according to RECIST 1.1
3. Adequate bone marrow function: Hb ≥100g/L and WCC ≥ 4.0 x 10^9/L and platelets ≥100 x 10^9/L.
4. Adequate liver function: ALT < 2 x ULN and bilirubin < 1.5 x ULN, (or if bilirubin is between 1.5-2x ULN, they must have a normal conjugated bilirubin). If liver metastases are present ALT must be < 5xULN
5. Adequate renal function: calculated creatinine clearance > 30 ml/min (Cockroft-Gault, See Appendix 7)
6. ECOG performance status of 0-2. Patients with performance status 2 are only eligible if the decline in performance status is due to metastatic prostate cancer.
7. Study treatment both planned and able to start within 7 days after randomisation.
8. Willing and able to comply with all study requirements, including treatment and required assessments
9. Has completed baseline HRQL questionnaires UNLESS is unable to complete because of limited literacy or vision
10. Signed, written, informed consent

4.3 *Exclusion criteria*

1. Prostate cancer with significant sarcomatoid or spindle cell or neuroendocrine small cell components
2. History of
    a. seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma).
    b. loss of consciousness or transient ischemic attack within 12 months of randomization
    c. significant cardiovascular disease within the last 3 months including: myocardial infarction, unstable angina, congestive heart failure (NYHA functional capacity class II or greater, Refer to Appendix 6), ongoing arrhythmias of Grade >2 [NCI CTCAE, version 4.03], thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism). Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed.
3. Life expectancy of less than 12 months.
4. History of another malignancy within 5 years prior to randomisation, except for either non-melanomatous carcinoma of the skin or, adequately treated, non-muscle-invasive urothelial carcinoma of the bladder (Tis, Ta and low grade T1 tumours).
5. Concurrent illness, including severe infection that might jeopardize the ability of the patient to undergo the procedures outlined in this protocol with reasonable safety
    a. HIV-infection is not an exclusion criterion if it is controlled with anti-retroviral drugs that are unaffected by concomitant enzalutamide.
6. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse;
7. Patients who are sexually active and not willing/able to use medically acceptable forms of barrier contraception.
8. Prior ADT for prostate cancer (including bilateral orchidectomy), except in the following settings:
    a. Started less than 12 weeks prior to randomisation AND PSA is stable or falling. The 12 weeks starts from whichever of the following occurs earliest: first dose of oral anti-androgen, LHRHA, or surgical castration.
    b. In the adjuvant setting, where the completion of adjuvant hormonal therapy was more than 12 months prior to randomisation AND the total duration of hormonal treatment did not exceed 24 months. For depot preparations, hormonal therapy is deemed to have started with the first dose and to have been completed when the next dose would otherwise have been due, e.g. 12 weeks after the last dose of depot goserelin 10.8mg.
9. Participation in other clinical trials of investigational agents for the treatment of prostate cancer or other diseases.

4.4 *Screening*

Written informed consent must be signed and dated by the participant, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed.

4.5 *Randomisation*

Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this study.

Following randomisation, participants will be allocated to receive either enzalutamide or NSAA in addition to their LHRHA (or surgical castration) via a central randomisation system that stratifies for volume of disease (high versus low), site, co-morbidities (ACE-27 0-1 versus 2-3) and use of anti-resorptive therapy - denosumab, zoledronic acid or neither at time of starting ADT. Treatment should be planned to start within 7 days after randomisation.

The instructions for the randomisation system provided in the Study Manual should be followed. Confirmation of each randomisation will be provided to the site.

Individuals may only be randomised once in this trial.

5 TREATMENT PLAN

Enzalutamide is the study intervention in this trial. Conventional NSAA are used only in the control group, as per an acceptable standard of care. Participants in both groups are treated with a LHRHA (or surgical castration), as per standard of care. Treatment with enzalutamide or NSAA will continue until evidence of clinical progression or prohibitive toxicity.

Androgen deprivation is to be given continuously in this trial. Intermittent androgen deprivation will be classified as a protocol violation.

5.1 *Study Treatment*

5.1.1 Study treatment: Enzalutamide (XTANDI® Astellas)

Enzalutamide is provided as 40 mg soft gelatine capsules administered as 160 mg (4 capsules) orally once daily until clinical disease progression or prohibitive toxicity.

Enzalutamide will be commenced within 7 days of randomisation. If a patient randomised to enzalutamide is already receiving a NSAA, then the NSAA will be stopped at randomisation and enzalutamide should be started within 7 days or randomisation.

Enzalutamide's potency is increased with the co-administration of strong CYP2C8 inhibitors e.g, gemfibrozil. In this trial, it is preferable that these medications are ceased prior to commencing enzalutamide. However if it is not possible for these medications to be ceased then participants will need to commence enzalutamide at 80mg daily. These participants will not be permitted to have their dose of enzalutamide increased to 160mg until they have ceased the co-administration of the strong CYP2C8 inhibitor.

5.1.2 Control Treatment: Non-Steroidal Anti-Androgen (NSAA)

Participants randomised to the control group will receive a conventional NSAA, i.e. bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg three times a day. The choice of NSAA is at the discretion of the treating clinician. Drug administration should be according to the product information guide. Cyproterone is NOT permitted.

The NSAA will be started within 7 days of randomisation.

The NSAA will be continued until clinical disease progression or prohibitive toxicity.

5.1.3 Required background therapy in both arms

All participants are to receive standard background therapy with a LHRHA or surgical castration, as per standard of care. The choice of the LHRHA or surgical castration is at the discretion of the treating clinician.

Administration of the LHRHA should be according to the product information guide. Options include but are not restricted to: goserelin, leuprorelin, triptorelin, and degarelix. Use of a 3-monthly depot preparation is encouraged because its administration will often correspond with protocol assessments.

If surgical castration with bilateral orchidectomy is to be used instead of a LHRHA, then it must be done less than 12 weeks before randomisation or within 7 days after randomisation.

5.1.4 Commencement of ADT prior to randomisation.

Patients who started androgen deprivation therapy less than 12 weeks prior to randomization may be eligible for this trial. If a patient is on a LHRHA, this may continue as planned. If an eligible patient is on an oral non-steroidal anti-androgen prior to randomization, then the oral anti-androgen will be stopped at randomization. If the participant is randomly assigned experimental treatment, they will then start enzalutamide within 7 days of randomisation; if the participant is randomly assigned control treatment, then the a suitable NSAA will be started within 7 days of randomisation (or continued). ADT started before randomisation is deemed to have started on the earliest date that either an anti-androgen or a LHRHA was administered.

5.2 *Dose modifications*

Enzalutamide: Participants who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with study drug. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day). Treatment interruption and re-initiation should be discussed with the study chair or delegate.

If enzalutamide is co-administered with a **strong** CYP2C8 inhibitor (e.g. gemfibrozil), then the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the **strong** CYP2C8 inhibitor is discontinued, then the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Conventional NSAA: should be used as per standard of care and according to the product information. NSAA should be stopped if significant abnormalities of liver dysfunction are observed during study treatment, eg the transaminases (AST or ALT) increase beyond 2-3 times the institutional upper limit of normal, or if the bilirubin increases above twice the upper limit of normal, as per the approved product information.

Background treatment with a LHRHA: There are no dose modifications for LHRHA. Intermittent hormonal therapy is not allowed.

5.3 *Concomitant Medications/Treatments*

5.3.1 Recommended

The following medications and treatments are standard of care for the prevention of osteoporosis during androgen deprivation therapy and should therefore be taken in this study:

- Calcium Carbonate: Patients will receive concomitant treatment with calcium carbonate at a dose of at least 500 mg orally per day every day, e.g., Caltrate™, Tums™. Calcium is best absorbed when taken with meals.

and

- Vitamin D: Patients will receive concomitant treatment with vitamin D by oral administration of any multivitamin containing at least 400 IU of vitamin D.

5.3.2 Permitted

The following medications and treatments are permitted in this study:

- Treatment for **bone metastases** as per clinical guidelines, if commenced prior to randomization and on a stable dose:
    - zoledronic acid or other bisphosphonates,
    - denosumab or other RANK-ligand inhibitors
    - Commencement of either of these classes of bone targeted therapy for metastatic bone disease beyond 6 weeks of commencing study treatment will be considered as evidence of disease progression.
- Treatment or prevention of **osteoporosis**
    - zoledronic acid e.g. Aclasta ® (5mg every 12 months)
    - denosumab e.g. Prolia® (60mg every 6 months)
    - Other approved agents
- Palliative radiation for sites of disease documented at time of randomisation is permissible if required within 6 weeks of commencing study treatment. In this situation, the participant may continue on study treatments.

  The requirement for palliative radiotherapy beyond 6 weeks of commencing study treatment should be deemed evidence of clinical progression and study treatment should be discontinued (see Section 5.5 Treatment discontinuation).

5.3.3 Use with caution

Some drugs affect the metabolism of enzalutamide. Enzalutamide is metabolised by the liver and the cytochrome P450 pathways 2C8 and 3A4 are responsible for the metabolism of enzalutamide. Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when combining enzalutamide with drugs that are affected by CYP450 metabolic pathways. Where possible these drugs should be avoided. In settings where avoidance of these drugs is not possible, suggestions for dose reductions for enzalutamide are described in Section 5.2.

Enzalutamide affects the metabolism of some drugs. Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted utilizing local laboratories.

5.3.4 Prohibited

The following should not be used during this study. Participants who require treatment with any of these agents will usually need to discontinue study treatment, and should be discussed with the Study Chair or delegate:

- Other investigational treatments

- St John's Wort
- Grapefruit juice

5.3.5 Concomitant medication reporting

Concomitant medications known to interact with the study medications will be recorded as well concomitant medications on development of SAEs.

5.4 *Compliance*

Participant medication compliance will be formally determined by a tablet count out of the sight of the patient at 4 and 12 weeks after randomisation and the participant counselled appropriately if significant non-compliance is determined. Compliance at subsequent visits will be assessed by questioning the participant and recording if treatment has been taken as prescribed, and if not, the reasons and number of days of treatment missed.

5.5 *Treatment discontinuation*

Study treatment with enzalutamide or NSAA will be permanently discontinued for any of the reasons below

- Clinical progressive disease (PD) is documented by a site investigator. PSA progression alone does not constitute clinical progression i.e if the participant has PSA progression alone they may remain on study drug until the criteria for clinical progression are met. See SECTION 7.3 for definition of clinical progression
- Delay of hormonal treatment for greater than 30 days due to treatment-related adverse events. Treatment interruptions and re-initiations should be discussed with the study chair or delegate.
- The investigator determines that continuation of treatment is not in the patient's best interest.
- Development of adverse events during the trial that would put the participant at risk if they continued study therapy e.g. seizures or liver toxicity, whilst on enzalutamide.
- The patient declines further study treatment, or withdraws their consent to participate in the study.

In addition, enzalutamide should be discontinued in the following circumstances:

- Required use of a concomitant treatment that is prohibited, as defined in section 5.3.2
- Failure to comply with the protocol, e.g. repeatedly failing to attend scheduled assessments. If a patient has failed to attend scheduled assessments in the study, the Investigator must determine the reasons.

The reasons for discontinuing study treatment will be documented in the participant's medical record and eCRF.

Follow up of participants who stop study treatment (enzalutamide or NSAA) should continue follow-up visits according to this protocol to allow collection of outcome data.

5.5.1 Subsequent treatment

Treatment after discontinuation of study treatment is at the discretion of the patient's clinician as per standard of care.

6 ASSESSMENT PLAN

6.1 *Schedule of assessments*

	Screening	Baseline[1]	On Study Treatment			After study treatment	
	Within 28 days prior to randomisation	Within 7 days prior to randomisation	Day 29[2] (±7 days)	Every 12 weeks (±1 week)[3] from randomisation until clinical progression[4]	At progression[5] (PSA and clinical) and end of treatment for reasons other than progression	30-42 days after the last dose of study treatment	Every 12 weeks (±2 weeks)
Informed consent	X						
Clinic assessment[6]	X	X	X	X	X	X	
Blood tests[7]:							
Haematology (CBE)	X	X	X				
Biochemistry (EUC, LFTs[8])	X	X	X	X	X		
PSA	X	X	X	X	X		
Bloods for translational research		X		X (wk 24 only)	X (first progression only)		
Imaging[9]:							
CT of abdomen and pelvis	X				X		
CXR or CT chest	X				X		
Whole body bone scan (WBBS)	X				X		
Compliance[10]			X	X (wk 12 only)			
Concomitant medications			Drugs used at the time of SAEs, and drugs known to interact with enzalutamide[11]				
Adverse Events[12]			X	X	X	X	
Quality of life assessments (EORTC QLQ C-30 PR-25, EQ-5D)		X	X	X	X	X	
Resource use form			X	X	X	X	
Patient status						X	X
Subsequent treatment for prostate cancer						X	X

Note: In the event that LHRHA or NSAA treatment was started within 12 weeks prior to randomisation, the pre-treatment PSA will be recorded as the baseline PSA, however the baseline CT and WBBS will still be required.

Footnotes:

1. If screening bloods were collected within 7 days prior to randomisation, baseline bloods do not need to be repeated.
2. Assessments on Day 29 is for adverse events and compliance.
3. 12-weekly assessments are intended to correspond with the 3 monthly depot of LHRHA if this is being administered at the trial site.
4. 12-weekly assessments are to continue until there is evidence of clinical progression. If PSA progression occurs without clinical progression, 12 weekly assessments continue.
5. PSA progression and clinical progression often occur at different times. If so, then these assessments must be recorded at both times. PSA progression is defined according to the PCWG2 criteria: first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later. Clinical progression is defined as evidence of progression or recurrence on imaging, clinical examination, development of cancer related symptoms, or initiation of other anticancer treatment for prostate cancer
6. Clinical assessment includes physical examination, performance status and weight.
7. Bloods tests include,

   1) Haematology: complete blood examination (CBE): Haemoglobin concentration, white cell count, platelet count, white cell differential.

   2) Biochemistry: electrolytes, urea, creatinine (EUC);
   liver function tests (LFT): bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT)

   3) Bloods for translational research are collected at baseline, week 24 and at the time of first evidence of progression (PSA or clinical).
8. Liver function tests must be checked every 4 weeks from commencement of study drug for the first 4 months. This does not require a clinic visit or other assessments.
9. Imaging at baseline must include a CT or MRI of the abdomen and pelvis, and a radio-isotope whole body bone scan (WBBS). The chest can be imaged with either a plain x-ray, or a CT scan. However if lung nodules are identified on the CXR, then a CT scan of the chest must be performed.
10. Formal count of treatment tablets in experimental group (enzalutamide) and control group (NSAA tablets) at weeks 4 and 12
11. Only in the group assigned enzalutamide
12. Adverse events categorised and graded according to CTCAE v4.03 till the 30 day safety assessment visit, 30 days after the study treatment ends.

6.2 *Assessment phase definitions and special circumstances*

6.2.1 Screening

All screening procedures must be performed within 28 days prior to randomisation, unless otherwise specified.

6.2.2 Baseline

All baseline procedures must be performed within 7 days prior to randomisation, and within 14 days prior to treatment commencement, unless otherwise specified.

6.2.3 On treatment

Assessments during treatment may be performed within 7 days of the specified timepoint, unless otherwise specified.

6.2.4 End of treatment and 30 day safety assessment

An end of treatment and safety assessment should be performed 30-42 days after the last dose of study treatment to include any adverse events occurring within 30 days after the last dose of study treatment.

6.2.5 Follow-up after completion of study treatment

Study-specific follow-up assessments should be completed at the specified timepoints (± 2 weeks).

Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol.

If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries.

7 OUTCOMES, ENDPOINTS AND OTHER MEASURES

7.1 *Overall Survival*

Overall survival is defined as the interval from the date of randomisation to date of death from any cause, or the date of last known follow-up alive.

7.2 *PSA Progression Free Survival*

PSA progression free survival (PFS) is defined as the interval from the date of randomisation to the date of first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last known follow-up without PSA progression.

PSA progression is defined as: a rise in PSA by more than 25% AND more than 2ng/mL above the nadir (lowest PSA point). This needs to be confirmed by a repeat PSA performed at least 3 weeks later. (See Appendix 3 for more details on the PCWG2 criteria).

7.3 *Clinical Progression Free Survival*

Clinical progression free survival (PFS) is defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression.

Clinical progression is defined by progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions see Appendix 3 & 4), development of symptoms attributable to cancer progression, or initiation of other anticancer treatment for prostate cancer.

7.4 *Safety (Adverse events worst grade according to NCI CTCAE v4.03)*

The NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.03) will be used to classify and grade the intensity of adverse events during study treatment.

7.5 *Health Related Quality of Life*

HRQL will be reported by participants using the EORTC core quality of life questionnaire (QLQ C-30) and prostate cancer specific module (PR-25). The EQ-5D-5L will be used to derive utility scores suitable for quality adjusted survival analyses. (See Appendix 1).

HRQL is a secondary outcome in this trial and the specific HRQL objective is to determine differential treatment effects by comparing scores between the randomly allocated groups. The underlying hypothesis is that there will be no important differences in HRQL between the two treatment groups.

The QLQ-C30 is a validated questionnaire developed to assess HRQL in cancer patients. It includes five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global

health and quality-of-life scale. The remaining single items assess additional symptoms commonly reported by cancer patients (dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea), as well as the perceived financial impact of the disease and treatment. (14)

The QLQ-PR25 is a 25 item module designed to assess HRQL in prostate cancer patients. It includes 5 multi-item scales assessing urinary symptoms, bowel symptoms, hormonal treatment-related symptoms, sexual activity, sexual function, and incontinence aids. (15)

The EQ-5D-5L is a standardised, self-rated measure of health status designed to provide a utility score suitable for use in health economic evaluations. It provides a descriptive classification based on self-assessment of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a 5 level rating scale of no problems, slight problems, moderate problems, severe problems and extreme problems. These scores are combined with a self-rating of health on a 20cm graduated, vertical, visual analogue scale from ‘the best health you can imagine’ to ‘the worst health you can imagine’.

7.6 *Health Outcomes Relative to Costs*

Information on the following areas of health-care resource usage will be collected: hospitalisations (for all participants by trial staff via a standard case record form (CRF), visits to health professionals (for Australian participants via Medicare benefits scheme (MBS) and for other

regions as specified separately in their Group Specific Appendix (GSA), and medications (for Australian participants via Pharmaceutical Benefits Scheme (PBS) and for other regions as separately specified in their GSA). Consent will be sought from Australian participants for access to their MBS and PBS records. Australian unit costs will be applied to the resource usage data (e.g. Diagnosis Related Groups (DRG) costs or similar for hospitalisations, and scheduled costs for medical visits and prescription items) to estimate the incremental cost of the addition of enzalutamide to standard treatment.

Quality-adjusted survival (QAS) time will be used to quantify the incremental effectiveness of adding enzalutamide to standard treatment. QAS will be calculated by applying utility weights for quality of life derived from the EQ5D to survival data using established methods. (16)

Economic evaluation in other regions will be undertaken at the discretion of the relevant regional trial coordinating centre.

7.7 *Tertiary/Correlative Objectives*

These will include exploratory studies of tissue and blood samples to identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes). Studies may include, but are not limited to:

- investigating variants of the androgen receptor (AR) - a steroid receptor transcription factor, and changes in plasma profiles (or plasma signature) in understanding mechanisms of resistance to enzalutamide;
- investigations of how enzalutamide may work in people with prostate cancer;
- studies that may help to understand the course of this cancer and related diseases;
- biomarkers may be RNA-based (single entity or entire expressed genome, RNA, miRNA), DNA-based (single entity or whole genome, germ line or tumour related), protein-based or other entities and the consent form will allow patients to allow or limit use of specimens;

The treating doctor of the participant will be notified of any analytically or clinically valid findings that may emerge significant to the participant or their family regarding cancer;

Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of biomarkers remains to be determined.

8 SAFETY REPORTING

8.1 *Definitions*

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

Adverse events include the following:

- All suspected adverse drug reactions
- All reactions from drug– overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug.

AEs must be reported as AEs even if they do not meet SAE criteria.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the participant is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

(i) The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(ii) Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

AEs and SAEs will be recorded from the date of randomisation until 30 days after the last dose of study treatment.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Participant Information Sheet and Informed Consent Form or elsewhere in the protocol. (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010)).

An event is causally related if there is a reasonable possibility that the drug [intervention] caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010).

8.2 *Reporting of Serious Adverse Events (including SUSARs)*

The investigator in all participating countries is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the NHMRC Clinical Trials Centre within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention.

SAE reports should be submitted to the CTC as per the procedure documented in the Study Manual.

The CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The CTC will be responsible for providing reports to the Lead HREC in Australia and New Zealand and the regional coordinating centres in the other regions.

The investigator must notify the local HREC as required.

The CTC will submit 'reportable safety events' to the TGA in Australia and Medsafe in NZ, and to the regional coordinating centre to provide to the regulatory authorities as required in other participating countries in which the study is being conducted within the requisite timeframes, with a copy to Astellas with a copy to Astellas.

As per regulatory requirements, a SUSAR needs to be reported as soon as possible and not later than 7 days for a fatal event and 15 days for a non-fatal event.

The following information will be recorded for each Serious Adverse Event**:**

- Event description including classification according to NCI CTCAE v4.03
- SAE criterion
- Attribution to study intervention (enzalutamide)
- Expectedness (listed in IB for enzalutamide)
- Action taken with study intervention (enzalutamide), including rechallenge (if done)
- Outcome of SAE including end date if resolved

8.3 *Pregnancy*

Pregnancy occurring in the partner of a participant participating in the study and up to 90 days after the completion of the study drug should be reported to the investigator and the NHMRC Clinical Trials Centre. The investigator should counsel the participant; discuss the risks of continuing with the pregnancy and the possible effects on the foetus. The partner should be counselled and followed as described above. The coordinating centre must be notified within 1 working day using the SAE form and the participant followed during the entire course of the pregnancy and

postpartum period. After obtaining participant and partner consent, parental and neonatal outcomes will be recorded even if they are completely normal.

9 CENTRAL REVIEW AND BIOSPECIMEN COLLECTION

9.1 *Central Tissue Collection*

Where available formalin-fixed paraffin-embedded (FFPE) tissue blocks of diagnostic tumour tissue will be collected for research (including potential future translational research relevant to this study). This diagnostic tissue may include biopsy of the primary tumour, biopsy or cytology of metastatic lesion. The tissue will be from archival tumour material – no additional biopsy of the participant is required. Tissue blocks will be collected at site and sent to a central lab for histology review. Patient consent will be sought for the conduct of translational studies (tertiary /correlative objectives) on these biospecimens. Refer to the Biological Sampling Handbook for the details relating to central tissue collection.

9.2 *Central Blood Collection*

Patient consent will be sought for collection of blood at 3 timepoints: baseline, week 24 from randomisation and at first evidence of progression (PSA or clinical, whichever comes first). Whole blood will be collected, processed and stored frozen at each trial site. The frozen samples will be transported later to a central lab for translational studies (tertiary /correlative objectives). Refer to the Biological Sampling Handbook for collection and processing procedures.

10 TREATMENT INFORMATION

10.1 *Enzalutamide (XTANDI® Astellas)*

10.1.1 Description

Enzalutamide is an androgen receptor inhibitor. It is provided as liquid-filled soft gelatine capsules each containing 40 mg enzalutamide for oral administration. Each bottle contains 120 capsules. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatine, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

Bottles of enzalutamide should be stored at a room temperature between 20ºC to 25ºC (68ºF to 77ºF), in a dry place and kept with container tightly closed.

Enzalutamide should not be handled by pregnant women. Full details on product handling information are provided in the Investigator Brochure and Pharmacy Manual.

10.1.2 Supply

Astellas is providing the study drug free of charge. Appropriately labelled enzalutamide will be distributed by a third party to each participating site from regional warehouses. Start-up supplies of enzalutamide will be dispatched once the institution has all requisite approvals in place.

Enzalutamide will be dispensed to study participants according to usual hospital practice at each participating institution.

Full details on drug ordering and supply is provided in the Pharmacy Manual

10.1.3 Study Drug Accountability

The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate.

Patients will be asked to return unused drug and empty drug containers at each return visit.

10.2 *Non-steroidal anti-androgen (NSAA)*

NSAA will be provided according to usual practice. Drug accountability will not be performed for NSAA.

10.3 *LHRHA (e.g. Goserelin, Leuprorelin, Degarelix)*

LHRHA will provided according to usual practice. Drug accountability will not be performed for LHRHA.

11 STATISTICAL CONSIDERATIONS

11.1 *Sample Size*

A trial comprising 1,100 participants that are followed until approximately 470 deaths are observed (e.g. over a 2 year recruitment with an additional follow-up of 3.5 years) provides over 80% power to detect a 25% reduction in the hazard of death with a 2-sided type 1 error of 0.05 assuming a 3-year survival rate of 65% amongst controls.

A 25% reduction in the hazard of death is considered clinically plausible in light of the results of the AFFIRM trial of enzalutamide versus placebo in castration-resistant metastatic prostate cancer after chemotherapy, which showed a 37% reduction in the hazard of death, (11) and the PREVAIL trial of enzalutamide versus placebo for castration resistant metastatic prostate cancer before chemotherapy, which showed a 30% reduction in the hazard of death (Medivation Press Release 22 Oct 2013: http://www.astellas.com/en/corporate/news/pdf/131022_1_Eg.pdf).

The design incorporates a formal interim analysis performed on overall survival once 2/3 of the required events are observed. The interim analysis allows for early rejection of the null hypothesis using an O'Brien-Fleming boundary. The critical value for $|Z_k|$ is 2.45 for the interim analysis and 2.00 for the final analysis. The conditional power of the study will also be calculated at the interim analysis.

11.2 *Statistical Analysis*

A statistical analysis plan will be prepared prior to data-lock, and contain additional detail on the methods described below.

All randomised participants will be eligible for inclusion in the full analysis set. Analysis of efficacy endpoints will be undertaken on participants in the full analysis set unless participants are deemed non-evaluable by the Trial Management Committee; all such decisions will be documented in the final study report. The safety population will comprise all randomised participants who received at any study medication. Participants will be analysed according to the regimen they actually received for the purposes of the safety analysis.

11.2.1 Timing of Analyses

An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Assuming the study is not terminated early, the final analysis is planned to be undertaken after the required number of deaths have occurred.

11.2.2 Analysis of Efficacy Endpoints

The primary analysis will be a comparison of overall survival (OS) in the two treatment arms using a log-rank test. Kaplan-Meier curves for OS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression. The sensitivity of treatment effect estimates to adjustment for baseline covariates will be explored.

Other time-to-event endpoints will be analysed in a comparable fashion to the primary endpoint. The QoL scores collected longitudinally will be analysed using appropriate linear models for repeated measures data.

11.2.3 Analysis of Safety Endpoints

A descriptive analysis of the AE data will be prepared for participants in the safety population. The number and percentage of participants who experience AEs will be tabulated according to CTCAE term/category, grade, and seriousness.

11.2.4 Analysis of Health Outcomes Relative to Costs

A within-trial estimate of the incremental cost-effectiveness of the addition of enzalutamide to standard treatment will be calculated in terms of Australian dollars per unit of quality adjusted survival (QAS) gained.

The incremental cost of the addition of enzalutamide to standard treatment will be estimated by applying Australian unit costs to the resource usage data (e.g. ANDRG costs for hospitalisations, and scheduled costs for MBS and PBS items). QAS will be calculated by applying utility weights for quality of life derived from the EQ-5D-5L to survival data using established methods. (16)

The feasibility of extrapolating beyond the within-trial estimate of cost-effectiveness using modelling methods will be explored.

11.3 *Interim analyses*

An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Results of the interim analysis will be reviewed by the study Independent Data Safety Monitoring Committee (IDSMC) described in Section 12.2. The IDSMC will also monitor selected safety endpoints. Consideration will be given to altering aspects of the study if:

- The results of the interim analysis yield clear evidence of benefit or harm based on the O'Brien-Fleming approach specified section 11.1.
- The conditional power of the study (evaluated at the time of the interim analysis) is unacceptably low (e.g. <20%)
- The accrual/event rate is insufficient to complete the study in a reasonable time frame.
- The rate of serious AEs (grade 3 to 5) in the enzalutamide arm is unacceptably high compared to the control arm.
- Medical or ethical reasons emerge affecting continued performance of the study.

12 ORGANISATION

The study is a collaboration between the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and the NHMRC Clinical Trials Centre, at the University of Sydney, which is the sponsor in Australia and New Zealand.

This international study will be conducted at a number of regional coordinating centres, each responsible for their own ethic and regulatory approvals, regional monitoring, medical oversight and facilitation of data collection and query resolution.

Overall study coordination, data acquisition and management and statistical analysis will be performed by the global coordinating centre, the NHMRC Clinical Trials Centre.

12.1 *Trial Management Committee*

The international Trial Management Committee (TMC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).

The international TMC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on interim analyses or other information.

Each regional trial coordinating centre will identify a clinical lead and a coordinating centre lead who will represent the region on the international TMC.

12.2 *Independent Safety and Data Monitoring Committee (ISDMC)*

The ISDMC will provide an independent assessment of emerging evidence from interim analyses and sources external to the trial, and make recommendations to the international TMC about potential modifications to the trial protocol and conduct. An ISDMC charter will provide details on the composition of the committee, the roles and responsibilities of committee members, the format of meetings and methods of information transfer, statistical issues and relationships with other committees.

13 ADMINISTRATIVE ASPECTS

13.1 *Ethics and regulatory compliance*

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations in other countries. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the CTC, study chair and HREC must be advised immediately.

13.2 *Confidentiality*

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC Clinical Trials Centre, University of Sydney and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

13.3 *Protocol amendments*

Changes and amendments to the protocol can only be made by the international Trial Management Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

13.4 *Data Handling and Record Keeping*

All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

a. Participant's name, contact information and protocol identification.

b. The date that the participant entered the study, and participant number.

c. A statement that informed consent was obtained (including the date).

d. Relevant medical history

e. Dates of all participant visits and results of key trial parameters.

f. Occurrence and status of any adverse events.

g. The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.

Patient-reported outcome data such as health-related quality of life data entered into the CRF will be considered as source.

All study-related documentation at Australian and New Zealand sites will be maintained for 15 years following completion of the study.

13.5 *Study Monitoring*

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC Clinical Trials Centre (CTC) or their delegates. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during the study for source data verification, review of the investigator's site file and drug handling records. The CTC or regional coordinating centres will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the participant gives authorised CTC staff direct access to their medical records and the study data.

13.6 *Audit and Inspection*

This study may be subject to audit or inspection by representatives of the collaborative group, Astellas, CTC or representatives of regulatory bodies (e.g. Therapeutic Goods Administration (TGA), as well as regulatory authorities in each region such as FDA or EMEA..

13.7 *Clinical Study Report*

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued and form the basis of a manuscript for publication. The Clinical Study Report or summary thereof will be provided to the study investigators, ANZUP, Astellas and the ethics committees. A lay summary of results will be prepared for patients and other interested parties.

13.8 *Publication Policy*

Authorship recognises the intellectual contributions of investigators and others to a study. It also identifies those who take public responsibility for the study. Authorship is defined as per ICMJE guidelines (www.icmje.org).The International Trial Management Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. The Writing Committee will develop a publication plan, including authorship, target journals, and expected dates of publication. The first publication will be the report of the full trial results based on the main protocol using the study group name with a list of specific contributions at the end. ANZUP and CTC will be acknowledged in all publications. All publications must receive prior written approval from the TMC prior to submission.

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15.1 Appendix 1: HRQL forms (EORTC QLQ C-30 & PR-25, EQ-5D-5L)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

During the last 4 weeks…	Not at all	A little	Quite a bit	Very much
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

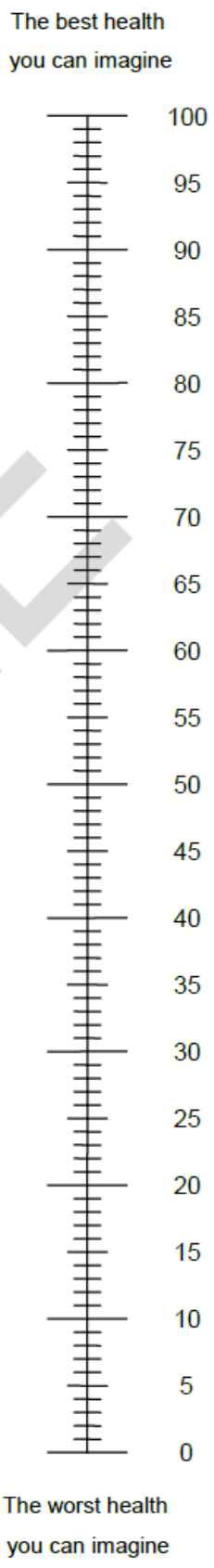
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



15.2 Appendix 2: ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol 1982. (17)

15.3 Appendix 3: Prostate Cancer Working Group 2 (PCWG2) Criteria

The sections that apply to this trial are the criteria for PSA response and progression, and the criteria for bone lesion "prevent/delay end points (progression)".

Variable	PCWG2 (2007)
PSA	- Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug - Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression - Ignore early rises (prior to 12 weeks) in determining PSA response **Decline from baseline**: - Record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend)† **No decline from baseline:** - PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	**For control/relieve/eliminate end points:** Use RECIST with caveats: - Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline - Record changes in nodal and visceral soft tissue sites separately - Record complete elimination of disease at any site separately - Confirm favorable change with second scan - Record changes using waterfall plot **For delay/prevent end points:** - Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies) - Note that for some treatments, a lesion may increase in size before it decreases.
Bone	**For control/relieve eliminate end points:** - Record outcome as new lesions or no new lesions - First scheduled reassessment: o No new lesions: continue therapy o New lesions: perform a confirmatory scan 6 or more weeks later - Confirmatory scan: o No new lesions: continue therapy o Additional new lesions: progression - Subsequent scheduled reassessments: o No new lesions: continue o New lesions: progression **For prevent/delay end points (progression):** - The appearance of 2 or more new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions§ - The date of progression is the date of the first scan that shows the change
Symptoms	Consider independently of other outcome measures - Document pain and analgesia at entry with a lead in period and measure repeatedly at 3- to 4-week intervals - Perform serial assessments of global changes in HRQOL, urinary or bowel compromise, pain management, additional anticancer therapy - Ignore early changes (≤ 12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression - Confirm response or progression of pain or HRQOL end points ≥ 3 weeks later

See Scher et al 2008 (18) for more details.

15.4 Appendix 4: Response Evaluation Criteria in Solid Tumours (RECIST 1.1)

These instructions are based on the guidelines recommended by Eisenhauer et al. (19).

The sections that apply to this trial are the criteria for progression of soft tissue lesions.

1 Evaluable for response.

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below

2 Disease and lesion definitions

1.1 *Measurable Disease*. Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as≥ 20 mm with chest x-ray, and as≥10 mm with CT scan (assuming slice thickness of 5mm or les s) or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres. Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

1.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

1.3 *Target Lesions*. When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions in total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological lymph nodes must meet the criterion of having a short axis of ≥ 15 mm by CT scan and only the *short* axis of these lymph nodes will contribute to the baseline sum. All other pathological lymph nodes (those with a short axis≥ 10 mm but <15 mm) should be considered non -target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of target lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions can not be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

1.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

Response Definitions

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of any specified tumour markers (no tumour markers for this trial). Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol. Confirmation of response is not required in this study.

Partial Response (PR): at least a 30% decrease in the sum of measures for target lesions (longest diameter for tumour lesions and short axis measure for target lymph nodes), taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol. Confirmation of response is not required in this study

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table: Integration of Target, non-Target and New lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of specified tumour markers, AND lymph nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks. from baseline [note, protocol may

				define; 6-8 weeks is recommended]
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of specified tumour markers AND lymph nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

2 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

3 Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment (or randomisation for randomized studies) until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

4 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent, unless the protocol specifies otherwise. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

4.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

4.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

4.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

4.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

4.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

4.6 *Tumour Markers*. Tumour markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. There are no specified tumour markers for this trial.

4.7 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

15.5 Appendix 5: TNM staging for prostate cancer

Pathologic staging

pT2	Organ confined.
pT2a	Unilateral, ≤½ of one side.
pT2b	Unilateral, involving >½ of side but not both sides.
pT2c	Bilateral disease.
pT3	Extraprostatic extension.
pT3a	Extraprostatic extension or microscopic invasion of bladder neck.[b]
pT3b	Seminal vesicle invasion.
pT4	Invasion of rectum, levator muscles, and/or pelvic wall.

p = Pathologic; T = Primary tumor.

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Stages

Stage	TNM	Description
I	T1a, N0, M0, G1	T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

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Stage	TNM	Description
IIA	T1a, N0, M0, G2–4	T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIA	T1b, N0, M0, any G	T1b = Tumor incidental histologic finding in >5% of tissue resected.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIA	T1c, N0, M0, any G	T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIB	T1, N0, M0, any G	T1 = Clinically inapparent tumor neither palpable nor visible by imaging.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIB	T2, N0, M0, any G	T2 = Tumor confined within prostate.[b]
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

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Stage	TNM	Description
III	T3, N0, M0, any G	T3 = Tumor extends through the prostate capsule.[c]
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

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Stage	TNM	Description
IV	T4, N0, M0, any G	T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
	Any T, N1, M0, any G	TX = Primary tumor cannot be assessed.
		T0 = No evidence of primary tumor.
		T1 = Clinically inapparent tumor not palpable or visible by imaging.
		T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		T1b = Tumor incidental histologic finding in >5% of tissue resected.
		T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).
		T2 = Tumor confined within prostate.[b]
		T2a = Tumor involves ≤50% of one lobe.
		T2b = Tumor involves >50% of one lobe but not both lobes.
		T2c = Tumor involves both lobes.
		T3 = Tumor extends through the prostate capsule.[c]
		T3a = Extracapsular extension (unilateral or bilateral).
		T3b = Tumor invades seminal vesicle(s).
		T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as the bladder, external sphincter, rectum, levator muscles, and/or pelvic wall.
		N1 = Metastasis in regional lymph node(s).
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

	Any T, any N, M1, any G	TX = Primary tumor cannot be assessed.
		T0 = No evidence of primary tumor.
		T1 = Clinically inapparent tumor not palpable or visible by imaging.
		T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		T1b = Tumor incidental histologic finding in >5% of tissue resected.
		T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).
		T2 = Tumor confined within prostate.[c]
		T2a = Tumor involves ≤50% of one lobe.
		T2b = Tumor involves >50% of one lobe but not both lobes.
		T2c = Tumor involves both lobes.
		T3 = Tumor extends through the prostate capsule.[c]
		T3a = Extracapsular extension (unilateral or bilateral).
		T3b = Tumor invades seminal vesicle(s).
		T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as the bladder, external sphincter, rectum, levator muscles, and/or pelvic wall.
		NX = Regional lymph nodes were not assessed.
		pNX = Regional nodes not sampled.
		N0 = No regional lymph node metastasis.
		pN0 = No positive regional nodes.
		N1 = Metastasis in regional lymph node(s).
		pN1 = Metastases in regional node(s).
		M1 = Distant metastasis.[a]
		M1a = Nonregional lymph node(s).
		M1b = Bone(s).
		M1c = Other site(s) with or without bone disease.
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade; p = Pathologic.

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[a] *When more than one site of metastasis is present, the most advanced category (pM1c) is used.*

[b] *Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.*

[c] *Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.*

15.6 Appendix 6: NYHA Heart Failure Classification

Reference: The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Criteria for use of the terms *minimal*, *moderately severe*, and *severe disease* cannot be defined precisely. Grading is based on the individual physician's judgment. The objective assessment of a patient with cardiac disease who has not had specific tests of cardiac structure or function is classified as undetermined.

The classification of patients according to cardiac functional capacity is only part of the information needed to plan the management of patients' activities. A prescription for physical activity should be based on information from many sources. Functional capacity is an estimate of what the patient's heart will allow the patient to do and should not be influenced by the character of the structural lesions or an opinion as to treatment or prognosis. A recommendation for physical activity is based not only on the amount of effort possible without discomfort but also on the nature and severity of the disease.

Following are examples of functional capacity and objective assessment classifications.

- A patient with minimal or no symptoms but a large pressure gradient across the aortic valve or severe obstruction of the left main coronary artery is classified: Functional Capacity I, Objective Assessment D
- A patient with a severe anginal syndrome but angiographically normal coronary arteries is classified: Functional Capacity IV, Objective Assessment A
- A patient with acute myocardial infarction, shock, reduced cardiac output, and elevated pulmonary artery wedge pressure is classified: Functional Capacity IV, Objective Assessment D
- A patient with mitral stenosis, moderate exertional dyspnea, and moderate reduction in mitral valve area is classified: Functional Capacity II or III, Objective Assessment C

Functional Capacity	**Objective Assessment**
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

15.7 Appendix 7: Adult Comorbidity Evalutation - 27

Adult Comorbidity Evaluation-27

Identify the important medical comorbidities and grade severity using the index.
Overall Comorbidity Score is defined according to the highest ranked single ailment, except in the case where two or more Grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score should be designated Grade 3.

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Cardiovascular System			
Myocardial Infarct	☐ MI ≤ 6 months	☐ MI > 6 months ago	☐ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	☐ Unstable angina	☐ Chronic exertional angina ☐ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) ☐ Recent (≤ 6 months) coronary stent	☐ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms ☐ Angina pectoris not requiring hospitalization ☐ CABG or PTCA (>6 mos.) ☐ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	☐ Hospitalized for CHF within past 6 months ☐ Ejection fraction < 20%	☐ Hospitalized for CHF >6 months prior ☐ CHF with dyspnea which limits activities	☐ CHF with dyspnea which has responded to treatment ☐ Exertional dyspnea ☐ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	☐ Ventricular arrhythmia ≤ 6 months	☐ Ventricular arrhythmia > 6 months ☐ Chronic atrial fibrillation or flutter ☐ Pacemaker	☐ Sick Sinus Syndrome ☐ Supraventricular tachycardia
Hypertension	☐ DBP≥130 mm Hg ☐ Severe malignant papilledema or other eye changes ☐ Encephalopathy	☐ DBP 115-129 mm Hg ☐ DBP 90-114 mm Hg while taking antihypertensive medications ☐ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	☐ DBP 90-114 mm Hg while not taking antihypertensive medications ☐ DBP <90 mm Hg while taking antihypertensive medications ☐ Hypertension, not otherwise specified
Venous Disease	☐ Recent PE (≤ 6 mos.) ☐ Use of venous filter for PE's	☐ DVT controlled with Coumadin or heparin ☐ Old PE > 6 months	☐ Old DVT no longer treated with Coumadin or Heparin
Peripheral Arterial Disease	☐ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago ☐ Untreated thoracic or abdominal aneurysm (≥6 cm)	☐ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago ☐ Chronic insufficiency	☐ Intermittent claudication ☐ Untreated thoracic or abdominal aneurysm (< 6 cm) ☐ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	☐ Marked pulmonary insufficiency ☐ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment ☐ Chronic supplemental O_2 ☐ CO_2 retention (pCO_2 > 50 torr) ☐ Baseline pO_2 < 50 torr ☐ FEV1 (< 50%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities ☐ FEV1 (51%-65%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment ☐ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	☐ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	☐ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	☐ Chronic hepatitis or cirrhosis without portal hypertension ☐ Acute hepatitis without cirrhosis ☐ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	☐ Recent ulcers(≤ 6 months ago) requiring blood transfusion	☐ Ulcers requiring surgery or transfusion > 6 months ago	☐ Diagnosis of ulcers treated with meds ☐ Chronic malabsorption syndrome ☐ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	☐ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	☐ Uncomplicated acute pancreatitis ☐ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	☐ Chronic pancreatitis w/o complications

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Renal System			
End-stage renal disease	☐ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis ☐ Acute dialysis	☐ Chronic Renal Insufficiency with creatinine >3 mg% ☐ Chronic dialysis	☐ Chronic Renal Insufficiency with creatinine 2-3 mg%.
Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	☐ Hospitalization ≤ 6 months for DKA ☐ Diabetes causing end-organ failure ☐ retinopathy ☐ neuropathy ☐ nephropathy* ☐ coronary disease* ☐ peripheral arterial disease*	☐ IDDM without complications ☐ Poorly controlled AODM with oral agents	☐ AODM controlled by oral agents only
Neurological System			
Stroke	☐ Acute stroke with significant neurologic deficit	☐ Old stroke with neurologic residual	☐ Stroke with no residual ☐ Past or recent TIA
Dementia	☐ Severe dementia requiring full support for activities of daily living	☐ Moderate dementia (not completely self-sufficient, needs supervising)	☐ Mild dementia (can take care of self)
Paralysis	☐ Paraplegia or hemiplegia requiring full support for activities of daily living	☐ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	☐ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	☐ Recent suicidal attempt ☐ Active schizophrenia	☐ Depression or bipolar disorder uncontrolled ☐ Schizophrenia controlled w/ meds	☐ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	☐ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	☐ Connective Tissue Disorder on steroids or immunosuppressant medications	☐ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	☐ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	☐ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	☐ Asymptomatic HIV+ patient. ☐ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	☐ Uncontrolled cancer ☐ Newly diagnosed but not yet treated ☐ Metastatic solid tumor	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago
Leukemia and Myeloma	☐ Relapse ☐ Disease out of control	☐ 1^{st} remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	☐ Relapse	☐ 1^{st} remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	☐ Delirium tremens	☐ Active alcohol abuse with social, behavioral, or medical complications	☐ H/o alcohol abuse but not presently drinking
Illicit Drugs	☐ Acute Withdrawal Syndrome	☐ Active substance abuse with social, behavioral, or medical complications	☐ H/o substance abuse but not presently using
Body Weight			
Obesity		☐ Morbid (i.e., BMI ≥ 38)	

OVERALL COMORBIDITY SCORE (Circle one.) **0** None **1** Mild **2** Moderate **3** Severe **9** Unknown

15.8 Appendix 8: Cockroft-Gault formula

Renal function (GFR) may be estimated with the Cockcroft–Gault formula, as follows:

Male participants:

Creatinine clearance (ml/minute) = $\frac{(140 - age) * weight}{0.814 * SerumCr}$

Units:
Age in years
Weight in kilograms
Serum creatinine (SerumCr) in micromoles per litre

Female participants: Use above formula but multiply calculated Creatinine clearance by 0.85

	ENZAMET Protocol Amendment from v1.0 11/11/2013 to v2.0 07/11/2014							
Change #	**Current Protocol version**	**Current Protocol date**	**Section needed amendment**	**Page number in amended version**	**Change**	**Current wording**	**Wording in amendment**	**Version change**
1	1.0	11-Nov-13	Title page: Project Manager & Regional coordinating centre - Canada &TBC	1	Updated information. Study team changes	Project Manager= TBA, Regional Coordinating Centre= Ireland, UK and Europe- Coordinating Centre Lead= Brian Moulton, Canada and North America= TBC, Region= TBC	Project Manager= Xanthi Coskinas, Regional Coordinating Centre= Ireland, UK and Europe- Coordinating Centre Lead= TBA, Canada and North America= NCIC CTG, Scott North, Wendy Parulekar. Region= Dana Farber Cancer Institute, DFCI. Christopher Sweeney, Coordinating Centre Lead= TBA	2.0
2	1.0	11-Nov-13	Abbreviations	3	Additional information		AE - Adverse Events DFCI - Dana Farber Cancer Institute CTCAE - National Cancer Institute Common Terminology Criteria for Adverse Events SAE - Serious Adverse Events	2.0
3	1.0	11-Nov-13	Synopsis: Design	6	Additional information	Open label, randomised, stratified, 2-arm, multicentre, phase 3 clinical trial	Open label, randomised, 2-arm, multicentre, phase 3 clinical trial, stratified for volume of disease, use of early docetaxel, antiresorptive therapy, study site and comorbidities.	2.0
4	1.0	11-Nov-13	Synopsis: Assessments	7	Correction	Blood tests for translational studies at baseline, day 29, week 25, and end of study treatment.	Blood tests for translational studies at baseline, day 29, week 24, and end of study treatment.	2.0
5	1.0	11-Nov-13	Schema	8	Additional stratification factor		"Early docetaxel use"	2.0
6	1.0	11-Nov-13	Schema	8	Clarification	"Non-steroidal anti androgens…"	"Conventional non-steroidal anti androgens…"	2.0
7	1.0	11-Nov-13	Background	12	Additional paragraphs regarding early docetaxel. Rationale for the addition of allowing use of early docetaxel in this setting.	The trial was stopped early and unblinded at the recommendation of the independent data and safety monitoring committee because of a substantial benefit in OS that met the pre-specified stopping rule: hazard ratio for overall survival 0.70; 95% confidence interval, 0.59-0.83, p<0.0001, median survival 32 versus 30 months) and radiological PFS (hazard ratio for radiological PFS 0.19; 95% confidence interval, 0.15-0.23, p < 0.0001). [Medivation Press Release, dated 22 October 2013. (http://www.astellas.com/en/corporate/news/pdf/131022_1_Eg.pdf).The purpose of this study is to determine whether enzalutamide in combination with androgen suppression can increase the longevity of men commencing androgen suppression for newly diagnosed metastatic prostate cancer.	The trial was stopped early and unblinded at the recommendation of the independent data and safety monitoring committee because of a substantial benefit in OS that met the pre-specified stopping rule: hazard ratio for overall survival 0.70; 95% confidence interval, 0.59-0.83, p<0.0001, median survival 32 versus 30 months) and radiological PFS (hazard ratio for radiological PFS 0.19; 95% confidence interval, 0.15-0.23, p < 0.0001). (20) "Early chemotherapy" refers to the combined use of ADT plus docetaxel as first line therapy for metastatic prostate cancer as tested in the CHAARTED trial (E3805).(21) In the CHAARTED trial, early chemotherapy consisted of docetaxel 75mg/m2 given for 6 cycles and was commenced a median of 1 month from the start of ADT. This improved median OS from 44 months with ADT alone to 57 months with early chemotherapy (HR 0.61, 95% CI 0.48-0.82, P=0.0003) and a median time to clinical progression of 33 months versus 20 months (HR 0.49, 95% CI 0.37-0.65, p<0.0001). The survival benefit was most evident in patients with high volume disease: HR 0.62, 95% CI 0.46-0.83, 17 month improvement in median OS from 32 to 49 months. There was a trend of similar magnitude for a survival benefit in men with low volume disease (HR 0.58, 95% CI 0.31-1.08), but the smaller number of events meant this was still within the play of chance. Early chemotherapy in GETUG15 did not result in a survival benefit. (23) However, the participants in GETUG15 were predominantly men with low volume disease (80% of study population) compared with CHAARTED where approximately one third of the participants had low volume disease. Despite no significant difference in OS, there were significant improvements in biochemical PFS and clinical PFS. Biochemical PFS in the group treated with ADT plus docetaxel was 23 months versus 13 months in the group treated with ADT alone (HR 0.72, 95% CI 0.57–0.91; p=0.005). Similarly, clinical PFS was significantly longer in the group treated with ADT and docetaxel than in the group given ADT alone (medians of 24 months versus 15 months, HR 0.75, 95% CI 0.59–0.94; p=0.015). Use of early chemotherapy is likely to become standard of care for selected men with hormone-naïve, metastatic prostate cancer. Version 2 of the ENZAMET trial protocol anticipates this likely change in standard practice by allowing and stratifying for the use of early chemotherapy with docetaxel. There are limited data about the use of docetaxel together with enzalutamide. A phase I trial showed no significant effect of enzalutamide on peak concentrations of docetaxel in men with castration-resistant, metastatic prostate cancer (Astellas; data on file). However, 4 of the 22 participants in this study experienced febrile neutropenia. More data are required to confirm the safety of using docetaxel together with enzalutamide. The purpose of ENZAMET is to determine whether enzalutamide in combination with androgen suppression can increase the longevity of men commencing androgen suppression for newly diagnosed metastatic prostate cancer.	2.0
8	1.0	11-Nov-13	3 Design	13	Addition of 5th stratification		5. Early use of docetaxel defined as use of docetaxel in conjunction with initiation of ADT	2.0
9	2.0	11-Nov-13	4.2 Exclusion Criteria	15	Additional criteria re chemotherapy use		Prior cytotoxic chemotherapy for prostate cancer, but up to 2 cycles of docetaxel chemotherapy for metastatic disease is permitted.as per section 5.3.2.4 is allowed.	2.0
10	1.0	11-Nov-13	4.5 Randomisation	16	Additional wording	Following randomisation, participants will be allocated to receive either enzalutamide or NSAA in addition to their LHRHA (or surgical castration) via a central randomisation system that stratifies for volume of disease (high versus low), site, co-morbidities (ACE-27 0-1 versus 2-3) and use of anti-resorptive therapy - denosumab, zoledronic acid or neither at time of starting ADT. Treatment should be planned to start within 7 days after randomisation	Prior to randomization, treating clinicians and participants must decide if early treatment with docetaxel is to be undertaken. Randomisation will be performed via a central randomization system that stratifies for volume of disease (high versus low), site, co-morbidities (ACE-27 0-1 versus 2-3), use of anti-resorptive therapy (denosumab, zoledronic acid or neither) at time of starting ADT, and planned use of docetaxel. The decisions regarding use of early docetaxel or of anti-resorptive therapy, must be made and documented prior to randomization. Participants will be randomly allocated (1:1) to receive either enzalutamide OR NSAA in addition to their LHRHA (or surgical castration). Study treatment should be planned to start within 7 days after randomisation.	2.0
11			5.1.2 Control Treatment: Non-steroidal anti androgen	17	Clarification of commencement of NSAA	The NSAA will be started within 7 days of randomisation.	The NSAA will be started within 7 days after randomisation, if not already started.	2.0
12	1.0	11-Nov-13	5.1.3 Required background treatment in both arms	17	Clarification of commencement of LHRHA and surgical castration	If surgical castration with bilateral orchidectomy is to be used instead of a LHRHA, then it must be done less than 12 weeks before randomisation or within 7 days after randomisation	If an LHRHA is to be used, then it must be started no earlier than 12 weeks before randomization, and preferably within 2 weeks after starting enzalutamide or NSAA. If surgical castration with bilateral orchidectomy is to be used instead of a LHRHA, then it must be performed less than 12 weeks before randomisation. Orchidectomy is permitted at any time after randomisation as long as ADT has been instituted already in accordance with protocol requirements.	2.0
13	1.0	11-Nov-13	5.1.4 Commencement of ADT prior to randomisation	17	Additional words	Patients who started androgen deprivation therapy less than 12 weeks prior to randomization may be eligible for this trial.	Patients who started androgen deprivation therapy less than 12 weeks prior to randomization for metastatic disease may be eligible for this trial.	2.0
14	1.0	11-Nov-13	5.2 Dose Modifications of study medications	17	Section title change from Dose Modifications to Dose Modification of study medications. Change dysfunction to function and Additional wording regarding NSAA re-dosing	NSAA should be stopped if significant abnormalities of liver dysfunction are observed during study treatment, eg the transaminases (AST or ALT) increase beyond 2-3 times the institutional upper limit of normal, or if the bilirubin increases above twice the upper limit of normal, as per the approved product information	NSAA should be stopped if significant abnormalities of liver function are observed during study treatment without a likely alternative explanation, e.g. the transaminases (AST or ALT) increase beyond 2-3 times the institutional upper limit of normal, or if the bilirubin increases above twice the upper limit of normal, as per the approved product information. Recommencement of NSAA may occur at the discretion of the investigator and with appropriate monitoring.	
15	1.0	11-Nov-13	5.3	18	Change of title	Concomitant Medications/Treatments	Concomitant Medications/Treatments (including early docetaxel use)	2.0
16	1.0	11-Nov-13	5.3.2 Permittted	18	Reversed the order of treatment or prevention of osteoporosis with treatment of bone metastases. Separation of palliative radiotherapy	The following medications and treatments are permitted in this study: • Treatment for bone metastases as per clinical guidelines, if commenced prior to randomization and on a stable dose: o zoledronic acid or other bisphosphonates, o denosumab or other RANK-ligand inhibitors o Commencement of either of these classes of bone targeted therapy for metastatic bone disease beyond 6 weeks of commencing study treatment will be considered as evidence of disease progression. • Treatment or prevention of osteoporosis o zoledronic acid e.g. Aclasta ® (5mg every 12 months) o denosumab e.g. Prolia® (60mg every 6 months) o Other approved agents • Palliative radiation for sites of disease documented at time of randomisation is permissible if required within 6 weeks of commencing study treatment. In this situation, the participant may continue on study treatments. The requirement for palliative radiotherapy beyond 6 weeks of commencing study treatment should be deemed evidence of clinical progression and study treatment should be discontinued (see Section 5.5 Treatment discontinuation).	5.3.2.1 Treatment or Prevention of Osteoporosis Treatment or prevention of osteoporosis o zoledronic acid e.g. Aclasta ® (5mg every 12 months) o denosumab e.g. Prolia® (60mg every 6 months) o Other approved agents 5.3.2.2. Treatment of Bone Metastases Treatment for bone metastases as per clinical guidelines, if commenced prior to randomization and on a stable dose: o zoledronic acid or other bisphosphonates, o denosumab or other RANK-ligand inhibitors o Commencement of either of these classes of bone targeted therapy for metastatic bone disease beyond 6 weeks of commencing study treatment will be considered as evidence of disease progression. 5.3.2.3 Palliative Radiotherapy Palliative radiation for sites of disease documented at time of randomisation is permissible if required within 6 weeks of commencing ADT. In this situation, the participant may continue on study treatments. The requirement for palliative radiotherapy beyond 6 weeks of commencing study treatment should be deemed evidence of clinical progression and study treatment should be discontinued (see Section 5.5 Treatment discontinuation).	2.0
17	1.0	11-Nov-13	5.3.2 Permitted New section added (5.3.2.4)	18	New section on early use of docetaxel. Docetaxel is a concomitant medication in this study. Its use is at the discretion of the treating physician a)-h)		5.3.2.4 Early use of docetaxel. The decision to use early docetaxel must be made and specified prior to randomization and is at the discretion of the treating physician and patient. Patients who have already commenced docetaxel prior to study entry are eligible for the ENZAMET trial if they are tolerating full doses of docetaxel (75mg/m2) with ADT, and meet all eligibility criteria for the trial while receiving docetaxel, and have had no more than 2 cycles prior to randomisation. For ENZAMET participants randomly allocated to the enzalutamide group who have not already started chemotherapy, the first dose of docetaxel should be given at least 4 weeks after starting enzalutamide, and no more than 6 weeks after randomisation. For ENZAMET participants randomly allocated to receive standard NSAA who have not already started docetaxel, the first dose of docetaxel should be given at least 4 weeks after starting the standard NSAA and no more than 6 weeks after randomisation. The minimum interval of 4 weeks is to establish that there is no evidence of significant hepatotoxicity that might increase the risk of docetaxel toxicity (serum ALT <3x ULN and serum bilirubin is either <ULN, or <1.5x ULN if the participant has Gilberts Syndrome). The maximum interval of 6 weeks after randomisation is to ensure that chemotherapy is completed by the week 24 follow-up visit. Participants unable to start docetaxel at 75mg/m2 should not be treated with early docetaxel in this trial. Docetaxel should be administered at 75mg/m2 every 21 days for a total of 6 cycles with dose reductions and modifications as specified below. The number of cycles and dose reductions of docetaxel will be recorded in the eCRF.	2.0
18	1.0	11-Nov-13	5.3.2.4.1 Dose modifications for docetaxel	19	Additional wording		5.3.2.4.1 Dose modifications for docetaxel: No more than two dose reductions of docetaxel should be allowed for any patient. If a patient who has had 2 dose reductions has toxicities requiring further dose reductions, then docetaxel should be stopped and they should be treated with androgen deprivation and the assigned NSAA or enzalutamide. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. All toxicities should be graded according to CTCAE version 4.0. Dose adjustments for toxicity should be made according to the following guidelines. If the dose level is reduced due to toxicity, then it will not be re-escalated in subsequent cycles. Treatment may be delayed no more than 3 weeks to allow recovery from toxicity. If treatment must be delayed longer than 3 weeks from the scheduled day of dosing, then docetaxel should be stopped and the patient should be treated with androgen deprivation alone. Dose Level Docetaxel (mg/m2) Level 0 75 mg/m2 Level - 1 65 mg/m2 Level - 2 55 mg/m2	2.0

							a) Myelosuppression Dose modifications are to be made based on the granulocyte and/or platelet count drawn prior to planned treatment (can be done the day prior to planned dose): Docetaxel Neutrophils / 109/L Day 1 of treatment Platelet / 109/L Day 1 of treatment No change > 1.5 or > 100 Delay and reduce one dose level* <1.500 or <100 NOTE: If a dose reduction is made, maintain the lower dose for all subsequent cycles. * If a dose is held due to myelosuppression, the patient will be retreated with a one level dose reduction once neutrophil count has recovered to at least 1.5 x 109/L and platelet count has recovered to at least 100 x 109/L. * If planned day 1 dose must be delayed for three consecutive weeks, discontinue docetaxel and continue on ADT alone.	
							Delay and dose modification after complicated neutropenia. Patients with afebrile Grade 4 neutropenia ☐ temperature ☐38.0 adequately treated and have clinically resolved before restarting therapy. If prior bacteremia, blood cultures must be negative on recheck. Patient can continue with chemotherapy dosing while on antibiotics. Use of growth factors is not required as the dose and schedule does not meet ASCO guidelines. If however, the investigator considers it in patients best interest growth factors can be used per investigator discretion.	
							b) Hepatic dysfunction ALT and Bilirubin will be evaluated pre-study and Day 1 (may be evaluated within 24 hours of day 1) of cycles 1-6 of docetaxel: Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions: Dose Modifications for Abnormal Liver Function Bilirubin ALT/ SGPT Action > ULN* or > 5 x ULN Wait ☐ 3 weeks. If recovered**, reduce docetaxel dose by one dose level. If not, discontinue docetaxel. ☐ ULN* and > 3 x ULN Reduce docetaxel by one dose level * For patients with Gilbert's Syndrome, wait if the bilirubin level is >1.5 its baseline value ** Recovery is < 3X ULN for ALT/SGPT and WNL for bilirubin. For patients with Gilbert's Syndrome, recovery is defined as a bilirubin level <1.5 its baseline value. Dose modifications are based on ALT/ SGPT alone due to the lack of specificity of AST/SGOT.	
							c) Stomatitis If stomatitis ≥ grade 2 is present on day 1 of any cycle, docetaxel should be held until stomatitis has resolved. If Grade 3/4 stomatitis occurs at any time, the dose of docetaxel will be reduced one dose level for all subsequent doses. If a second Grade 3/4 stomatitis event is incurred, docetaxel will be reduced one more dose level. If a third Grade 3/4 stomatitis event occurs, the docetaxel should be ceased.	
							d) Peripheral neuropathy If ☐ Grade 3, the patient should discontinue docetaxel. If Grade 2, the docetaxel should be held and the patient should be retreated upon recovery to a ☐ Grade 1 toxicity with a dose reduction of docetaxel by one level. If Grade 2 or greater neurotoxicity persists for more than 3 weeks, the patient should discontinue docetaxel.	
							e) Hypersensitivity reactions for docetaxel Docetaxel should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for docetaxel hypersensitivity reactions. Grade 4 Hypersensitivity is defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion. Patients with two episodes of Grade 3 hypersensitivity reactions or one Grade 4 hypersensitivty reaction should discontinue docetaxel.	
							f) Diarrhea If patients experience >grade 2 diarrhea and concurrent grade 3 or 4 neutropenia, hold Docetaxel until ANC>1000/mm3 and diarrhea ≤ grade 2. If patients experience significant diarrhea (>3 loose stools/24hrs over baseline), they should be treated prophylactically in subsequent cycles with loperamide or diphenoxylate. If patient experiences >grade 2 diarrhea despite prophylaxis, docetaxel should be reduced one dose level. If patients experience > grade 2 diarrhea despite prophylaxis AND dose reduction, they should discontinue docetaxel.	
							g) Other toxic effects possibly related to docetaxel: If toxicities ☐ Grade 2, manage the patient symptomatically if possible, and retreat without dose reduction. If toxicities reduction.	
							h) Delay of therapy: If docetaxel has to be delayed for more than 3 weeks from planned day of dosing because of any toxicity, then docetaxel should be stopped and the patient should be treated with LHRHA plus assigned NSAA or enzalutamide.	
19	1.0	11-Nov-13	5.3.3 Use with caution	22	Added wording "strong inducers or inhibitors"	Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when combining enzalutamide with drugs that are affected by CYP450 metabolic pathways.	Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when combining enzalutamide with drugs that are strong inducers or inhibitors of these CYP450 metabolic pathways.	2.0
20	1.0	11-Nov-13	6.1 Schedule of Assessments table	24	Clarification		Fasting for glucose, HbA1C,lipids at timepoints- baseline, week 24 only, At progression	2.0
21	1.0	11-Nov-13	6.1 Schedule of Assessments table	24	Clarification	Bloods for translational research	Fasting bloods for translational research	2.0
22	1.0	11-Nov-13	6.1 Schedule of Assessments table	24	Clarification	CT of abdomen and pelvis	CT / MRI of abdomen and pelvis	2.0
23			6.1 Schedule of Assessments table	25	Footnote 6 Clarification of collection of history details & measurement of waist circumference	Clinical assessment includes physical examination, performance status and weight.	Clinical assessment includes history and physical examination, performance status, weight and waist circumference.	2.0
24	1.0	11-Nov-13	6.1 Schedule of Assessments table	25	Footnote 7- Additional timelines	Footnote 7c) Bloods for translational research are collected at baseline, week 24 and at the time of first evidence of progression (PSA or clinical)	Fasting bloods for i) glucose, HbA1C, lipids (standard of care) and ii) storage for further metabolic research and biomarker studies for those participants consenting for to translational research. These samples should be drawn at the specified timepoint plus or minus 7 days. These samples must be taken after standard overnight fasting.	2.0
25	1.0	11-Nov-13	6.1 Schedule of Assessments table	25	Footnote 8- Additional timelines for blood tests relating to docetaxel	Liver function tests must be checked every 4 weeks from commencement of study drug for the first 4 months. This does not require a clinic visit or other assessments.	Clinical assessment, haematology and biochemistry tests should be performed prior to each cycle of docetaxel as per institutional standard of care. Liver function tests must be checked every 4 weeks from commencement of study drugs (LHRHA and assigned enzalutamide or NSAA) for the first 4 months. This does not require a clinic visit or other assessments.	2.0
26	1.0	11-Nov-13	7.7 Tertiary/Correlative Objectives	28	Clarification		Metabolic studies including glucose, HbA1C, lipids, insulin and IGF	2.0
27	1.0	11-Nov-13	8.2 Reporting of Serious Adverse Events (including SUSARs)	29	Correction	As per regulatory requirements, a SUSAR needs to be reported as soon as possible and not later than 7 days for a fatal event and 15 days for a non-fatal event.	As per regulatory requirements, a SUSAR needs to be reported as soon as possible and not later than 7 days for a fatal or life threatening event and 15 days for a non-fatal or non- life threatening event.	2.0
28	1.0	11-Nov-13	10.1.1	31	Correction	Enzalutamide should not be handled by pregnant women. Full details on product handling information are provided in the Investigator Brochure and Pharmacy Manual.	Full details on product handling information are provided in the Product information, Investigator Brochure and Pharmacy Manual.	2.0
29	1.0	11-Nov-13	11.1 Sample size	32	Updated information	A 25% reduction in the hazard of death is considered clinically plausible in light of the results of the AFFIRM trial of enzalutamide versus placebo in castration-resistant metastatic prostate cancer after chemotherapy, which showed a 37% reduction in the hazard of death, (11) and the PREVAIL trial of enzalutamide versus placebo for castration resistant metastatic prostate cancer before chemotherapy, which showed a 30% reduction in the hazard of death (Medivation Press Release 22 Oct 2013: http://www.astellas.com/en/corporate/news/pdf/131022_1_Eg.pdf).	A 25% reduction in the hazard of death is considered clinically plausible in light of the results of the AFFIRM trial of enzalutamide versus placebo in castration-resistant metastatic prostate cancer after chemotherapy, which showed a 37% reduction in the hazard of death, (11) and the PREVAIL trial of enzalutamide versus placebo for castration resistant metastatic prostate cancer before chemotherapy, which showed a 29% reduction in the hazard of death. (20)	2.0
30	1.0	11-Nov-13	11.2.2 Analysis of efficacy timepoints	32	Clarification	The sensitivity of treatment effect estimates to adjustment for baseline covariates will be explored.	The sensitivity of treatment effect estimates to adjustment for baseline covariates, including stratification factors, will be explored.	2.0

31	1.0	11-Nov-13	11.2.3 Analysis of safety endpoints	32	Updated information	A descriptive analysis of the AE data will be prepared for participants in the safety population. The number and percentage of participants who experience AEs will be tabulated according to CTCAE term/category, grade, and seriousness.	A descriptive analysis of the adverse events (AE) data will be prepared for participants in the safety population. The number and percentage of participants who experience AEs will be tabulated according to CTCAE term/category, grade, and seriousness. Safety will be monitored on an ongoing basis with regular review of Serious Adverse Events (SAE) by the Trial Management Committee. The frequency of complicated neutropenia (febrile neutropenia or infection G3-4 with neutropenia G3-4) will be monitored in real time in the first 49 participants having early docetaxel in each of the 2 randomly allocated treatment groups. Consideration will be given to modifying the protocol if complicated neutropenia is observed in 8 or more of the first 49 participants allocated enzalutamide with early docetaxel, or in 8 or more of the first 49 participants in allocated NSAA with early docetaxel. These numbers are required to distinguish the observed rate (of complicated neutropenia in each treatment group) from a rate of 25% (unacceptably high, alternate hypothesis) versus an assumed rate of 8% (acceptably low, null hypothesis) using a one-sample binomial test with 1-sided type 1 and type 2 errors of 5%.	2.0
32		11-Nov-13	11.3 Interim Analysis	33	Clarification	An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Results of the interim analysis will be reviewed by the study Independent Data Safety Monitoring Committee (IDSMC) described in Section 12.2. The IDSMC will also monitor selected safety endpoints. Consideration will be given to altering aspects of the study if: • The results of the interim analysis yield clear evidence of benefit or harm based on the O'Brien-Fleming approach specified section 11.1. • The conditional power of the study (evaluated at the time of the interim analysis) is unacceptably low (e.g. <20%) • The accrual/event rate is insufficient to complete the study in a reasonable time frame. • The rate of serious AEs (grade 3 to 5) in the enzalutamide arm is unacceptably high compared to the control arm. • Medical or ethical reasons emerge affecting continued performance of the study.	An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Results of the interim analysis will be reviewed by the study Independent Data Safety Monitoring Committee (IDSMC) described in Section 12.2. The IDSMC will also monitor selected safety endpoints, accrual and event rates. Consideration will be given to altering aspects of the study if: • The results of the interim analyses yield clear evidence of benefit or harm based on the O'Brien-Fleming approach specified section 11.1. • The conditional power of the study (evaluated at the time of the interim analyses) is unacceptably low (e.g. <20%) • The accrual/event rate is insufficient to complete the study in a reasonable time frame. • The rate of serious AEs (grade 3 to 5) in the enzalutamide arm is unacceptably high compared to the control arm. • The rate of complicated neutropenia in those receiving early docetaxel is unacceptably high (see Section 11.2.3). • Medical or ethical reasons emerge affecting continued performance of the study.	2.0
33	1.0	11-Nov-13	14 References	37	Additional references added		20. Beer TM, Armstrong AJ, Sternberg CN, et al. Enzalutamide in men with chemotherapy-naive metastatic prostate cancer (mCRPC): Results of phase III PREVAIL study. Journal of Clinical Oncology, 2014 Genitourinary Cancers Symposium (January 30 - February 1, 2014). Vol 32, No 4_suppl (February 1 Supplement), 2014: LBA1 21. Sweeney C, Chen YH, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial. J Clin Oncol 32:5s, 2014 (suppl; abstr LBA2). 22. A Phase 1b, Open-label, Safety and Tolerability Study of Oral MDV3100 in Combination with Docetaxel in Men with Advanced Prostate Cancer. MDV 3100-06 Clinical Trials Report. NCT01565928; Astellas, data on file. mdv3100-clr-en-src01, 2014. 23. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncology, 14(2), 149-58.	2.0

Minor administrative changes have also been made to formats and sub-section orders but these changes have not been documented above.

	ENZAMET Protocol Amendment from v2.0 07/Nov/2014 to v3 01/Mar/2018							
Change #	**Current Protocol version**	**Current Protocol date**	**Section amended**	**Page number in amended version**	**Change**	**Current wording**	**Wording in amendment**	**Version change**
1	2.0	07-Nov-14	Title page: Coordinating Centre & Coordinating Centre Lead	1	Updated information. Study team changes	Coordinating Centre for Ireland, UK and Europe= ICORG, Coordinating Centre Lead= TBA. Coordinating Centre for Canada= NCIC CTG, Coordinating Centre Lead= Wendy Parulekar	Coordinating Centre for Ireland, UK and Europe= Cancer Trials Ireland (CTRIAL-IE), Coordinating Centre Lead= Bryan Hennessy. Coordinating Centre for Canada= Canadian Cancer Trials Group (CCTG), Coordinating Centre Lead= Francisco Vera- Badillo	3.0
2	2.0	07-Nov-14	5.2 Dose modifications of study medications - Enzalutamide	17	Additional information	Enzalutamide: Participants who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with study drug. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day). Treatment interruption and re-initiation should be discussed with the study chair or delegate. If enzalutamide is co-administered with a strong CYP2C8 inhibitor (e.g. gemfibrozil), then the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, then the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.	Enzalutamide: Participants who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with study drug. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day). Treatment interruption and re-initiation should be discussed with the study chair or delegate. The dose of enzalutamide can be reduced to 120 mg/day for chronic long term grade 2 adverse events (including but not limited to fatigue or cognitive impairment) at the site investigator's discretion. The dose reduction and justification must be documented in the patient's notes. Dose modifications for other scenarios may be considered for the wellbeing of the participant, with the approval of the study sponsor and documentation in the medical record. If enzalutamide is co-administered with a strong CYP2C8 inhibitor (e.g. gemfibrozil), then the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, then the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.	3.0
3	2.0	07-Nov-14	5.3.1Concomitant Medications/Treatments (including early docetaxel use)- Recommended	18	Clarification	Recommended The following medications and treatments are standard of care for the prevention of osteoporosis during androgen deprivation therapy and should therefore be taken in this study: • Calcium Carbonate: Patients will receive concomitant treatment with calcium carbonate at a dose of at least 500 mg orally per day every day, e.g., CaltrateTM, TumsTM. Calcium is best absorbed when taken with meals. and • Vitamin D: Patients will receive concomitant treatment with vitamin D by oral administration of any multivitamin containing at least 400 IU of vitamin D.	Recommended The following medications and treatments are standard of care for the prevention of osteoporosis during androgen deprivation therapy and should therefore be taken in this study: • Calcium Carbonate: Patients will receive concomitant treatment with calcium carbonate at a dose of at least 500 mg orally per day every day, e.g., CaltrateTM, TumsTM. Calcium is best absorbed when taken with meals. and • Vitamin D: Patients will receive concomitant treatment with vitamin D by oral administration of at least 400 IU of vitamin D.	3.0
4	2.0	07-Nov-14	5.3.2.4.1 Dose modifications for docetaxel-Myelosuppression	20	Correction	a) Myelosuppression Dose modifications are to be made based on the granulocyte and/or platelet count drawn prior to planned treatment (can be done the day prior to planned dose): Docetaxel Neutrophils/10^9/L Day 1 of treament Platelet/10^9/L Day 1 of treatment No change >1.5 or > 100 Delay and reduce one dose level* <1.500 or < 100 NOTE: If a dose reduction is made, maintain the lower dose for all subsequent cycles. * If a dose is held due to myelosuppression, the patient will be retreated with a one level dose reduction once neutrophil count has recovered to at least 1.5 x 10^9/L and platelet count has recovered to at least 100 x 10^9/L. * If planned day 1 dose must be delayed for three consecutive weeks, discontinue docetaxel and continue on ADT alone.	a) Myelosuppression Dose modifications are to be made based on the granulocyte and/or platelet count drawn prior to planned treatment (can be done the day prior to planned dose): Docetaxel Neutrophils/10^9/L Day 1 of treament Platelet/10^9/L Day 1 of treatment No change ≥ 1.5 and ≥ 100 Delay and reduce one dose level* <1.5 or < 100 NOTE: If a dose reduction is made, maintain the lower dose for all subsequent cycles. * If a dose is held due to myelosuppression, the patient will be retreated with a one level dose reduction once neutrophil count has recovered to at least 1.5 x 10^9/L and platelet count has recovered to at least 100 x 10^9/L. * If planned day 1 dose must be delayed for three consecutive weeks, discontinue docetaxel and continue on ADT alone.	3.0
5	2.0	07-Nov-14	5.3.3 Use with caution	22	Additional information	Some drugs affect the metabolism of enzalutamide. Enzalutamide is metabolised by the liver and the cytochrome P450 pathways 2C8 and 3A4 are responsible for the metabolism of enzalutamide. Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when combining enzalutamide with drugs that are strong inducers or inhibitors of these CYP450 metabolic pathways. Where possible these drugs should be avoided. In settings where avoidance of these drugs is not possible, suggestions for dose reductions for enzalutamide are described in Section 5.2. Enzalutamide affects the metabolism of some drugs. Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted utilizing local laboratories.	Some drugs affect the metabolism of enzalutamide. Enzalutamide is metabolised by the liver and the cytochrome P450 pathways 2C8 and 3A4 are responsible for the metabolism of enzalutamide. Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when combining enzalutamide with drugs that are strong inducers or inhibitors of these CYP450 metabolic pathways. Where possible these drugs should be avoided. In settings where avoidance of these drugs is not possible, suggestions for dose reductions for enzalutamide are described in Section 5.2. Enzalutamide affects the metabolism of some drugs. Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted utilizing local laboratories. The 'Use with caution' medication list included in this protocol is not exhaustive. Please refer to the current approved enzalutamide Investigator Brochure.	3.0
6	2.0	07-Nov-14	5.4 Compliance	22	Clarification	Participant medication compliance will be formally determined by a tablet count out of the sight of the patient at 4 and 12 weeks after randomisation and the participant counselled appropriately if significant non-compliance is determined. Compliance at subsequent visits will be assessed by questioning the participant and recording if treatment has been taken as prescribed, and if not, the reasons and number of days of treatment missed.	Participant medication compliance will be formally determined by a count of tablets performed at the time of clinic review and out of sight of the participant at 4 and 12 weeks after randomisation. The participant will be counselled appropriately if significant non-compliance is determined. Compliance at subsequent visits will be assessed at the time of clinic review by questioning the participant, recording if treatment has been taken as prescribed and, if not, the reasons and number of days of treatment missed.	3.0
7	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 6	25	Clarification	Clinical assessment includes history and physical examination, performance status, weight and waist circumference.	A clinical assessment should be done at each study visit. Clinical assessment includes history, physical examination, performance status, and weight.The waist circumference need only be done and recorded at the baseline visit (both in the eCRF and in the patient's medical records). All visits after baseline include a review of any adverse events and physical examination as per standard of care for a patient at this stage of their disease and treatment. The fact that the patient has been seen and examined at that assessment, along with any relevant findings, should be recorded in the patient's notes.	3.0
8	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 7	25	Clarification	Bloods tests include, 1) Haematology: complete blood examination (CBE): Haemoglobin concentration, white cell count, platelet count, white cell differential. 2) Biochemistry: electrolytes, urea, creatinine (EUC); liver function tests (LFT): bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT) 3) Fasting bloods for i) glucose, HbA1C, lipids (standard of care) and ii) storage for further metabolic research and biomarker studies for those participants consenting to translational research. These samples should be drawn at the specified timepoint plus or minus 7 days. These samples must be taken after standard overnight fasting.	Bloods tests include, 1) Haematology: complete blood examination (CBE): Haemoglobin concentration, white cell count, platelet count, white cell differential. 2) Biochemistry: electrolytes, urea, creatinine (EUC); liver function tests (LFT): bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT) 3) Fasting bloods for i) glucose, HbA1C, lipids (standard of care) and ii) storage for further metabolic research and biomarker studies for those participants consenting to translational research. Baseline samples can be drawn within 7 days prior to start of randomised study treatment. Week 24 and first progression samples should be drawn at the specified timepoint plus or minus 7 days. These samples must be taken after standard overnight fasting. Fasting bloods due at PSA progression should be taken when PSA progression is confirmed by a second value 3 or more weeks later (i.e. a confirmed rising trend). For translational research bloods - even if the patient has not fasted, proceed with collecting the bloods. Then record that the patient has not fasted in the translational research documentation and eCRF.	3.0
9	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 9	26	Clarification	Imaging at baseline must include a CT or MRI of the abdomen and pelvis, and a radio-isotope whole body bone scan (WBBS). The chest can be imaged with either a plain x-ray, or a CT scan. However if lung nodules are identified on the CXR, then a CT scan of the chest must be performed.	Imaging at baseline must include a CT or MRI of the abdomen and pelvis, and a radio-isotope whole body bone scan (WBBS). Baseline scans are permitted up to 35 days before study treatment begins, provided that the patient starts study medication within 7 days after randomisation (window of 28 days before randomization + 7 days after randomization = 35 days in total). The chest can be imaged with either a plain x-ray, or a CT scan. However if lung nodules are identified on the CXR, then a CT scan of the chest must be performed. Scans at EOT, for any reason, should be done within 6 weeks. If PSA progression occurs within 6 weeks before EOT then the imaging (CT/MRI, CXR/CT chest and WBBS) does not need to be repeated. If the PSA progression occurs more than 6 weeks then the imaging does need to be repeated. If a patient subsequently commences other anticancer treatment within 6 weeks of the EOT scans, the scans do not need to be repeated, otherwise if > 6 weeks from the EOT scans, the scans should be repeated.	3.0
10	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 10	26	Clarification	Formal count of treatment tablets in experimental group (enzalutamide) and control group (NSAA tablets) at weeks 4 and 12	Formal count, in the clinic, of treatment tablets in experimental group (enzalutamide) and control group (NSAA tablets) at weeks 4 and 12. The enzalutamide bottles should be sent to pharmacy for drug reconciliation and destruction.	3.0
11	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 13	26	Additional wording		The following should be documented in the patient's medical notes: duration of any hospital stays, number of hospital visits, and number of office and clinic visits, since the last assessment. This includes review of correspondence from other sites confirming these hospital stays or visits. The outcome of this check should be recorded in the patient's notes. Note that admissions to hospital, or adverse events prolonging hospital stays, may constitute Serious Adverse Events.	3.0
12	2.0	07-Nov-14	6.2.5 Follow-up after completion of study treatment	27	Clarification	Study-specific follow-up assessments should be completed at the specified timepoints (± 2 weeks). Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol. If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries.	Study-specific follow-up assessments should be completed at the specified timepoints (± 2 weeks). Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol. If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries. Participants who discontinue protocol treatment (NSAA or enzalutamide) before clinical progression (for example stopped because of toxicity, patient or clinician preference, or PSA progression without clinical progression), should have the following assessments: 1. End of treatment assessments as per the protocol Schedule of Assessments 'At progression (PSA and clinical) and end of treatment for reasons other than progression' column. 2. A safety assessment performed 30-42 days after the last dose of study treatment 3. Continuing follow-up every 12 weeks until clinical progression, as per the "Every 12 weeks (±1 week) from randomisation until clinical progression" column of the Schedule of Assessments (underneath On Study Treatment). This is to ensure we have data about the time of any subsequent PSA and/or clinical progression. Translational bloods should be collected at the times of PSA and clinical progression, not when study treatment is stopped for other reasons.	3.0

13	2.0	07-Nov-14	7.7 Tertiary/Correlative Objectives	29	Clarification	These will include exploratory studies of tissue and blood samples to identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes). Studies may include, but are not limited to: - investigating variants of the androgen receptor (AR) - a steroid receptor transcription factor, and changes in plasma profiles (or plasma signature) in understanding mechanisms of resistance to enzalutamide; - investigations of how enzalutamide may work in people with prostate cancer; - studies that may help to understand the course of this cancer and related diseases; - biomarkers may be RNA-based (single entity or entire expressed genome, RNA, miRNA), DNA-based (single entity or whole genome, germ line or tumour related), protein-based or other entities and the consent form will allow patients to allow or limit use of specimens; - Metabolic studies including glucose, HbA1C, lipids, insulin, and IGF The treating doctor of the participant will be notified of any analytically or clinically valid findings that may emerge significant to the participant or their family regarding cancer; Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of biomarkers remains to be determined.	These will include exploratory studies of tissue and blood samples to identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes). Studies may include, but are not limited to: - investigating variants of the androgen receptor (AR) - a steroid receptor transcription factor, and changes in plasma profiles (or plasma signature) in understanding mechanisms of resistance to enzalutamide; - investigations of how enzalutamide may work in people with prostate cancer; - studies that may help to understand the course of this cancer and related diseases; - biomarkers may be RNA-based (single entity or entire expressed genome, RNA, miRNA), DNA-based (single entity or whole genome, germ line or tumour related), protein-based or other entities and the consent form will allow patients to allow or limit use of specimens; - Metabolic studies including glucose, HbA1C, lipids, insulin, and IGF The treating doctor of the participant will be notified of any analytically or clinically valid findings that may emerge significant to the participant or their family regarding cancer; Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment is a rapidly evolving research area, the definitive list of biomarkers remains to be determined.	3.0
14	2.0	07-Nov-14	8.1 Safety Reporting- Definitions- Adverse Events	30	Clarification	An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below). Adverse events include the following: - All suspected adverse drug reactions - All reactions from drug– overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate) - Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses - Injury or accidents. - Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination) - Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test). Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug. AEs must be reported as AEs even if they do not meet SAE criteria.	An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below). Adverse events include the following: - All suspected adverse drug reactions - All reactions from drug– overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate) - Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses - Injury or accidents. - Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination) - Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test). Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug. AEs must be reported as AEs even if they do not meet SAE criteria. All .adverse events should be recorded and graded in the patient's medical record, and in the eCRF form associated with the relevant visit.	3.0
15	2.0	07-Nov-14	8.2 Reporting of Serious Adverse Events (including SUSARs)	31	Additional information	The investigator in all participating countries is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the NHMRC Clinical Trials Centre within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention. SAE reports should be submitted to the CTC as per the procedure documented in the Study Manual. The CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The CTC will be responsible for providing reports to the Lead HREC in Australia and New Zealand and the regional coordinating centres in the other regions. The investigator must notify the local HREC as required. The CTC will submit 'reportable safety events' to the TGA in Australia and Medsafe in NZ, and to the regional coordinating centre to provide to the regulatory authorities as required in other participating countries in which the study is being conducted within the requisite timeframes, with a copy to Astellas with a copy to Astellas. As per regulatory requirements, a SUSAR needs to be reported as soon as possible and not later than 7 days for a fatal or life threatening event and 15 days for a non-fatal or non- life threatening event. The following information will be recorded for each Serious Adverse Event: • Event description including classification according to CTCAE v4.03 • SAE criterion • Attribution to study intervention (enzalutamide) • Expectedness (listed in IB for enzalutamide) • Action taken with study intervention (enzalutamide), including rechallenge (if done) • Outcome of SAE including end date if resolved	The investigator in all participating countries is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the NHMRC Clinical Trials Centre within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention. SAE reports should be submitted to the CTC as per the procedure documented in the Study Manual. The CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The CTC will be responsible for providing reports to the Lead HREC in Australia and New Zealand and the regional coordinating centres in the other regions. The investigator must notify the local HREC as required. The CTC will submit 'reportable safety events' to the TGA in Australia and Medsafe in NZ, and to the regional coordinating centre to provide to the regulatory authorities as required in other participating countries in which the study is being conducted within the requisite timeframes, with a copy to Astellas with a copy to Astellas. As per regulatory requirements, a SUSAR needs to be reported as soon as possible and not later than 7 days for a fatal or life threatening event and 15 days for a non-fatal or non- life threatening event. The following information will be recorded for each Serious Adverse Event*: • Event description including classification according to CTCAE v4.03 • SAE criterion • Attribution to study intervention (enzalutamide) • Action taken with study intervention (enzalutamide), including rechallenge (if done) • Outcome of SAE including end date if resolved *Please note that site staff (investigators, data-managers, study nurses) should not complete the expectedness fields for SAE. Assessments of expectedness for SAE will be completed by the trial sponsor. Surgical/medical procedures that require an overnight admission as an inpatient should be reported as an SAE, but the diagnosis labelling the SAE should be the problem being treated, not the procedure being done. For example, if a patient is admitted for such an operation, then the SAE should be labelled with the diagnosis/problem for which the operation was done, not the operation itself. For example, overnight admission for excision of localised skin cancer should be reported as a new malignancy, not as an excision. This includes both planned (elective) and emergency procedures.	3.0
16	2.0	07-Nov-14	10.1.3 Study Drug Accountability	32	Additional information	The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate. Patients will be asked to return unused drug and empty drug containers at each return visit.	The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate. Patients will be asked to return unused drug and empty drug containers at each return visit. Drug accountability logs will be requested, as required, from each pharmacy for central review by each regional coordinating centre.	3.0
17	2.0	07-Nov-14	11.1 Sample size	33	Additional information	A trial comprising 1,100 participants that are followed until approximately 470 deaths are observed (e.g. over a 2 year recruitment with an additional follow-up of 3.5 years) provides over 80% power to detect a 25% reduction in the hazard of death with a 2-sided type 1 error of 0.05 assuming a 3-year survival rate of 65% amongst controls. A 25% reduction in the hazard of death is considered clinically plausible in light of the results of the AFFIRM trial of enzalutamide versus placebo in castration-resistant metastatic prostate cancer after chemotherapy, which showed a 37% reduction in the hazard of death, (11) and the PREVAIL trial of enzalutamide versus placebo for castration resistant metastatic prostate cancer before chemotherapy, which showed a 29% reduction in the hazard of death. (20) The design incorporates a formal interim analysis performed on overall survival once 2/3 of the required events are observed. The interim analysis allows for early rejection of the null hypothesis using an O'Brien-Fleming boundary. The critical value for |Zk| is 2.45 for the interim analysis and 2.00 for the final analysis. The conditional power of the study will also be calculated at the interim analysis.	A trial comprising 1,100 participants that are followed until approximately 470 deaths are observed (e.g. over a 2 year recruitment with an additional follow-up of 3.5 years) provides over 80% power to detect a 25% reduction in the hazard of death with a 2-sided type 1 error of 0.05 assuming a 3- year survival rate of 65% amongst controls. A 25% reduction in the hazard of death is considered clinically plausible in light of the results of the AFFIRM trial of enzalutamide versus placebo in castration-resistant metastatic prostate cancer after chemotherapy, which showed a 37% reduction in the hazard of death, (11) and the PREVAIL trial of enzalutamide versus placebo for castration resistant metastatic prostate cancer before chemotherapy, which showed a 29% reduction in the hazard of death. (20) The design incorporates formal interim analyses performed on overall survival using the Lan-DeMets O'Brien-Fleming spending function approach.	3.0
18	2.0	07-Nov-14	11.2.1 Timing of analyses	33	Updated timing of analyses transferred to new Section 11.4	11.2.1 An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Assuming the study is not terminated early, the final analysis is planned to be undertaken after the required number of deaths have occurred.	Please see new Section 11.4, below	3.0
19		07-Nov-14	11.2.2 Analysis of Efficacy Endpoints	33	Changed to 11.2.1 -Analysis of Efficacy Endpoints - additional information added	The primary analysis will be a comparison of overall survival (OS) in the two treatment arms using a log-rank test. Kaplan-Meier curves for OS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression. The sensitivity of treatment effect estimates to adjustment for baseline covariates, including stratification factors, will be explored. Other time-to-event endpoints will be analysed in a comparable fashion to the primary endpoint. The QoL scores collected longitudinally will be analysed using appropriate linear models for repeated measures data.	The primary analysis will be a comparison of overall survival (OS) in the two treatment arms using a log-rank test. Kaplan-Meier curves for OS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression. Other time-to-event endpoints will be analysed in a comparable fashion to the primary endpoint. The sensitivity of the treatment effect estimate on OS to adjustment for baseline covariates, including stratification factors, will be explored. Subgroup analyses will be performed for geographical region, volume of disease strata, and docetaxel strata (additional analyses may be specified in the statistical analysis plan). An evaluation of the treatment effect in the subgroup of high volume disease patients in the docetaxel stratum will also be performed. These subgroup analyses will be performed on OS, and repeated for PSA PFS and clinical PFS endpoints. The QoL scores collected longitudinally will be analysed using appropriate linear models for repeated measures data. Subgroup analyses on QoL endpoints will be performed by docetaxel strata and by symptom severity on baseline QoL.	3.0
20	2.0	07-Nov-14	11.2.3 Analysis of Safety Endpoints	34	Changed to 11.2.2 Analysis of Safety Endpoints	Section number change only	Section number change only	3.0
21	2.0	07-Nov-14	11.2.4 Analysis of Health Outcomes Relative to Costs	34	Changed to 11.2.3 Analysis of Health Outcomes Relative to Costs	Section number change only	Section number change only	3.0
22	2.0	07-Nov-14	11.3 Interim analyses	34	Clarification	An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Results of the interim analysis will be reviewed by the study Independent Data Safety Monitoring Committee (IDSMC) described in Section 12.2. The IDSMC will also monitor selected safety endpoints, accrual and event rates. Consideration will be given to altering aspects of the study if: • The results of the interim analyses yield clear evidence of benefit or harm based on the O'Brien-Fleming approach specified section 11.1. • The conditional power of the study (evaluated at the time of the interim analyses) is unacceptably low (e.g. <20%) • The accrual/event rate is insufficient to complete the study in a reasonable time frame. • The rate of serious AEs (grade 3 to 5) in the enzalutamide arm is unacceptably high compared to the control arm. • The rate of complicated neutropenia in those receiving early docetaxel is unacceptably high (see Section 11.2.3). • Medical or ethical reasons emerge affecting continued performance of the study.	Interim analyses on OS are planned as per Section 11.4. Interim results will be reviewed by the study Independent Data Safety Monitoring Committee (IDSMC) described in Section 12.2. The IDSMC will also monitor selected safety endpoints, accrual and event rates. Consideration will be given to altering aspects of the study if: • The results of the interim analyses on OS yield clear evidence of benefit or harm based on the Lan-DeMets O'Brien-Fleming spending function approach (Section 11.4). • The conditional power of the study (evaluated at the time of the interim analyses) is unacceptably low (e.g. <20%) • The accrual/event rate is insufficient to complete the study in a reasonable time frame. • The rate of serious AEs (grade 3 to 5) in the enzalutamide arm is unacceptably high compared to the control arm. • The rate of complicated neutropenia in those receiving early docetaxel is unacceptably high (see Section 11.2.2). • Medical or ethical reasons emerge affecting continued performance of the study.	3.0

23	2.0	07-Nov-14	11.4 Frequency and timing of Interim Analyses	34	Additional information		Versions 1 and 2 of the ENZAMET protocol specified an interim analysis on OS would be performed at 67% of the required events (i.e. 470 deaths, see Section 11.1). Following simultaneous publication in June 2017 of two randomized controlled trials, LATITUDE[24] and STAMPEDE[25], the ENZAMET Trial Management Committee decided to add two extra interim analyses at 50% and 80% of required events. No interim efficacy data from ENZAMET was considered or used to reach this decision. The Lan-DeMets O'Brien-Fleming spending function approach will be used, and remains the appropriate technique for evaluating these analysis results. LATITUDE and STAMPEDE evaluated abiraterone (a CYP17 inhibitor) in a similar clinical setting to ENZAMET. Both studies obtained estimated HRs for OS that were more impressive than had been hypothesised when these studies were designed. Abiraterone has a different mechanism of action to enzalutamide (i.e. inhibition of androgen synthesis versus blocking the androgen receptor), but both drugs target the androgen-signalling pathway. Abiraterone and enzalutamide have similar effects on survival time in castration-resistant prostate cancer.[6, 7] Thus the results of LATITUDE and STAMPEDE have major implications for informing the hypothesised effect that enzalutamide may have on OS in ENZAMET. However, the control event rate for ENZAMET is anticipated to be lower than for LATITUDE or STAMPEDE because those trials did not mandate the use of an NSAA in their control arms, or have provision for early docetaxel use. These factors could possibly also attenuate the observed effect of enzalutamide in ENZAMET relative to the observed effects of abiraterone in LATITUDE and STAMPEDE. Taking all these considerations into account, and without appraising any interim ENZAMET outcome results, the international ENZAMET Trial Management Committee concluded that a stronger treatment effect than originally hypothesized is plausible, and decided to conduct interim analyses at 50%, 67%, and 80% of the required events to minimize delays in the detection of such an effect.	3.0
24	2.0	07-Nov-14	12.1 Trial Steering Committee	35	Clarification	The international Trial Management Committee (TMC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). The international TMC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on interim analyses or other information. Each regional trial coordinating centre will identify a clinical lead and a coordinating centre lead who will represent the region on the international TMC.	The International Trial Steering Committee (ITSC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). The ITSC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on interim analyses or other information. Each regional trial coordinating centre will identify a clinical lead and a coordinating centre lead who will represent the region on the ITSC.	3.0
25	2.0	07-Nov-14	13.8 Publication Policy	37	Clarification	Authorship recognises the intellectual contributions of investigators and others to a study. It also identifies those who take public responsibility for the study. Authorship is defined as per ICMJE guidelines (www.icmje.org).The International Trial Management Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. The Writing Committee will develop a publication plan, including authorship, target journals, and expected dates of publication. The first publication will be the report of the full trial results based on the main protocol using the study group name with a list of specific contributions at the end. ANZUP and CTC will be acknowledged in all publications. All publications must receive prior written approval from the TMC prior to submission.	Authorship recognises the intellectual contributions of investigators and others to a study. It also identifies those who take public responsibility for the study. Authorship is defined as per ICMJE guidelines (www.icmje.org).The International Trial Steering Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. The Writing Committee will develop a publication plan, including authorship, target journals, and expected dates of publication. The first publication will be the report of the full trial results based on the main protocol using the study group name with a list of specific contributions at the end. ANZUP and CTC will be acknowledged in all publications. All publications must receive prior written approval from the International Trial Steering Committee prior to submission.	3.0
26	2.0	07-Nov-14	References	39	Addition of references 24 and 25		24. Fizazi, K., et al., Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. New England Journal of Medicine, 2017. 377(4): p. 352-360. 25. James, N.D., et al., Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. New England Journal of Medicine, 2017. 377(4): p. 338-351.	3.0

Minor administrative changes have also been made to formats and sub-section orders but these changes have not been documented above.

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: ENZAMET

Protocol number: ANZUP 1304
Protocol version: Version 2, 7 November, 2014
Supersedes Version 1 (11 November, 2013)

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The University of Sydney

Protocol Development Working Party

In addition to those listed on the previous page, the following individuals also made substantial contributions to this protocol:

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ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse events
AR	Androgen receptor
CT	Computed tomography (scan)
CRF	Case report form
CTC	NHMRC Clinical Trials Centre, University of Sydney
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DFCI	Dana Farber Cancer Institute
DRG	Diagnosis Related Groups
EBRT	External beam radiation therapy
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	Euroqol 5 item preference-based measure of health (5L)
FDHT	Fluoro dihydrotestosterone
GSA	Group Specific Appendix
HRQL	Health-Related Quality of Life
IC_{50}	50% maximal inhibitory concentration
ICER	Incremental cost effectiveness ratio
ICORG	All Ireland Cooperative Oncology Research Group
LHRHA	Luteinizing Hormone Releasing Hormone Analogue
MBS	Medicare Benefits Scheme (Australia)
NCIC CTG	Canadian NCIC Clinical Trials Group
NSAA	Non-steroidal anti androgen
OS	Overall survival
PBS	Pharmaceutical Benefits Scheme (Australia)
PCWG2	Prostate Cancer Working Group 2 (see Appendix 3)
PFS	Progression free survival
PR-25	EORTC Quality of Life Questionnaire for Prostate Cancer (25 items)
PSA	Prostate Specific Antigen
QLQ-C30	EORTC Core Quality of Life Questionnaire (30 items)
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
ULN	Upper limit of normal range
USYD	University of Sydney
WBBS	Whole Body Bone Scan

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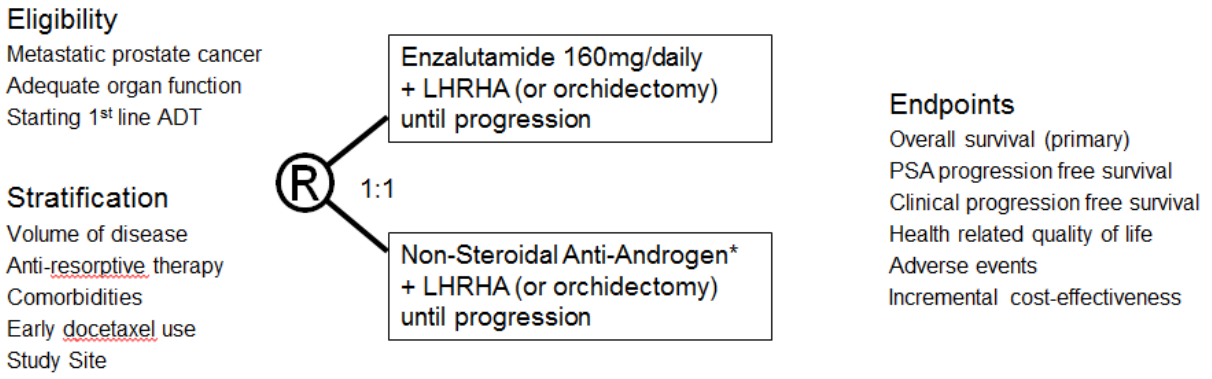
SYNOPSIS

Background	Combined androgen deprivation therapy (ADT) with a luteinising hormone releasing hormone analogue (LHRHA) or surgical castration, plus a conventional non-steroidal anti-androgen (NSAA: bicalutamide, nilutamide, or flutamide), is widely used as initial treatment for hormone-sensitive prostate cancer. Meta-analysis of RCTs showed a 3% absolute improvement in 5 year survival rates with the addition of a conventional NSAA to a LHRHA or surgical castration (1). Residual, low level androgen receptor AR signalling, or agonist activity from conventional NSAA, may provide a stimulatory signal to hormone-sensitive prostate cancer cells. We hypothesize that early use of enzalutamide, a more potent and effective androgen receptor blocker, will reduce residual androgen receptor signalling, and thereby improve outcomes.
General aim	To determine the effectiveness of enzalutamide, versus a conventional NSAA, when combined with a LHRHA or surgical castration, as first line androgen deprivation therapy (ADT).
Primary objective (endpoint)	To determine effects on: 1) Overall survival (death from any cause)
Secondary objectives (endpoints)	To determine effects on: 2) Prostate specific antigen progression free survival (PCGW2) 3) Clinical progression free survival (imaging, symptoms, signs) 4) Adverse events (CTCAE v4.03) 5) Health related quality of life (EORTC QLQ C-30, PR-25 and EQ-5D-5L) 6) Health outcomes relative to costs (incremental cost effectiveness ratio)
Tertiary/Correlative objectives	7) To identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes)
Design	Open label, randomised, 2-arm, multi-centre, phase 3 clinical trial, stratified for volume of disease, use of early docetaxel, antiresorptive therapy, study site, and comorbidities.
Population	The target population is men with metastatic prostate cancer commencing androgen deprivation therapy. Key eligibility criteria include metastatic prostate cancer, adequate organ function and ECOG performance status 0-2.
Study treatments	Participants randomised to: • Enzalutamide 160mg daily, by mouth, until disease progression or prohibitive toxicity (experimental group). OR • Conventional NSAA, by mouth, until disease progression or prohibitive toxicity (control group). All participants are treated with a LHRHA or surgical castration.

Assessments	Assessments at baseline, day 29, week 12, and then every 12 weeks from randomisation until evidence of clinical progression. Imaging with CT scan and whole body bone scan at baseline and at evidence of PSA or clinical progression (whichever occurs first). Blood tests for translational studies at baseline, day 29, week 24, and end of study treatment.
Statistical considerations	A trial of 1,100 participants followed until approximately 470 deaths are observed (e.g. 2 year recruitment plus 3.5 years follow-up) provides at least 80% power to detect a 25% reduction in the hazard of death with a logrank test evaluated at the 2-sided 5% level of significance assuming a 3-year survival rate of 65% amongst controls.

SCHEMA



1,100 participants
2 years accrual + 3.5 years minimum additional follow-up
80% power to detect 25% reduction in the hazard of death from any cause, assuming an OS rate at 3 years of 65% in the control group

*Conventional Non-Steroidal Anti-Androgens: bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg tid

1 BACKGROUND

Prostate cancer is often diagnosed when apparently localized to the prostate gland. However, metastatic disease can occur after surgery or radiation therapy given with curative intent or present as de novo metastatic disease. For cancer that has spread beyond the prostate, androgen suppression for hormone sensitive disease and then subsequent new generation hormonal therapies (enzalutamide, abiraterone), cytotoxic therapy and vaccine therapy for castration resistant prostate cancer (CRPC) can delay and/or cause cancer regression and increase the chance a man will live longer but are not able to cure metastatic prostate cancer. This protocol is based on the hypothesis that earlier use of a therapy shown to be effective in the more advanced state of castration resistant prostate cancer will prevent or delay the emergence of castration resistant disease and will prolong overall survival. As such this protocol aims to determine whether the potent second generation androgen receptor inhibitor, enzalutamide can enhance the ability of androgen suppression to increase the longevity of men commencing androgen suppression for newly metastatic prostate cancer.

The current treatment for patients commencing hormonal therapy for metastatic prostate cancer is androgen suppression either by LHRH analogue therapy or orchidectomy as monotherapy or in combination with an anti-androgen, also known as combined androgen deprivation therapy. Survival varies depending on the extent of disease at commencement of therapy. With the advent of the PSA test many patients are commenced on hormonal therapy at a very early stage (biochemical recurrence) and subjected to the long-term effects of androgen deprivation including osteoporosis. However, if patients with an asymptomatic rising PSA after definitive local therapy are observed until they develop overt metastatic disease (i.e. evident by imaging techniques), the median time from PSA relapse to clinical progression is approximately 8 years. In the pre-PSA era, studies relied upon bone scan and CT scans to document the presence of metastatic disease.

The median overall survival for men commencing androgen deprivation therapy with clinically evident metastatic disease (i.e. not PSA only disease) is about 30 months(1). This information is derived from a meta-analysis including 8,275 men in 27 randomized trials comparing castration alone (medical or surgical) versus combined androgen deprivation therapy including an oral, peripheral anti-androgen (previously known as maximal or combined androgen blockade). This individually updated patient-data meta-analysis showed that overall survival was not improved by the addition of a peripheral anti-androgen when all trials were analysed together. However, a planned subgroup analysis showed that overall survival at 5 years was approximately 3% higher (2p=0.005) in patients assigned combined androgen blockade including a Non-Steroidal Anti-Androgen (NSAA, nilutamide or flutamide) than control patients, and approximately 3% lower (2p=0.04) in patients assigned cyproterone compared with control patients.

The treatment of patients with newly diagnosed metastatic disease is heterogeneous. Some clinicians start treatment with castration alone, and only add a peripheral anti-androgen on progression, while others start treatment with combined androgen deprivation therapy. Both approaches are considered within the range of standard practice. Progression on combined androgen deprivation therapy eventually occurs in most patients, and is thought to be related to either residual low level AR signalling or to agonist activity from older anti-androgens. These may provide a survival signal or escape mechanism to metastatic hormone-sensitive prostate cancer cells. It is possible that a more effective and profound AR blockade with a more potent androgen receptor blocker like enzalutamide might therefore eliminate any such survival signal and improve progression free survival.

Phase 3 studies are ongoing or have recently been performed with the goal of improving the efficacy or tolerability of therapy for metastatic disease. Specifically, intermittent versus continuous dosing LHRH analogue suppression of testosterone in men who responded to therapy has been reported in a large randomized phase 3 SWOG trial (2). Specifically, in this study of 3040 men, 1535 achieved a PSA of < 4 in the induction phase and were randomized. The Hazard Ratio for death with intermittent dosing was 1.10; 90% CI - 0.99 to 1.23 and exceeded the upper boundary for non-inferiority (i.e. cannot rule out a 20% greater risk of death

with intermittent versus continuous therapy). However, there were too few events to rule out significant inferiority of intermittent therapy. A number of studies are comparing ADT plus docetaxel versus ADT alone in men commencing therapy for newly metastatic prostate cancer. The French study of 385 patients reported improvements in times to PSA and clinical progression but not overall survival (3). The US based ECOG E3805 CHAARTED study with 780 patients and the UK STAMPEDE study had not reported their outcomes by July of 2013. Studies of ADT with or without cytochrome P450 inhibitors (abiraterone and TAK700) with activity in CRPC were commenced in 2012 and 2013.

Once progression is documented with a testosterone less than 50ng/dL, the disease is referred to as castration resistant prostate cancer. Recent advances in our understanding of the molecular basis of CRPC have led to a growing number of innovative therapies that target these resistance mechanisms. Moreover, six agents prolong the longevity of a man with CRPC. These include two cytotoxic agents (docetaxel (4) and cabazitaxel (5)), two hormonal therapies (abiraterone (6) and enzalutamide (7)), an alpha-emitting radiopharmaceutical (radium-223 chloride(8)) and an immune therapy (sipuleucel-T (9)). Denosumab, a RANK-ligand inhibitor blocking NFκB mediated effects in the bone micro-environment, delays bone events, such as pathological fractures, more effectively than the bisphosphonate, zoledronic acid. (10) Unfortunately, none of these therapies cure CRPC.

A rational strategy to improve the efficacy of testosterone suppression for patients commencing therapy for metastatic prostate cancer would be to take agents which are proven to be effective in the metastatic setting and attempt to use them when starting therapy for metastatic disease. Enzalutamide has proven highly effective at reducing overall mortality in men with castrate-resistant metastatic prostate cancer and has a tolerable side-effect profile, making it an attractive candidate for testing in the up-front metastatic setting (11). Enzalutamide is a rationally-designed second generation androgen receptor (AR) inhibitor which competitively binds the AR with great potency. Additionally, enzalutamide inhibits nuclear translocation of activated AR and inhibits the association of activated AR with DNA (12).

Preclinical Data with Enzalutamide

Using the non-steroidal agonist RU59603 as the parent scaffold compound, Sawyers and colleagues identified two oral diarylthiohydantoins, RD162 and enzalutamide, from a screen of non-steroidal anti-androgens that retain anti-androgen activity in the setting of increased AR expression (12). Both compounds have enhanced affinity for the AR (5-8 fold) compared to the anti-androgen bicalutamide. Enzalutamide competitively binds the AR with an **IC_{50}** of 36 nM compared to 160 nM for bicalutamide. Additionally, enzalutamide inhibits nuclear translocation of activated AR, inhibits DNA binding to androgen response elements, and inhibits recruitment of co-activators, even in the setting of AR over expression and in prostate cancer cells resistant to anti-androgens. By contrast with bicalutamide, enzalutamide is a pure antagonist with no detectable agonist effects in LNCaP/AR prostate cells, which over express AR. The drug also induces regression of established LNCaP/AR xenograft tumours growing in castrated male mice, a model in which bicalutamide treatment only slows tumour growth.

Clinical Data with Enzalutamide

A phase I/II first in man study in patients with progressive, metastatic CRPC was initiated in July 2007 to assess safety, pharmacokinetics, tolerability, and antitumor activity (13). After administration of one dose, the drug was rapidly absorbed, and median time to Cmax was one hour (range 0.42 minutes – 4 hours). The t1/2 was about 1 week (range 3 – 10 days) and was not affected by dose. Full pharmacokinetic profiles were linear and consistent over the dose range study. Plasma concentrations reached steady state after one month of treatment. Once achievement of steady state, the Cmin in individual patients remained constant for several months, suggesting time-linear pharmacokinetics. Due to slow clearance from plasma, the daily fluctuation in steady-state enzalutamide concentrations was low. The mean Cmax/Cmin was 1.2 (range 1.14-1.3) indicating that the average difference between the peak and trough concentrations was ≤ 30%. AR binding was assessed in 22 patients at doses from 60-480 mg daily with FHDT-PET. All patients showed clear reduction of FDHT uptake (range 20-100%).

Fatigue was the most frequently reported adverse event, with dose-dependent increases of grade 3 fatigue (0% at 150 mg/day, 9% at 240 mg/day, 15% at 360 mg/day, and 20% at 480

mg/day). The dose of 240 mg/day was defined as the maximum tolerated dose. At doses of 240 mg and above, an increasing proportion of patients needed dose reductions for fatigue. Dose reductions were needed in 1 of 29 patients (3%) that received 240 mg/day, 3 of 28 patients (11%) that received 360 mg/day, and 5 of 22 patients (23%) that received 480 mg/day, and 0 of 58 patients that received 30, 60, or 150 mg/day. After dose reductions, the symptoms resolved. Only 1 patient discontinued treatment due to fatigue with an onset coinciding with PSA rise. Overall, the most common mild (grade 2) adverse events were fatigue (n = 38, 27.1%), nausea (n = 12, 8.6%), dyspnoea (n = 11, 7.9%), anorexia (n = 8, 5.7%), and back pain (n = 8, 5.7%). Fatigue, nausea, and anorexia were the only mild adverse events with an increasing incidence as the dose of enzalutamide was increased. None of the grade 2 events required dose modification or the discontinuation of treatment, apart from 1 patient treated at 480 mg/day who had nausea at baseline and stopped therapy after 7 weeks.

Two witnessed seizures occurred in patients receiving doses of 600 and 360 mg/day, and 1 possible seizure occurred at 480 mg/day. Both patients also had complicated medical problems that could have contributed to their seizures. Other causes of treatment discontinuation included rash in 1 patient that received 480 mg/day after 10 days and in 1 patient that received 600 mg/day after 3 days, and a myocardial infarction after 15 weeks of therapy in a patient with a history of diabetes, hypertension, and hypercholesterolemia that received 360 mg/day. All patients recovered without sequelae. No deaths and no other drug-related SAEs were reported.

In regard to efficacy, antitumor effects were noted at all doses including >50% declines in PSA in 78 (56%) patients, response in soft tissue in 13 (22%) of 59 patients, stabilized bone disease in 61 (56%) of 109 patients, and conversion from unfavourable to favourable circulating tumour cell (CTC) counts in 25 (49%) of 51 patients. Disease regression was dose dependent between daily doses of 30 mg and 150 mg, however no additional benefit was noted above this threshold.

Based on these results, two placebo-controlled, randomized phase 3 studies (AFFIRM and PREVAIL) were initiated to evaluate the efficacy and safety of enzalutamide in patient with advanced prostate cancer. The AFFIRM study evaluated the safety and efficacy of enzalutamide in 1,199 patients with CRPC after chemotherapy with docetaxel (11). Patients were randomized in a 2:1 ratio to receive oral enzalutamide at a dose of 160 mg per day or placebo. The primary endpoint was OS. The study was stopped after a planned interim analysis at the time of 520 deaths. The median OS was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR 0.63, 95% CI 0.53-0.75, p<0.001). The superiority of enzalutamide over placebo was shown with respect to all secondary endpoints: ≥50% PSA reduction (54% vs. 2%, p<0.001), soft-tissue response rate (29% vs. 4%, p<0.001), the quality-of-life response rate (43% vs. 18%, p<0.001), time to PSA progression (8.3 vs. 3.0 months, p<0.001), time to first SRE (16.7 vs. 13.3 months, p<0.001).

The rates of AEs between the enzalutamide and placebo group were similar. The enzalutamide group had a lower incidence of adverse events of grade 3 or above (45.3% vs. 53.1%). The median time to first AE was 12.6 months in the enzalutamide group compared to 4.2 months in the placebo group. There was a higher incidence of all grades of fatigue, diarrhoea, hot flushes, musculoskeletal pain, and headache in the enzalutamide group compared to placebo. Cardiac disorders were noted in 6% of patients receiving enzalutamide and in 8% of patients receiving placebo. Hypertension was observed in 6.6% of patients in the enzalutamide group compared to 3.3% in the placebo group. LFT abnormalities were reported as adverse events in 1% and 2% of the enzalutamide and placebo group, respectively. Five of the 800 patients in the enzalutamide group (0.6%) were reported to have seizures and no seizures were reported in the placebo group. One case of status epilepticus required medical intervention while the other four seizures were self-limited. There were potentially predisposing factors in several patients, including two patients who had brain metastases, one patient who had inadvertently been administered lidocaine intravenously, and one patient with brain atrophy in the context of heavy alcohol use and initiation of haloperidol. Based on the results of this trial, the FDA approved enzalutamide August 2012 for the treatment of patients with metastatic CRPC who have previously received docetaxel.

Results were recently released from the second interim analysis of PREVAIL, a double-blinded, randomized, placebo-controlled trial, investigating the effectiveness of 160mg daily enzalutamide in patients with metastatic CRPC who had not yet received chemotherapy. The trial was stopped early and unblinded at the recommendation of the independent data and safety monitoring committee because of a substantial benefit in OS that met the pre-specified stopping rule: hazard ratio for overall survival 0.70; 95% confidence interval, 0.59-0.83, p<0.0001, median survival 32 versus 30 months) and radiological PFS (hazard ratio for radiological PFS 0.19; 95% confidence interval, 0.15-0.23, p < 0.0001). (20)

"Early chemotherapy" refers to the combined use of ADT plus docetaxel as first line therapy for metastatic prostate cancer as tested in the CHAARTED trial (E3805).(21) In the CHAARTED trial, early chemotherapy consisted of docetaxel 75mg/m^2 given for 6 cycles and was commenced a median of 1 month from the start of ADT. This improved median OS from 44 months with ADT alone to 57 months with early chemotherapy (HR 0.61, 95% CI 0.48-0.82, P=0.0003) and a median time to clinical progression of 33 months versus 20 months (HR 0.49, 95% CI 0.37-0.65, p<0.0001). The survival benefit was most evident in patients with high volume disease: HR 0.62, 95% CI 0.46-0.83, 17 month improvement in median OS from 32 to 49 months. There was a trend of similar magnitude for a survival benefit in men with low volume disease (HR 0.58, 95% CI 0.31-1.08), but the smaller number of events meant this was still within the play of chance.

Early chemotherapy in GETUG15 did not result in a survival benefit. (23) However, the participants in GETUG15 were predominantly men with low volume disease (80% of study population) compared with CHAARTED where approximately one third of the participants had low volume disease. Despite no significant difference in OS, there were significant improvements in biochemical PFS and clinical PFS. Biochemical PFS in the group treated with ADT plus docetaxel was 23 months versus 13 months in the group treated with ADT alone (HR 0.72, 95% CI 0.57–0.91; p=0.005). Similarly, clinical PFS was significantly longer in the group treated with ADT and docetaxel than in the group given ADT alone (medians of 24 months versus 15 months, HR 0.75, 95% CI 0.59–0.94; p=0.015).

Use of early chemotherapy is likely to become standard of care for selected men with hormone-naïve, metastatic prostate cancer. Version 2 of the ENZAMET trial protocol anticipates this likely change in standard practice by allowing and stratifying for the use of early chemotherapy with docetaxel.

There are limited data about the use of docetaxel together with enzalutamide. A phase I trial showed no significant effect of enzalutamide on peak concentrations of docetaxel in men with castration-resistant, metastatic prostate cancer (Astellas; data on file). However, 4 of the 22 participants in this study experienced febrile neutropenia. More data are required to confirm the safety of using docetaxel together with enzalutamide.

The purpose of ENZAMET is to determine whether enzalutamide in combination with androgen suppression can increase the longevity of men commencing androgen suppression for newly diagnosed metastatic prostate cancer.

2 AIM AND OBJECTIVES

General aim	To determine the effectiveness of enzalutamide versus a conventional NSAA, when combined with a LHRHA or surgical castration, as first line androgen deprivation therapy (ADT).
Primary objective (endpoint)	To determine effects on: 1) Overall survival (death from any cause)
Secondary objectives (endpoints)	To determine effects on: 2) Prostate specific antigen progression free survival (PCGW2) 3) Clinical progression free survival (imaging, symptoms, signs) 4) Adverse events (CTCAE v4.03) 5) Health related quality of life (EORTC QLQ C-30, PR-25 and EQ-5D-5L) 6) Health outcomes relative to costs (incremental cost effectiveness ratio)
Tertiary/Correlative objectives	7) To identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes)

3 DESIGN

This is a multicentre, open label, randomised, phase 3 trial.

Participants will be allocated to treatment via a central randomisation system that stratifies for:

1. High volume disease (yes versus no), characterised as:
   - 4 or more bone metastases, one of which is outside the vertebral column and pelvis AND/OR
   - Visceral metastases (e.g. lung, pleura, liver, adrenal and others)

   Lymph node involvement or bladder invasion do NOT qualify as visceral disease.
2. Study site
3. Concomitant “anti-resorptive” therapy to delay skeletal related events when commencing ADT (denosumab, zoledronic acid or any other therapy at doses proven to prevent SRE. This does not include the use of these drugs at lower doses or frequencies for the treatment or prevention of osteoporosis).
4. Co-morbidities according to the Adult Co-morbidity Evaluation (ACE-27: 0-1 vs 2-3)
5. Early use of docetaxel defined as use of docetaxel in conjunction with initiation of ADT.

4 STUDY POPULATION

Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of randomisation. All enquiries about eligibility should be addressed by contacting the CTC prior to randomisation.

4.1 Target Population

Men starting first line androgen deprivation therapy for metastatic prostate cancer.

4.2 Inclusion criteria

1. Male aged 18 or older with metastatic adenocarcinoma of the prostate defined by
   - Documented histopathology or cytopathology of prostate adenocarcinoma from a biopsy of a metastatic site

     OR
   - Documented histopathology of prostate adenocarcinoma from a TRUS biopsy, radical prostatectomy, or TURP and metastatic disease consistent with prostate cancer.

     OR
   - Metastatic disease typical of prostate cancer (i.e. involving bone or pelvic lymph nodes or para-aortic lymph nodes) AND a serum concentration of PSA that is rising and >20ng/mL
2. Target or non-target lesions according to RECIST 1.1
3. Adequate bone marrow function: Hb ≥100g/L and WCC ≥ 4.0 x 10^9/L and platelets ≥100 x 10^9/L.
4. Adequate liver function: ALT < 2 x ULN and bilirubin < 1.5 x ULN, (or if bilirubin is between 1.5-2x ULN, they must have a normal conjugated bilirubin). If liver metastases are present ALT must be < 5xULN
5. Adequate renal function: calculated creatinine clearance > 30 ml/min (Cockroft-Gault, See Appendix 7)
6. ECOG performance status of 0-2. Patients with performance status 2 are only eligible if the decline in performance status is due to metastatic prostate cancer.
7. Study treatment both planned and able to start within 7 days after randomisation.
8. Willing and able to comply with all study requirements, including treatment and required assessments
9. Has completed baseline HRQL questionnaires UNLESS is unable to complete because of limited literacy or vision
10. Signed, written, informed consent

4.3 Exclusion criteria

1. Prostate cancer with significant sarcomatoid or spindle cell or neuroendocrine small cell components
2. History of
    a. seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma).
    b. loss of consciousness or transient ischemic attack within 12 months of randomization
    c. significant cardiovascular disease within the last 3 months including: myocardial infarction, unstable angina, congestive heart failure (NYHA functional capacity class II or greater, Refer to Appendix 6), ongoing arrhythmias of Grade >2 [CTCAE, version 4.03], thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism). Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed.
3. Life expectancy of less than 12 months.
4. History of another malignancy within 5 years prior to randomisation, except for either non-melanomatous carcinoma of the skin or, adequately treated, non-muscle-invasive urothelial carcinoma of the bladder (Tis, Ta and low grade T1 tumours).
5. Concurrent illness, including severe infection that might jeopardize the ability of the patient to undergo the procedures outlined in this protocol with reasonable safety
    a. HIV-infection is not an exclusion criterion if it is controlled with anti-retroviral drugs that are unaffected by concomitant enzalutamide.
6. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse;
7. Patients who are sexually active and not willing/able to use medically acceptable forms of barrier contraception.
8. Prior ADT for prostate cancer (including bilateral orchidectomy), except in the following settings:
    a. Started less than 12 weeks prior to randomisation AND PSA is stable or falling. The 12 weeks starts from whichever of the following occurs earliest: first dose of oral anti-androgen, LHRHA, or surgical castration.
    b. In the adjuvant setting, where the completion of adjuvant hormonal therapy was more than 12 months prior to randomisation AND the total duration of hormonal treatment did not exceed 24 months. For depot preparations, hormonal therapy is deemed to have started with the first dose and to have been completed when the next dose would otherwise have been due, e.g. 12 weeks after the last dose of depot goserelin 10.8mg.
9. Prior cytotoxic chemotherapy for prostate cancer, but up to 2 cycles of docetaxel chemotherapy for metastatic disease is permitted.as per section 5.3.2.4 is allowed.
10. Participation in other clinical trials of investigational agents for the treatment of prostate cancer or other diseases.

4.4 Screening

Written informed consent must be signed and dated by the participant, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed.

4.5 Randomisation

Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this study.

Prior to randomization, treating clinicians and participants must decide if early treatment with docetaxel is to be undertaken. Randomisation will be performed via a central randomization system that stratifies for volume of disease (high versus low), site, co-morbidities (ACE-27 0-1 versus 2-3), use of anti-resorptive therapy (denosumab, zoledronic acid or neither) at time of starting ADT, and planned use of docetaxel. The decisions regarding use of early docetaxel or of anti-resorptive therapy, must be made and documented prior to randomization.

Participants will be randomly allocated (1:1) to receive either enzalutamide OR NSAA in addition to their LHRHA (or surgical castration). Study treatment should be planned to start within 7 days after randomisation.

The instructions for the randomisation system provided in the Study Manual should be followed. Confirmation of each randomisation will be provided to the site.

Individuals may only be randomised once in this trial.

5 TREATMENT PLAN

Enzalutamide is the study intervention in this trial. Conventional NSAA are used only in the control group, as per an acceptable standard of care. Participants in both groups are treated with a LHRHA (or surgical castration), as per standard of care. Treatment with enzalutamide or NSAA will continue until evidence of clinical progression or prohibitive toxicity.

Androgen deprivation is to be given continuously in this trial. Intermittent androgen deprivation will be classified as a protocol violation.

5.1 Study Treatment

5.1.1 Study treatment: Enzalutamide (XTANDI® Astellas)

Enzalutamide is provided as 40 mg soft gelatine capsules administered as 160 mg (4 capsules) orally once daily until clinical disease progression or prohibitive toxicity.

Enzalutamide will be commenced within 7 days of randomisation. If a patient randomised to enzalutamide is already receiving a NSAA, then the NSAA will be stopped at randomisation and enzalutamide should be started within 7 days or randomisation.

Enzalutamide's potency is increased with the co-administration of strong CYP2C8 inhibitors e.g, gemfibrozil. In this trial, it is preferable that these medications are ceased prior to commencing enzalutamide. However if it is not possible for these medications to be ceased then participants will need to commence enzalutamide at 80mg daily. These participants will not be permitted to have their dose of enzalutamide increased to 160mg until they have ceased the co-administration of the strong CYP2C8 inhibitor.

5.1.2 Control Treatment: Non-Steroidal Anti-Androgen (NSAA)

Participants randomised to the control group will receive a conventional NSAA, i.e. bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg three times a day. The choice of NSAA is at the discretion of the treating clinician. Drug administration should be according to the product information. Cyproterone is NOT permitted.

The NSAA will be started within 7 days after randomisation, if not already started.

The NSAA will be continued until clinical disease progression or prohibitive toxicity.

5.1.3 Required background therapy in both arms

All participants are to receive standard background therapy with a LHRHA or surgical castration, as per standard of care. The choice of the LHRHA or surgical castration is at the discretion of the treating clinician.

Administration of the LHRHA should be according to the product information guide. Options include but are not restricted to: goserelin, leuprorelin, triptorelin, or degarelix. Use of a 3-monthly depot preparation is encouraged because its administration will often correspond with protocol assessments.

If an LHRHA is to be used, then it must be started no earlier than 12 weeks before randomization, and preferably within 2 weeks after starting enzalutamide or NSAA.

If surgical castration with bilateral orchidectomy is to be used instead of a LHRHA, then it must be performed less than 12 weeks before randomisation. Orchidectomy is permitted at any time after randomisation as long as ADT has been instituted already in accordance with protocol requirements.

5.1.4 Commencement of ADT prior to randomisation.

Patients who started androgen deprivation therapy less than 12 weeks prior to randomization for metastatic disease may be eligible for this trial. If a patient is on a LHRHA, this may continue as planned. If an eligible patient is on an oral non-steroidal anti-androgen prior to randomization, then the oral anti-androgen will be stopped at randomization. If the participant is randomly assigned experimental treatment, they will then start enzalutamide within 7 days of randomisation; if the participant is randomly assigned control treatment, then the a suitable NSAA will be started within 7 days of randomisation (or continued). ADT started before randomisation is deemed to have started on the earliest date that either an anti-androgen or a LHRHA was administered.

5.2 Dose modifications of study medications

Enzalutamide: Participants who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with study drug. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day). Treatment interruption and re-initiation should be discussed with the study chair or delegate.

If enzalutamide is co-administered with a **strong** CYP2C8 inhibitor (e.g. gemfibrozil), then the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the **strong** CYP2C8 inhibitor is discontinued, then the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Conventional NSAA: should be used as per standard of care and according to the product information. NSAA should be stopped if significant abnormalities of liver function are observed during study treatment without a likely alternative explanation, e.g. the transaminases (AST or ALT) increase beyond 2-3 times the institutional upper limit of normal, or if the bilirubin increases above twice the upper limit of normal, as per the approved product information. Recommencement of NSAA may occur at the discretion of the investigator and with appropriate monitoring.

Background treatment with a LHRHA: There are no dose modifications for LHRHA. Intermittent hormonal therapy is not allowed.

5.3 Concomitant Medications/Treatments (including early docetaxel use)

5.3.1 Recommended

The following medications and treatments are standard of care for the prevention of osteoporosis during androgen deprivation therapy and should therefore be taken in this study:

- Calcium Carbonate: Patients will receive concomitant treatment with calcium carbonate at a dose of at least 500 mg orally per day every day, e.g., Caltrate™, Tums™. Calcium is best absorbed when taken with meals.

and

- Vitamin D: Patients will receive concomitant treatment with vitamin D by oral administration of any multivitamin containing at least 400 IU of vitamin D.

5.3.2 Permitted

The following medications and treatments are permitted in this study:

5.3.2.1 Treatment or Prevention of Osteoporosis

Treatment or prevention of **osteoporosis**

- zoledronic acid e.g. Aclasta ® (5mg every 12 months)
- denosumab e.g. Prolia® (60mg every 6 months)
- Other approved agents

5.3.2.2. Treatment of Bone Metastases

Treatment for **bone metastases** as per clinical guidelines, if commenced prior to randomization and on a stable dose:

- zoledronic acid or other bisphosphonates,
- denosumab or other RANK-ligand inhibitors
- Commencement of either of these classes of bone targeted therapy for metastatic bone disease beyond 6 weeks of commencing study treatment will be considered as evidence of disease progression.

5.3.2.3 Palliative Radiotherapy

Palliative radiation for sites of disease documented at time of randomisation is permissible if required within 6 weeks of commencing ADT. In this situation, the participant may continue on study treatments.

The requirement for palliative radiotherapy beyond 6 weeks of commencing study treatment should be deemed evidence of clinical progression and study treatment should be discontinued (see Section 5.5 Treatment discontinuation).

5.3.2.4 Early use of docetaxel

The decision to use early docetaxel must be made and specified prior to randomization and is at the discretion of the treating physician and patient.

Patients who have already commenced docetaxel prior to study entry are eligible for the ENZAMET trial if they are tolerating full doses of docetaxel (75mg/m^2) with ADT, and meet all eligibility criteria for the trial while receiving docetaxel, and have had no more than 2 cycles prior to randomisation.

For ENZAMET participants randomly allocated to the enzalutamide group who have not already started chemotherapy, the first dose of docetaxel should be given at least 4 weeks after starting enzalutamide, and no more than 6 weeks after randomisation.

For ENZAMET participants randomly allocated to receive standard NSAA who have not already started docetaxel, the first dose of docetaxel should be given at least 4 weeks after starting the standard NSAA and no more than 6 weeks after randomisation.

The minimum interval of 4 weeks is to establish that there is no evidence of significant hepatotoxicity that might increase the risk of docetaxel toxicity (serum ALT <3x ULN and serum bilirubin is either <ULN, or <1.5x ULN if the participant has Gilberts Syndrome). The maximum interval of 6 weeks after randomisation is to ensure that chemotherapy is completed by the week 24 follow-up visit. Participants unable to start docetaxel at 75mg/m^2 should not be treated with early docetaxel in this trial.

Docetaxel should be administered at 75mg/m^2 every 21 days for a total of 6 cycles with dose reductions and modifications as specified below. The number of cycles and dose reductions of docetaxel will be recorded in the eCRF.

5.3.2.4.1 Dose modifications for docetaxel:

No more than two dose reductions of docetaxel should be allowed for any patient. If a patient who has had 2 dose reductions has toxicities requiring further dose reductions, then docetaxel should be stopped and they should be treated with androgen deprivation and the assigned NSAA or enzalutamide. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. **All toxicities should be graded according to CTCAE version 4.03.**

Dose adjustments for toxicity should be made according to the following guidelines. If the dose level is reduced due to toxicity, then it will not be re-escalated in subsequent cycles. Treatment may be delayed no more than 3 weeks to allow recovery from toxicity. If treatment must be delayed longer than 3 weeks from the scheduled day of dosing, then docetaxel should be stopped and the patient should be treated with androgen deprivation alone.

Dose Level	Docetaxel (mg/m^2)
Level 0	75 mg/m^2
Level - 1	65 mg/m^2
Level - 2	55 mg/m^2

a) Myelosuppression

Dose modifications are to be made based on the granulocyte and/or platelet count drawn prior to planned treatment (can be done the day prior to planned dose):

Docetaxel	Neutrophils / 10^9/L Day 1 of treatment		Platelet / 10^9/L Day 1 of treatment
No change	> 1.5	or	> 100
Delay and reduce one dose level*	<1.500	or	<100

NOTE: If a dose reduction is made, maintain the lower dose for all subsequent cycles.

* If a dose is held due to myelosuppression, the patient will be retreated with a one level dose reduction once neutrophil count has recovered to at least 1.5 x 10^9/L and platelet count has recovered to at least 100 x 10^9/L.

* If planned day 1 dose must be delayed for three consecutive weeks, discontinue docetaxel and continue on ADT alone.

Delay and dose modification after complicated neutropenia. Patients with afebrile Grade 4 neutropenia ≥ 7 days, or Grade 3-4 neutropenia associated with fever (one reading of oral temperature > 38.5°C, or three readings of oral temperature >38.0°C in a 24-hour period) can be retreated with a 1-level dose reduction once the absolute neutrophil count has increased to 1.5 x 109/L. The fever must have resolved and if an infection is identified, it must be adequately treated and have clinically resolved before restarting therapy. If prior bacteremia, blood cultures must be negative on recheck. Patient can continue with chemotherapy dosing while on antibiotics. Use of growth factors is not required as the dose and schedule does not meet ASCO guidelines. If however, the investigator considers it in patients best interest growth factors can be used per investigator discretion.

b) Hepatic dysfunction

ALT and Bilirubin will be evaluated pre-study and Day 1 (may be evaluated within 24 hours of day 1) of cycles 1-6 of docetaxel:

Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Dose Modifications for Abnormal Liver Function

Bilirubin		**ALT/ SGPT**	**Action**
> ULN*	or	> 5 x ULN	Wait ≤ 3 weeks. If recovered**, reduce docetaxel dose by one dose level. If not, discontinue docetaxel.
≤ ULN*	and	> 3 x ULN	Reduce docetaxel by one dose level

* For patients with Gilbert's Syndrome, wait if the bilirubin level is >1.5 its baseline value

** Recovery is < 3X ULN for ALT/SGPT and WNL for bilirubin. For patients with Gilbert's Syndrome, recovery is defined as a bilirubin level <1.5 its baseline value. Dose modifications are based on ALT/ SGPT alone due to the lack of specificity of AST/SGOT.

c) Stomatitis

If stomatitis ≥ grade 2 is present on day 1 of any cycle, docetaxel should be held until stomatitis has resolved. If Grade 3/4 stomatitis occurs at any time, the dose of docetaxel will be reduced one dose level for all subsequent doses. If a second Grade 3/4 stomatitis event is incurred, docetaxel will be reduced one more dose level. If a third Grade 3/4 stomatitis event occurs, the docetaxel should be ceased.

d) Peripheral neuropathy

If ≥ Grade 3, the patient should discontinue docetaxel.

If Grade 2, the docetaxel should be held and the patient should be retreated upon recovery to a ≤ Grade 1 toxicity with a dose reduction of docetaxel by one level.

If Grade 2 or greater neurotoxicity persists for more than 3 weeks, the patient should discontinue docetaxel.

e) Hypersensitivity reactions for docetaxel

Docetaxel should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for docetaxel hypersensitivity reactions.

Grade 4 Hypersensitivity is defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion.

Patients with two episodes of Grade 3 hypersensitivity reactions or one Grade 4 hypersensitivty reaction should discontinue docetaxel.

f) Diarrhea

If patients experience >grade 2 diarrhea and concurrent grade 3 or 4 neutropenia, hold docetaxel until ANC>1000/mm^3 and diarrhea ≤ grade 2.

If patients experience significant diarrhea (>3 loose stools/24hrs over baseline), they should be treated prophylactically in subsequent cycles with loperamide or diphenoxylate. If patient experiences >grade 2 diarrhea despite prophylaxis, docetaxel should be reduced one dose level. If patients experience > grade 2 diarrhea despite prophylaxis AND dose reduction, they should discontinue docetaxel.

g) Other toxic effects possibly related to docetaxel:

If toxicities ≤ Grade 2, manage the patient symptomatically if possible, and retreat without dose reduction.

If toxicities ≥ Grade 3 and clinically significant (not mentioned above), docetaxel should be withheld (except for anemia as patients can be transfused) until resolution to ≤ Grade 1 or baseline and patients treated with a one dose level reduction.

h) Delay of therapy:

If docetaxel has to be delayed for more than 3 weeks from planned day of dosing because of any toxicity, then docetaxel should be stopped and the patient should be treated with LHRHA plus assigned NSAA or enzalutamide.

5.3.3 Use with caution

Some drugs affect the metabolism of enzalutamide. Enzalutamide is metabolised by the liver and the cytochrome P450 pathways 2C8 and 3A4 are responsible for the metabolism of enzalutamide. Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when

combining enzalutamide with drugs that are strong inducers or inhibitors of these CYP450 metabolic pathways. Where possible these drugs should be avoided. In settings where avoidance of these drugs is not possible, suggestions for dose reductions for enzalutamide are described in Section 5.2.

Enzalutamide affects the metabolism of some drugs. Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted utilizing local laboratories.

5.3.4 Prohibited

The following should not be used during this study. Participants who require treatment with any of these agents will usually need to discontinue study treatment, and should be discussed with the Study Chair or delegate:

- Other investigational treatments
- St John's Wort
- Grapefruit juice

5.3.5 Concomitant medication reporting

Concomitant medications known to interact with the study medications will be recorded as well concomitant medications on development of SAEs.

5.4 Compliance

Participant medication compliance will be formally determined by a tablet count out of the sight of the patient at 4 and 12 weeks after randomisation and the participant counselled appropriately if significant non-compliance is determined. Compliance at subsequent visits will be assessed by questioning the participant and recording if treatment has been taken as prescribed, and if not, the reasons and number of days of treatment missed.

5.5 Treatment discontinuation

Study treatment with enzalutamide or NSAA will be permanently discontinued for any of the reasons below

- Clinical progressive disease (PD) is documented by a site investigator. PSA progression alone does not constitute clinical progression i.e. if the participant has PSA progression alone they may remain on study drug until the criteria for clinical progression are met. See SECTION 7.3 for definition of clinical progression
- Delay of hormonal treatment for greater than 30 days due to treatment-related adverse events. Treatment interruptions and re-initiations should be discussed with the study chair or delegate.
- The investigator determines that continuation of treatment is not in the patient's best interest.
- Development of adverse events during the trial that would put the participant at risk if they continued study therapy e.g. seizures or liver toxicity, whilst on enzalutamide.
- The patient declines further study treatment, or withdraws their consent to participate in the study.

In addition, enzalutamide should be discontinued in the following circumstances:

- Required use of a concomitant treatment that is prohibited, as defined in section 5.3.4

- Failure to comply with the protocol, e.g. repeatedly failing to attend scheduled assessments. If a patient has failed to attend scheduled assessments in the study, the Investigator must determine the reasons.

The reasons for discontinuing study treatment will be documented in the participant's medical record and eCRF.

Follow up of participants who stop study treatment (enzalutamide or NSAA) should continue follow-up visits according to this protocol to allow collection of outcome data.

5.5.1 Subsequent treatment

Treatment after discontinuation of study treatment is at the discretion of the patient's clinician as per standard of care.

6 ASSESSMENT PLAN

6.1 Schedule of assessments

	Screening	Baseline[1]	On Study Treatment			After study treatment	
	Within 28 days prior to randomisation	Within 7 days prior to randomisation	Day 29[2] (±7 days)	Every 12 weeks (±1 week)[3] from randomisation until clinical progression[4]	At progression[5] (PSA and clinical) and end of treatment for reasons other than progression	30-42 days after the last dose of study treatment	Every 12 weeks (±2 weeks)
Informed consent	X						
Clinic assessment[6]	X	X	X	X	X	X	
Blood tests[7]:							
Haematology (CBE)	X	X	X				
Biochemistry (EUC, LFTs[8])	X	X	X	X	X		
PSA	X	X	X	X	X		
Fasting for glucose, HbA1C, lipids		X		X (wk 24 only)	X		
Fasting bloods for translational research		X		X (wk 24 only)	X (first progression only)		
Imaging[9]:							
CT/MRI of abdomen and pelvis	X				X		
CXR or CT chest	X				X		
Whole body bone scan (WBBS)	X				X		
Compliance[10]			X	X (wk 12 only)			
Concomitant medications			Drugs used at the time of SAEs, and drugs known to interact with enzalutamide[11]				
Adverse Events[12]			X	X	X	X	
Quality of life assessments (EORTC QLQ C-30 PR-25, EQ-5D)		X	X	X	X	X	
Resource use form			X	X	X	X	
Patient status						X	X
Subsequent treatment for prostate cancer						X	X

Note: In the event that LHRHA or NSAA treatment was started within 12 weeks prior to randomisation, the pre-treatment PSA will be recorded as the baseline PSA, however the baseline CT and WBBS will still be required.

Footnotes:

1. If screening bloods were collected within 7 days prior to randomisation, baseline bloods do not need to be repeated.
2. Assessments on Day 29 is for adverse events and compliance.
3. 12-weekly assessments are intended to correspond with the 3 monthly depot of LHRHA if this is being administered at the trial site.
4. 12-weekly assessments are to continue until there is evidence of clinical progression. If PSA progression occurs without clinical progression, 12 weekly assessments continue.
5. PSA progression and clinical progression often occur at different times. If so, then these assessments must be recorded at both times. PSA progression is defined according to the PCWG2 criteria: first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later. Clinical progression is defined as evidence of progression or recurrence on imaging, clinical examination, development of cancer related symptoms, or initiation of other anticancer treatment for prostate cancer
6. Clinical assessment includes history and physical examination, performance status, weight and waist circumference.
7. Bloods tests include,

   1) Haematology: complete blood examination (CBE): Haemoglobin concentration, white cell count, platelet count, white cell differential.

   2) Biochemistry: electrolytes, urea, creatinine (EUC);
   liver function tests (LFT): bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT)

   3) Fasting bloods for
   i) glucose, HbA1C, lipids (standard of care) and
   ii) storage for further metabolic research and biomarker studies for those participants consenting to translational research.
   These samples should be drawn at the specified timepoint plus or minus 7 days. These samples must be taken after standard overnight fasting.
8. Clinical assessment, haematology and biochemistry tests should be performed prior to each cycle of docetaxel as per institutional standard of care. Liver function tests must be checked every 4 weeks from commencement of study drugs (LHRHA and assigned enzalutamide or NSAA) for the first 4 months. This does not require a clinic visit or other assessments.
9. Imaging at baseline must include a CT or MRI of the abdomen and pelvis, and a radio-isotope whole body bone scan (WBBS). The chest can be imaged with either a plain x-ray, or a CT scan. However if lung nodules are identified on the CXR, then a CT scan of the chest must be performed.
10. Formal count of treatment tablets in experimental group (enzalutamide) and control group (NSAA tablets) at weeks 4 and 12
11. Only in the group assigned enzalutamide
12. Adverse events categorised and graded according to CTCAE v4.03 till the 30 day safety assessment visit, 30 days after the study treatment ends.

6.2 Assessment phase definitions and special circumstances

6.2.1 Screening

All screening procedures must be performed within 28 days prior to randomisation, unless otherwise specified.

6.2.2 Baseline

All baseline procedures must be performed within 7 days prior to randomisation, and within 14 days prior to treatment commencement, unless otherwise specified.

6.2.3 On treatment

Assessments during treatment may be performed within 7 days of the specified timepoint, unless otherwise specified.

6.2.4 End of treatment and 30 day safety assessment

An end of treatment and safety assessment should be performed 30-42 days after the last dose of study treatment to include any adverse events occurring within 30 days after the last dose of study treatment.

6.2.5 Follow-up after completion of study treatment

Study-specific follow-up assessments should be completed at the specified timepoints (± 2 weeks).

Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol.

If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries.

7 OUTCOMES, ENDPOINTS AND OTHER MEASURES

7.1 Overall Survival

Overall survival is defined as the interval from the date of randomisation to date of death from any cause, or the date of last known follow-up alive.

7.2 PSA Progression Free Survival

PSA progression free survival (PFS) is defined as the interval from the date of randomisation to the date of first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last known follow-up without PSA progression.

PSA progression is defined as: a rise in PSA by more than 25% AND more than 2ng/mL above the nadir (lowest PSA point). This needs to be confirmed by a repeat PSA performed at least 3 weeks later. (See Appendix 3 for more details on the PCWG2 criteria).

7.3 Clinical Progression Free Survival

Clinical progression free survival (PFS) is defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression.

Clinical progression is defined by progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions see Appendix 3 & 4), development of symptoms attributable to cancer progression, or initiation of other anticancer treatment for prostate cancer.

7.4 Safety (Adverse events worst grade according to NCI CTCAE *v4.03)*

The NCI Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.03) will be used to classify and grade the intensity of adverse events during study treatment.

7.5 Health Related Quality of Life

HRQL will be reported by participants using the EORTC core quality of life questionnaire (QLQ C-30) and prostate cancer specific module (PR-25). The EQ-5D-5L will be used to derive utility scores suitable for quality adjusted survival analyses. (See Appendix 1).

HRQL is a secondary outcome in this trial and the specific HRQL objective is to determine differential treatment effects by comparing scores between the randomly allocated groups. The underlying hypothesis is that there will be no important differences in HRQL between the two treatment groups.

The QLQ-C30 is a validated questionnaire developed to assess HRQL in cancer patients. It includes five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. The remaining single items assess additional symptoms commonly reported by cancer patients (dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea), as well as the perceived financial impact of the disease and treatment. (14)

The QLQ-PR25 is a 25 item module designed to assess HRQL in prostate cancer patients. It includes 5 multi-item scales assessing urinary symptoms, bowel symptoms, hormonal treatment-related symptoms, sexual activity, sexual function, and incontinence aids. (15)

The EQ-5D-5L is a standardised, self-rated measure of health status designed to provide a utility score suitable for use in health economic evaluations. It provides a descriptive classification based on self-assessment of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a 5 level rating scale of no problems, slight problems, moderate problems, severe problems and extreme problems. These scores are combined with a self-rating of health on a 20cm graduated, vertical, visual analogue scale from ‘the best health you can imagine’ to ‘the worst health you can imagine’.

7.6 Health Outcomes Relative to Costs

Information on the following areas of health-care resource usage will be collected: hospitalisations (for all participants by trial staff via a standard case record form (CRF), visits to health professionals (for Australian participants via Medicare benefits scheme (MBS) and for other regions as specified separately in their Group Specific Appendix (GSA), and medications (for Australian participants via Pharmaceutical Benefits Scheme (PBS) and for other regions as separately specified in their GSA). Consent will be sought from Australian participants for access to their MBS and PBS records. Australian unit costs will be applied to the resource usage data (e.g. Diagnosis Related Groups (DRG) costs or similar for hospitalisations, and scheduled costs for medical visits and prescription items) to estimate the incremental cost of the addition of enzalutamide to standard treatment.

Quality-adjusted survival (QAS) time will be used to quantify the incremental effectiveness of adding enzalutamide to standard treatment. QAS will be calculated by applying utility weights for quality of life derived from the EQ5D to survival data using established methods. (16)

Economic evaluation in other regions will be undertaken at the discretion of the relevant regional trial coordinating centre.

7.7 Tertiary/Correlative Objectives

These will include exploratory studies of tissue and blood samples to identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes). Studies may include, but are not limited to:

- investigating variants of the androgen receptor (AR) - a steroid receptor transcription factor, and changes in plasma profiles (or plasma signature) in understanding mechanisms of resistance to enzalutamide;
- investigations of how enzalutamide may work in people with prostate cancer;
- studies that may help to understand the course of this cancer and related diseases;
- biomarkers may be RNA-based (single entity or entire expressed genome, RNA, miRNA), DNA-based (single entity or whole genome, germ line or tumour related), protein-based or other entities and the consent form will allow patients to allow or limit use of specimens;

- Metabolic studies including glucose, HbA1C, lipids, insulin, and IGF

The treating doctor of the participant will be notified of any analytically or clinically valid findings that may emerge significant to the participant or their family regarding cancer;

Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of biomarkers remains to be determined.

8 SAFETY REPORTING

8.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

Adverse events include the following:

- All suspected adverse drug reactions
- All reactions from drug– overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug.

AEs must be reported as AEs even if they do not meet SAE criteria.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the participant is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

(i) The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(ii) Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

AEs and SAEs will be recorded from the date of randomisation until 30 days after the last dose of study treatment.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Participant Information Sheet and Informed Consent Form or elsewhere in the protocol. (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010)).

An event is causally related if there is a reasonable possibility that the drug [intervention] caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010).

8.2 Reporting of Serious Adverse Events (including SUSARs)

The investigator in all participating countries is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the NHMRC Clinical Trials Centre within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention.

SAE reports should be submitted to the CTC as per the procedure documented in the Study Manual.

The CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The CTC will be responsible for providing reports to the Lead HREC in Australia and New Zealand and the regional coordinating centres in the other regions.

The investigator must notify the local HREC as required.

The CTC will submit 'reportable safety events' to the TGA in Australia and Medsafe in NZ, and to the regional coordinating centre to provide to the regulatory authorities as required in other participating countries in which the study is being conducted within the requisite timeframes, with a copy to Astellas with a copy to Astellas.

As per regulatory requirements, a SUSAR needs to be reported as soon as possible and not later than 7 days for a fatal or life threatening event and 15 days for a non-fatal or non- life threatening event.

The following information will be recorded for each Serious Adverse Event**:**

- Event description including classification according to CTCAE v4.03
- SAE criterion
- Attribution to study intervention (enzalutamide)
- Expectedness (listed in IB for enzalutamide)
- Action taken with study intervention (enzalutamide), including rechallenge (if done)
- Outcome of SAE including end date if resolved

8.3 Pregnancy

Pregnancy occurring in the partner of a participant participating in the study and up to 90 days after the completion of the study drug should be reported to the investigator and the NHMRC Clinical Trials Centre. The investigator should counsel the participant; discuss the risks of continuing with the pregnancy and the possible effects on the foetus. The partner should be counselled and followed as described above. The coordinating centre must be notified within 1 working day using the SAE form and the participant followed during the entire course of the pregnancy and postpartum period. After obtaining participant and partner consent, parental and neonatal outcomes will be recorded even if they are completely normal.

9 CENTRAL REVIEW AND BIOSPECIMEN COLLECTION

9.1 Central Tissue Collection

Where available formalin-fixed paraffin-embedded (FFPE) tissue blocks of diagnostic tumour tissue will be collected for research (including potential future translational research relevant to this study). This diagnostic tissue may include biopsy of the primary tumour, biopsy or cytology of metastatic lesion. The tissue will be from archival tumour material – no additional biopsy of the participant is required. Tissue blocks will be collected at site and sent to a central lab for histology review. Patient consent will be sought for the conduct of translational studies (tertiary /correlative objectives) on these biospecimens. Refer to the Biological Sampling Handbook for the details relating to central tissue collection.

9.2 Central Blood Collection

Patient consent will be sought for collection of blood at 3 timepoints: baseline, week 24 from randomisation and at first evidence of progression (PSA or clinical, whichever comes first). Whole blood will be collected, processed and stored frozen at each trial site. The frozen samples will be transported later to a central lab for translational studies (tertiary /correlative objectives). Refer to the Biological Sampling Handbook for collection and processing procedures.

10 TREATMENT INFORMATION

10.1 Enzalutamide (XTANDI® Astellas)

10.1.1 Description

Enzalutamide is an androgen receptor inhibitor. It is provided as liquid-filled soft gelatine capsules each containing 40 mg enzalutamide for oral administration. Each bottle contains 120 capsules. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatine, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

Bottles of enzalutamide should be stored at a room temperature between 20ºC to 25ºC (68ºF to 77ºF), in a dry place and kept with container tightly closed.

Full details on product handling information are provided in the Product information, Investigator Brochure and Pharmacy Manual.

10.1.2 Supply

Astellas is providing the study drug free of charge. Appropriately labelled enzalutamide will be distributed by a third party to each participating site from regional warehouses. Start-up supplies of enzalutamide will be dispatched once the institution has all requisite approvals in place.

Enzalutamide will be dispensed to study participants according to usual hospital practice at each participating institution.

Full details on drug ordering and supply is provided in the Pharmacy Manual

10.1.3 Study Drug Accountability

The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate.

Patients will be asked to return unused drug and empty drug containers at each return visit.

10.2 Non-steroidal anti-androgen (NSAA)

NSAA will be provided according to usual practice. Drug accountability will not be performed for NSAA.

10.3 LHRHA (e.g. Goserelin, Leuprorelin, Degarelix)

LHRHA will provided according to usual practice. Drug accountability will not be performed for LHRHA.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size

A trial comprising 1,100 participants that are followed until approximately 470 deaths are observed (e.g. over a 2 year recruitment with an additional follow-up of 3.5 years) provides over 80% power to detect a 25% reduction in the hazard of death with a 2-sided type 1 error of 0.05 assuming a 3-year survival rate of 65% amongst controls.

A 25% reduction in the hazard of death is considered clinically plausible in light of the results of the AFFIRM trial of enzalutamide versus placebo in castration-resistant metastatic prostate cancer after chemotherapy, which showed a 37% reduction in the hazard of death, (11) and the PREVAIL trial of enzalutamide versus placebo for castration resistant metastatic prostate cancer before chemotherapy, which showed a 29% reduction in the hazard of death. (20)

The design incorporates a formal interim analysis performed on overall survival once 2/3 of the required events are observed. The interim analysis allows for early rejection of the null hypothesis using an O'Brien-Fleming boundary. The critical value for $|Z_k|$ is 2.45 for the interim analysis and 2.00 for the final analysis. The conditional power of the study will also be calculated at the interim analysis.

11.2 Statistical Analysis

A statistical analysis plan will be prepared prior to data-lock, and contain additional detail on the methods described below.

All randomised participants will be eligible for inclusion in the full analysis set. Analysis of efficacy endpoints will be undertaken on participants in the full analysis set unless participants are deemed non-evaluable by the Trial Management Committee; all such decisions will be documented in the final study report. The safety population will comprise all randomised participants who received at any study medication. Participants will be analysed according to the regimen they actually received for the purposes of the safety analysis.

11.2.1 Timing of Analyses

An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Assuming the study is not terminated early, the final analysis is planned to be undertaken after the required number of deaths have occurred.

11.2.2 Analysis of Efficacy Endpoints

The primary analysis will be a comparison of overall survival (OS) in the two treatment arms using a log-rank test. Kaplan-Meier curves for OS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression. The sensitivity of treatment effect estimates to adjustment for baseline covariates, including stratification factors, will be explored.

Other time-to-event endpoints will be analysed in a comparable fashion to the primary endpoint. The QoL scores collected longitudinally will be analysed using appropriate linear models for repeated measures data.

11.2.3 Analysis of Safety Endpoints

A descriptive analysis of the adverse events (AE) data will be prepared for participants in the safety population. The number and percentage of participants who experience AEs will be tabulated according to CTCAE term/category, grade, and seriousness. Safety will be monitored on an ongoing basis with regular review of Serious Adverse Events (SAE) by the Trial Management Committee.

The frequency of complicated neutropenia (febrile neutropenia or infection G3-4 with neutropenia G3-4) will be monitored in real time in the first 49 participants having early docetaxel in each of the 2 randomly allocated treatment groups. Consideration will be given to modifying the protocol if

complicated neutropenia is observed in 8 or more of the first 49 participants allocated enzalutamide with early docetaxel, or in 8 or more of the first 49 participants in allocated NSAA with early docetaxel. These numbers are required to distinguish the observed rate (of complicated neutropenia in each treatment group) from a rate of 25% (unacceptably high, alternate hypothesis) versus an assumed rate of 8% (acceptably low, null hypothesis) using a one-sample binomial test with 1-sided type 1 and type 2 errors of 5%.

11.2.4 Analysis of Health Outcomes Relative to Costs

A within-trial estimate of the incremental cost-effectiveness of the addition of enzalutamide to standard treatment will be calculated in terms of Australian dollars per unit of quality adjusted survival (QAS) gained.

The incremental cost of the addition of enzalutamide to standard treatment will be estimated by applying Australian unit costs to the resource usage data (e.g. ANDRG costs for hospitalisations, and scheduled costs for MBS and PBS items). QAS will be calculated by applying utility weights for quality of life derived from the EQ-5D-5L to survival data using established methods. (16)

The feasibility of extrapolating beyond the within-trial estimate of cost-effectiveness using modelling methods will be explored.

11.3 Interim analyses

An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Results of the interim analysis will be reviewed by the study Independent Data Safety Monitoring Committee (IDSMC) described in Section 12.2. The IDSMC will also monitor selected safety endpoints, accrual and event rates. Consideration will be given to altering aspects of the study if:

- The results of the interim analyses yield clear evidence of benefit or harm based on the O'Brien-Fleming approach specified section 11.1.
- The conditional power of the study (evaluated at the time of the interim analyses) is unacceptably low (e.g. <20%)
- The accrual/event rate is insufficient to complete the study in a reasonable time frame.
- The rate of serious AEs (grade 3 to 5) in the enzalutamide arm is unacceptably high compared to the control arm.
- The rate of complicated neutropenia in those receiving early docetaxel is unacceptably high (see Section 11.2.3).
- Medical or ethical reasons emerge affecting continued performance of the study.

12 ORGANISATION

The study is a collaboration between the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and the NHMRC Clinical Trials Centre, at the University of Sydney, which is the sponsor in Australia and New Zealand.

This international study will be conducted at a number of regional coordinating centres, each responsible for their own ethic and regulatory approvals, regional monitoring, medical oversight and facilitation of data collection and query resolution.

Overall study coordination, data acquisition and management and statistical analysis will be performed by the global coordinating centre, the NHMRC Clinical Trials Centre.

12.1 Trial Management Committee

The international Trial Management Committee (TMC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations

from other study committees and external bodies (e.g. ethics committees).

The international TMC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on interim analyses or other information.

Each regional trial coordinating centre will identify a clinical lead and a coordinating centre lead who will represent the region on the international TMC.

12.2 Independent Safety and Data Monitoring Committee (ISDMC)

The ISDMC will provide an independent assessment of emerging evidence from interim analyses and sources external to the trial, and make recommendations to the international TMC about potential modifications to the trial protocol and conduct. An ISDMC charter will provide details on the composition of the committee, the roles and responsibilities of committee members, the format of meetings and methods of information transfer, statistical issues and relationships with other committees.

13 ADMINISTRATIVE ASPECTS

13.1 Ethics and regulatory compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations in other countries. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the CTC, study chair and HREC must be advised immediately.

13.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC Clinical Trials Centre, University of Sydney and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

13.3 Protocol amendments

Changes and amendments to the protocol can only be made by the international Trial Management Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

13.4 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source

documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

a. Participant's name, contact information and protocol identification.

b. The date that the participant entered the study, and participant number.

c. A statement that informed consent was obtained (including the date).

d. Relevant medical history

e. Dates of all participant visits and results of key trial parameters.

f. Occurrence and status of any adverse events.

g. The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.

Patient-reported outcome data such as health-related quality of life data entered into the CRF will be considered as source.

All study-related documentation at Australian and New Zealand sites will be maintained for 15 years following completion of the study.

13.5 Study Monitoring

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC Clinical Trials Centre (CTC) or their delegates. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during the study for source data verification, review of the investigator's site file and drug handling records. The CTC or regional coordinating centres will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the participant gives authorised CTC staff direct access to their medical records and the study data.

13.6 Audit and Inspection

This study may be subject to audit or inspection by representatives of the collaborative group, Astellas, CTC or representatives of regulatory bodies (e.g. Therapeutic Goods Administration (TGA), as well as regulatory authorities in each region such as FDA or EMEA..

13.7 Clinical Study Report

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued and form the basis of a manuscript for publication. The Clinical Study Report or summary thereof will be provided to the study investigators, ANZUP, Astellas and the ethics committees. A lay summary of results will be prepared for patients and other interested parties.

13.8 Publication Policy

Authorship recognises the intellectual contributions of investigators and others to a study. It also identifies those who take public responsibility for the study. Authorship is defined as per ICMJE guidelines (www.icmje.org).The International Trial Management Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. The Writing Committee will develop a publication plan, including authorship, target journals, and expected dates of publication. The first publication will be the report of the full trial results based on the main protocol using the study group name with a list of specific contributions at the end. ANZUP and CTC will be acknowledged in all publications. All publications must receive prior written approval from the TMC prior to submission.

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15 LIST OF APPENDICES

15.1 Appendix 1: HRQL forms (EORTC QLQ C-30 & PR-25, EQ-5D-5L)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

During the last 4 weeks…	Not at all	A little	Quite a bit	Very much
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

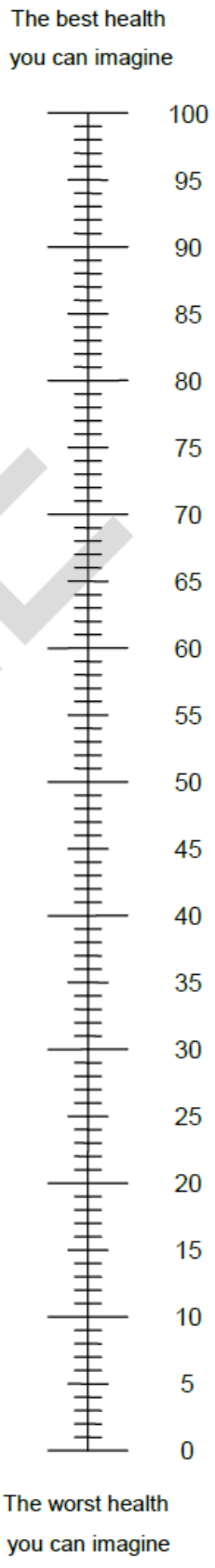
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



15.2 Appendix 2: ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol 1982. [1]

15.3 Appendix 3: Prostate Cancer Working Group 2 (PCWG2) Criteria

The sections that apply to this trial are the criteria for PSA response and progression, and the criteria for bone lesion "prevent/delay end points (progression).

Variable	PCWG2 (2007)
PSA	- Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug - Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression - Ignore early rises (prior to 12 weeks) in determining PSA response **Decline from baseline**: - Record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) **No decline from baseline:** - PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	**For control/relieve/eliminate end points:** Use RECIST with caveats: - Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline - Record changes in nodal and visceral soft tissue sites separately - Record complete elimination of disease at any site separately - Confirm favorable change with second scan - Record changes using waterfall plot **For delay/prevent end points:** - Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies) - Note that for some treatments, a lesion may increase in size before it decreases.
Bone	**For control/relieve eliminate end points:** - Record outcome as new lesions or no new lesions - First scheduled reassessment: o No new lesions: continue therapy o New lesions: perform a confirmatory scan 6 or more weeks later - Confirmatory scan: o No new lesions: continue therapy o Additional new lesions: progression - Subsequent scheduled reassessments: o No new lesions: continue o New lesions: progression **For prevent/delay end points (progression):** - The appearance of 2 or more new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions - The date of progression is the date of the first scan that shows the change
Symptoms	Consider independently of other outcome measures - Document pain and analgesia at entry with a lead in period and measure repeatedly at 3- to 4-week intervals - Perform serial assessments of global changes in HRQOL, urinary or bowel compromise, pain management, additional anticancer therapy - Ignore early changes (≤ 12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression - Confirm response or progression of pain or HRQOL end points ≥ 3 weeks later

See Scher et al 2008 [2] for more details.

15.4 Appendix 4: Response Evaluation Criteria in Solid Tumours (RECIST 1.1)

These instructions are based on the guidelines recommended by Eisenhauer et al. (19).
The sections that apply to this trial are the criteria for progression of soft tissue lesions.

1 Evaluable for response.

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below

2 Disease and lesion definitions

1.1 *Measurable Disease*. Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥10 mm with CT scan (assuming slice thickness of 5mm or less) or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres. Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

1.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

1.3 *Target Lesions*. When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions in total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological lymph nodes must meet the criterion of having a short axis of ≥ 15 mm by CT scan and only the *short* axis of these lymph nodes will contribute to the baseline sum. All other pathological lymph nodes (those with a short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of target lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions can not be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

1.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

Response Definitions

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of any specified tumour markers (no tumour markers for this trial). Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol. Confirmation of response is not required in this study.

Partial Response (PR): at least a 30% decrease in the sum of measures for target lesions (longest diameter for tumour lesions and short axis measure for target lymph nodes), taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol. Confirmation of response is not required in this study

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table: Integration of Target, non-Target and New lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of specified tumour markers, AND lymph nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks. from baseline [note, protocol may define; 6-8 weeks is recommended]
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of specified tumour markers AND lymph nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

2 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

3 Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment (or randomisation for randomized studies) until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

4 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent, unless the protocol specifies otherwise. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

4.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

4.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

4.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

4.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

4.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

4.6 *Tumour Markers*. Tumour markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. There are no specified tumour markers for this trial.

4.7 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

15.5 Appendix 5: TNM staging for prostate cancer

Pathologic staging

pT2	Organ confined.
pT2a	Unilateral, ≤½ of one side.
pT2b	Unilateral, involving >½ of side but not both sides.
pT2c	Bilateral disease.
pT3	Extraprostatic extension.
pT3a	Extraprostatic extension or microscopic invasion of bladder neck.[b]
pT3b	Seminal vesicle invasion.
pT4	Invasion of rectum, levator muscles, and/or pelvic wall.

p = Pathologic; T = Primary tumor.

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Stages

Stage	TNM	Description
I	T1a, N0, M0, G1	T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

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Stage	TNM	Description
IIA	T1a, N0, M0, G2–4	T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIA	T1b, N0, M0, any G	T1b = Tumor incidental histologic finding in >5% of tissue resected.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIA	T1c, N0, M0, any G	T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIB	T1, N0, M0, any G	T1 = Clinically inapparent tumor neither palpable nor visible by imaging.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIB	T2, N0, M0, any G	T2 = Tumor confined within prostate.[b]
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

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Stage	TNM	Description
III	T3, N0, M0, any G	T3 = Tumor extends through the prostate capsule.[c]
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

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Stage	TNM	Description
IV	T4, N0, M0, any G	T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
	Any T, N1, M0, any G	TX = Primary tumor cannot be assessed.
		T0 = No evidence of primary tumor.
		T1 = Clinically inapparent tumor not palpable or visible by imaging.
		T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		T1b = Tumor incidental histologic finding in >5% of tissue resected.
		T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).
		T2 = Tumor confined within prostate.[b]
		T2a = Tumor involves ≤50% of one lobe.
		T2b = Tumor involves >50% of one lobe but not both lobes.
		T2c = Tumor involves both lobes.
		T3 = Tumor extends through the prostate capsule.[c]
		T3a = Extracapsular extension (unilateral or bilateral).
		T3b = Tumor invades seminal vesicle(s).
		T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as the bladder, external sphincter, rectum, levator muscles, and/or pelvic wall.
		N1 = Metastasis in regional lymph node(s).
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

	Any T, any N, M1, any G	TX = Primary tumor cannot be assessed.
		T0 = No evidence of primary tumor.
		T1 = Clinically inapparent tumor not palpable or visible by imaging.
		T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		T1b = Tumor incidental histologic finding in >5% of tissue resected.
		T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).
		T2 = Tumor confined within prostate.[c]
		T2a = Tumor involves ≤50% of one lobe.
		T2b = Tumor involves >50% of one lobe but not both lobes.
		T2c = Tumor involves both lobes.
		T3 = Tumor extends through the prostate capsule.[c]
		T3a = Extracapsular extension (unilateral or bilateral).
		T3b = Tumor invades seminal vesicle(s).
		T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as the bladder, external sphincter, rectum, levator muscles, and/or pelvic wall.
		NX = Regional lymph nodes were not assessed.
		pNX = Regional nodes not sampled.
		N0 = No regional lymph node metastasis.
		pN0 = No positive regional nodes.
		N1 = Metastasis in regional lymph node(s).
		pN1 = Metastases in regional node(s).
		M1 = Distant metastasis.[a]
		M1a = Nonregional lymph node(s).
		M1b = Bone(s).
		M1c = Other site(s) with or without bone disease.
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade; p = Pathologic.

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[a] *When more than one site of metastasis is present, the most advanced category (pM1c) is used.*

[b] *Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.*

[c] *Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.*

15.6 Appendix 6: NYHA Heart Failure Classification

Reference: The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Criteria for use of the terms *minimal*, *moderately severe*, and *severe disease* cannot be defined precisely. Grading is based on the individual physician's judgment. The objective assessment of a patient with cardiac disease who has not had specific tests of cardiac structure or function is classified as undetermined.

The classification of patients according to cardiac functional capacity is only part of the information needed to plan the management of patients' activities. A prescription for physical activity should be based on information from many sources. Functional capacity is an estimate of what the patient's heart will allow the patient to do and should not be influenced by the character of the structural lesions or an opinion as to treatment or prognosis. A recommendation for physical activity is based not only on the amount of effort possible without discomfort but also on the nature and severity of the disease.

Following are examples of functional capacity and objective assessment classifications.

- A patient with minimal or no symptoms but a large pressure gradient across the aortic valve or severe obstruction of the left main coronary artery is classified: Functional Capacity I, Objective Assessment D
- A patient with a severe anginal syndrome but angiographically normal coronary arteries is classified: Functional Capacity IV, Objective Assessment A
- A patient with acute myocardial infarction, shock, reduced cardiac output, and elevated pulmonary artery wedge pressure is classified: Functional Capacity IV, Objective Assessment D
- A patient with mitral stenosis, moderate exertional dyspnea, and moderate reduction in mitral valve area is classified: Functional Capacity II or III, Objective Assessment C

Functional Capacity	**Objective Assessment**
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

15.7 Appendix 7: Adult Comorbidity Evalutation - 27

Adult Comorbidity Evaluation-27

Identify the important medical comorbidities and grade severity using the index.
Overall Comorbidity Score is defined according to the highest ranked single ailment, except in the case where two or more Grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score should be designated Grade 3.

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Cardiovascular System			
Myocardial Infarct	☐ MI ≤ 6 months	☐ MI > 6 months ago	☐ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	☐ Unstable angina	☐ Chronic exertional angina ☐ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) ☐ Recent (≤ 6 months) coronary stent	☐ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms ☐ Angina pectoris not requiring hospitalization ☐ CABG or PTCA (>6 mos.) ☐ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	☐ Hospitalized for CHF within past 6 months ☐ Ejection fraction < 20%	☐ Hospitalized for CHF >6 months prior ☐ CHF with dyspnea which limits activities	☐ CHF with dyspnea which has responded to treatment ☐ Exertional dyspnea ☐ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	☐ Ventricular arrhythmia ≤ 6 months	☐ Ventricular arrhythmia > 6 months ☐ Chronic atrial fibrillation or flutter ☐ Pacemaker	☐ Sick Sinus Syndrome ☐ Supraventricular tachycardia
Hypertension	☐ DBP≥130 mm Hg ☐ Severe malignant papilledema or other eye changes ☐ Encephalopathy	☐ DBP 115-129 mm Hg ☐ DBP 90-114 mm Hg while taking antihypertensive medications ☐ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	☐ DBP 90-114 mm Hg while not taking antihypertensive medications ☐ DBP <90 mm Hg while taking antihypertensive medications ☐ Hypertension, not otherwise specified
Venous Disease	☐ Recent PE (≤ 6 mos.) ☐ Use of venous filter for PE's	☐ DVT controlled with Coumadin or heparin ☐ Old PE > 6 months	☐ Old DVT no longer treated with Coumadin or Heparin
Peripheral Arterial Disease	☐ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago ☐ Untreated thoracic or abdominal aneurysm (≥6 cm)	☐ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago ☐ Chronic insufficiency	☐ Intermittent claudication ☐ Untreated thoracic or abdominal aneurysm (< 6 cm) ☐ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	☐ Marked pulmonary insufficiency ☐ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment ☐ Chronic supplemental O_2 ☐ CO_2 retention (pCO_2 > 50 torr) ☐ Baseline pO_2 < 50 torr ☐ FEV1 (< 50%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities ☐ FEV1 (51%-65%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment ☐ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	☐ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	☐ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	☐ Chronic hepatitis or cirrhosis without portal hypertension ☐ Acute hepatitis without cirrhosis ☐ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	☐ Recent ulcers(≤ 6 months ago) requiring blood transfusion	☐ Ulcers requiring surgery or transfusion > 6 months ago	☐ Diagnosis of ulcers treated with meds ☐ Chronic malabsorption syndrome ☐ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	☐ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	☐ Uncomplicated acute pancreatitis ☐ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	☐ Chronic pancreatitis w/o complications

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Renal System			
End-stage renal disease	☐ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis ☐ Acute dialysis	☐ Chronic Renal Insufficiency with creatinine >3 mg% ☐ Chronic dialysis	☐ Chronic Renal Insufficiency with creatinine 2-3 mg%.
Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	☐ Hospitalization ≤ 6 months for DKA ☐ Diabetes causing end-organ failure ☐ retinopathy ☐ neuropathy ☐ nephropathy* ☐ coronary disease* ☐ peripheral arterial disease*	☐ IDDM without complications ☐ Poorly controlled AODM with oral agents	☐ AODM controlled by oral agents only
Neurological System			
Stroke	☐ Acute stroke with significant neurologic deficit	☐ Old stroke with neurologic residual	☐ Stroke with no residual ☐ Past or recent TIA
Dementia	☐ Severe dementia requiring full support for activities of daily living	☐ Moderate dementia (not completely self-sufficient, needs supervising)	☐ Mild dementia (can take care of self)
Paralysis	☐ Paraplegia or hemiplegia requiring full support for activities of daily living	☐ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	☐ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	☐ Recent suicidal attempt ☐ Active schizophrenia	☐ Depression or bipolar disorder uncontrolled ☐ Schizophrenia controlled w/ meds	☐ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	☐ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	☐ Connective Tissue Disorder on steroids or immunosuppressant medications	☐ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	☐ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	☐ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	☐ Asymptomatic HIV+ patient. ☐ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	☐ Uncontrolled cancer ☐ Newly diagnosed but not yet treated ☐ Metastatic solid tumor	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago
Leukemia and Myeloma	☐ Relapse ☐ Disease out of control	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	☐ Relapse	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	☐ Delirium tremens	☐ Active alcohol abuse with social, behavioral, or medical complications	☐ H/o alcohol abuse but not presently drinking
Illicit Drugs	☐ Acute Withdrawal Syndrome	☐ Active substance abuse with social, behavioral, or medical complications	☐ H/o substance abuse but not presently using
Body Weight			
Obesity		☐ Morbid (i.e., BMI ≥ 38)	

OVERALL COMORBIDITY SCORE (Circle one.)	**0**	**1**	**2**	**3**	**9**
	None	**Mild**	**Moderate**	**Severe**	**Unknown**

15.8 Appendix 8: Cockroft-Gault formula

Renal function (GFR) may be estimated with the Cockcroft–Gault formula, as follows:

Male participants:

Creatinine clearance (ml/minute) = $\frac{(140 - age) * weight}{0.814 * SerumCr}$

Units:
Age in years
Weight in kilograms
Serum creatinine (SerumCr) in micromoles per litre

Female participants: Use above formula but multiply calculated Creatinine clearance by 0.85

	ENZAMET Protocol Amendment from v2.0 07/Nov/2014 to v3 01/Mar/2018							
Change #	**Current Protocol version**	**Current Protocol date**	**Section amended**	**Page number in amended version**	**Change**	**Current wording**	**Wording in amendment**	**Version change**
1	2.0	07-Nov-14	Title page: Coordinating Centre & Coordinating Centre Lead	1	Updated information. Study team changes	Coordinating Centre for Ireland, UK and Europe= ICORG, Coordinating Centre Lead= TBA. Coordinating Centre for Canada= NCIC CTG, Coordinating Centre Lead= Wendy Parulekar	Coordinating Centre for Ireland, UK and Europe= Cancer Trials Ireland (CTRIAL-IE), Coordinating Centre Lead= Bryan Hennessy. Coordinating Centre for Canada= Canadian Cancer Trials Group (CCTG), Coordinating Centre Lead= Francisco Vera- Badillo	3.0
2	2.0	07-Nov-14	5.2 Dose modifications of study medications - Enzalutamide	17	Additional information	Enzalutamide: Participants who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with study drug. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day). Treatment interruption and re-initiation should be discussed with the study chair or delegate. If enzalutamide is co-administered with a strong CYP2C8 inhibitor (e.g. gemfibrozil), then the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, then the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.	Enzalutamide: Participants who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with study drug. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day). Treatment interruption and re-initiation should be discussed with the study chair or delegate. The dose of enzalutamide can be reduced to 120 mg/day for chronic long term grade 2 adverse events (including but not limited to fatigue or cognitive impairment) at the site investigator's discretion. The dose reduction and justification must be documented in the patient's notes. Dose modifications for other scenarios may be considered for the wellbeing of the participant, with the approval of the study sponsor and documentation in the medical record. If enzalutamide is co-administered with a strong CYP2C8 inhibitor (e.g. gemfibrozil), then the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, then the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.	3.0
3	2.0	07-Nov-14	5.3.1Concomitant Medications/Treatments (including early docetaxel use)- Recommended	18	Clarification	Recommended The following medications and treatments are standard of care for the prevention of osteoporosis during androgen deprivation therapy and should therefore be taken in this study: • Calcium Carbonate: Patients will receive concomitant treatment with calcium carbonate at a dose of at least 500 mg orally per day every day, e.g., CaltrateTM, TumsTM. Calcium is best absorbed when taken with meals. and • Vitamin D: Patients will receive concomitant treatment with vitamin D by oral administration of any multivitamin containing at least 400 IU of vitamin D.	Recommended The following medications and treatments are standard of care for the prevention of osteoporosis during androgen deprivation therapy and should therefore be taken in this study: • Calcium Carbonate: Patients will receive concomitant treatment with calcium carbonate at a dose of at least 500 mg orally per day every day, e.g., CaltrateTM, TumsTM. Calcium is best absorbed when taken with meals. and • Vitamin D: Patients will receive concomitant treatment with vitamin D by oral administration of at least 400 IU of vitamin D.	3.0
4	2.0	07-Nov-14	5.3.2.4.1 Dose modifications for docetaxel-Myelosuppression	20	Correction	a) Myelosuppression Dose modifications are to be made based on the granulocyte and/or platelet count drawn prior to planned treatment (can be done the day prior to planned dose): Docetaxel Neutrophils/10^9/L Day 1 of treament Platelet/10^9/L Day 1 of treatment No change >1.5 or > 100 Delay and reduce one dose level* <1.500 or < 100 NOTE: If a dose reduction is made, maintain the lower dose for all subsequent cycles. * If a dose is held due to myelosuppression, the patient will be retreated with a one level dose reduction once neutrophil count has recovered to at least 1.5 x 10^9/L and platelet count has recovered to at least 100 x 10^9/L. * If planned day 1 dose must be delayed for three consecutive weeks, discontinue docetaxel and continue on ADT alone.	a) Myelosuppression Dose modifications are to be made based on the granulocyte and/or platelet count drawn prior to planned treatment (can be done the day prior to planned dose): Docetaxel Neutrophils/10^9/L Day 1 of treament Platelet/10^9/L Day 1 of treatment No change ≥ 1.5 and ≥ 100 Delay and reduce one dose level* <1.5 or < 100 NOTE: If a dose reduction is made, maintain the lower dose for all subsequent cycles. * If a dose is held due to myelosuppression, the patient will be retreated with a one level dose reduction once neutrophil count has recovered to at least 1.5 x 10^9/L and platelet count has recovered to at least 100 x 10^9/L. * If planned day 1 dose must be delayed for three consecutive weeks, discontinue docetaxel and continue on ADT alone.	3.0
5	2.0	07-Nov-14	5.3.3 Use with caution	22	Additional information	Some drugs affect the metabolism of enzalutamide. Enzalutamide is metabolised by the liver and the cytochrome P450 pathways 2C8 and 3A4 are responsible for the metabolism of enzalutamide. Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when combining enzalutamide with drugs that are strong inducers or inhibitors of these CYP450 metabolic pathways. Where possible these drugs should be avoided. In settings where avoidance of these drugs is not possible, suggestions for dose reductions for enzalutamide are described in Section 5.2. Enzalutamide affects the metabolism of some drugs. Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted utilizing local laboratories.	Some drugs affect the metabolism of enzalutamide. Enzalutamide is metabolised by the liver and the cytochrome P450 pathways 2C8 and 3A4 are responsible for the metabolism of enzalutamide. Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when combining enzalutamide with drugs that are strong inducers or inhibitors of these CYP450 metabolic pathways. Where possible these drugs should be avoided. In settings where avoidance of these drugs is not possible, suggestions for dose reductions for enzalutamide are described in Section 5.2. Enzalutamide affects the metabolism of some drugs. Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted utilizing local laboratories. The 'Use with caution' medication list included in this protocol is not exhaustive. Please refer to the current approved enzalutamide Investigator Brochure.	3.0
6	2.0	07-Nov-14	5.4 Compliance	22	Clarification	Participant medication compliance will be formally determined by a tablet count out of the sight of the patient at 4 and 12 weeks after randomisation and the participant counselled appropriately if significant non-compliance is determined. Compliance at subsequent visits will be assessed by questioning the participant and recording if treatment has been taken as prescribed, and if not, the reasons and number of days of treatment missed.	Participant medication compliance will be formally determined by a count of tablets performed at the time of clinic review and out of sight of the participant at 4 and 12 weeks after randomisation. The participant will be counselled appropriately if significant non-compliance is determined. Compliance at subsequent visits will be assessed at the time of clinic review by questioning the participant, recording if treatment has been taken as prescribed and, if not, the reasons and number of days of treatment missed.	3.0
7	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 6	25	Clarification	Clinical assessment includes history and physical examination, performance status, weight and waist circumference.	A clinical assessment should be done at each study visit. Clinical assessment includes history, physical examination, performance status, and weight.The waist circumference need only be done and recorded at the baseline visit (both in the eCRF and in the patient's medical records). All visits after baseline include a review of any adverse events and physical examination as per standard of care for a patient at this stage of their disease and treatment. The fact that the patient has been seen and examined at that assessment, along with any relevant findings, should be recorded in the patient's notes.	3.0
8	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 7	25	Clarification	Bloods tests include, 1) Haematology: complete blood examination (CBE): Haemoglobin concentration, white cell count, platelet count, white cell differential. 2) Biochemistry: electrolytes, urea, creatinine (EUC); liver function tests (LFT): bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT) 3) Fasting bloods for i) glucose, HbA1C, lipids (standard of care) and ii) storage for further metabolic research and biomarker studies for those participants consenting to translational research. These samples should be drawn at the specified timepoint plus or minus 7 days. These samples must be taken after standard overnight fasting.	Bloods tests include, 1) Haematology: complete blood examination (CBE): Haemoglobin concentration, white cell count, platelet count, white cell differential. 2) Biochemistry: electrolytes, urea, creatinine (EUC); liver function tests (LFT): bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT) 3) Fasting bloods for i) glucose, HbA1C, lipids (standard of care) and ii) storage for further metabolic research and biomarker studies for those participants consenting to translational research. Baseline samples can be drawn within 7 days prior to start of randomised study treatment. Week 24 and first progression samples should be drawn at the specified timepoint plus or minus 7 days. These samples must be taken after standard overnight fasting. Fasting bloods due at PSA progression should be taken when PSA progression is confirmed by a second value 3 or more weeks later (i.e. a confirmed rising trend). For translational research bloods - even if the patient has not fasted, proceed with collecting the bloods. Then record that the patient has not fasted in the translational research documentation and eCRF.	3.0
9	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 9	26	Clarification	Imaging at baseline must include a CT or MRI of the abdomen and pelvis, and a radio-isotope whole body bone scan (WBBS). The chest can be imaged with either a plain x-ray, or a CT scan. However if lung nodules are identified on the CXR, then a CT scan of the chest must be performed.	Imaging at baseline must include a CT or MRI of the abdomen and pelvis, and a radio-isotope whole body bone scan (WBBS). Baseline scans are permitted up to 35 days before study treatment begins, provided that the patient starts study medication within 7 days after randomisation (window of 28 days before randomization + 7 days after randomization = 35 days in total). The chest can be imaged with either a plain x-ray, or a CT scan. However if lung nodules are identified on the CXR, then a CT scan of the chest must be performed. Scans at EOT, for any reason, should be done within 6 weeks. If PSA progression occurs within 6 weeks before EOT then the imaging (CT/MRI, CXR/CT chest and WBBS) does not need to be repeated. If the PSA progression occurs more than 6 weeks then the imaging does need to be repeated. If a patient subsequently commences other anticancer treatment within 6 weeks of the EOT scans, the scans do not need to be repeated, otherwise if > 6 weeks from the EOT scans, the scans should be repeated.	3.0
10	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 10	26	Clarification	Formal count of treatment tablets in experimental group (enzalutamide) and control group (NSAA tablets) at weeks 4 and 12	Formal count, in the clinic, of treatment tablets in experimental group (enzalutamide) and control group (NSAA tablets) at weeks 4 and 12. The enzalutamide bottles should be sent to pharmacy for drug reconciliation and destruction.	3.0
11	2.0	07-Nov-14	6.1 Schedule of Assessments table-Footnote 13	26	Additional wording		The following should be documented in the patient's medical notes: duration of any hospital stays, number of hospital visits, and number of office and clinic visits, since the last assessment. This includes review of correspondence from other sites confirming these hospital stays or visits. The outcome of this check should be recorded in the patient's notes. Note that admissions to hospital, or adverse events prolonging hospital stays, may constitute Serious Adverse Events.	3.0
12	2.0	07-Nov-14	6.2.5 Follow-up after completion of study treatment	27	Clarification	Study-specific follow-up assessments should be completed at the specified timepoints (± 2 weeks). Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol. If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries.	Study-specific follow-up assessments should be completed at the specified timepoints (± 2 weeks). Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol. If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries. Participants who discontinue protocol treatment (NSAA or enzalutamide) before clinical progression (for example stopped because of toxicity, patient or clinician preference, or PSA progression without clinical progression), should have the following assessments: 1. End of treatment assessments as per the protocol Schedule of Assessments 'At progression (PSA and clinical) and end of treatment for reasons other than progression' column. 2. A safety assessment performed 30-42 days after the last dose of study treatment 3. Continuing follow-up every 12 weeks until clinical progression, as per the "Every 12 weeks (±1 week) from randomisation until clinical progression" column of the Schedule of Assessments (underneath On Study Treatment). This is to ensure we have data about the time of any subsequent PSA and/or clinical progression. Translational bloods should be collected at the times of PSA and clinical progression, not when study treatment is stopped for other reasons.	3.0

13	2.0	07-Nov-14	7.7 Tertiary/Correlative Objectives	29	Clarification	These will include exploratory studies of tissue and blood samples to identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes). Studies may include, but are not limited to: - investigating variants of the androgen receptor (AR) - a steroid receptor transcription factor, and changes in plasma profiles (or plasma signature) in understanding mechanisms of resistance to enzalutamide; - investigations of how enzalutamide may work in people with prostate cancer; - studies that may help to understand the course of this cancer and related diseases; - biomarkers may be RNA-based (single entity or entire expressed genome, RNA, miRNA), DNA-based (single entity or whole genome, germ line or tumour related), protein-based or other entities and the consent form will allow patients to allow or limit use of specimens; - Metabolic studies including glucose, HbA1C, lipids, insulin, and IGF The treating doctor of the participant will be notified of any analytically or clinically valid findings that may emerge significant to the participant or their family regarding cancer; Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of biomarkers remains to be determined.	These will include exploratory studies of tissue and blood samples to identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes). Studies may include, but are not limited to: - investigating variants of the androgen receptor (AR) - a steroid receptor transcription factor, and changes in plasma profiles (or plasma signature) in understanding mechanisms of resistance to enzalutamide; - investigations of how enzalutamide may work in people with prostate cancer; - studies that may help to understand the course of this cancer and related diseases; - biomarkers may be RNA-based (single entity or entire expressed genome, RNA, miRNA), DNA-based (single entity or whole genome, germ line or tumour related), protein-based or other entities and the consent form will allow patients to allow or limit use of specimens; - Metabolic studies including glucose, HbA1C, lipids, insulin, and IGF The treating doctor of the participant will be notified of any analytically or clinically valid findings that may emerge significant to the participant or their family regarding cancer; Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment is a rapidly evolving research area, the definitive list of biomarkers remains to be determined.	3.0
14	2.0	07-Nov-14	8.1 Safety Reporting- Definitions- Adverse Events	30	Clarification	An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below). Adverse events include the following: - All suspected adverse drug reactions - All reactions from drug– overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate) - Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses - Injury or accidents. - Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination) - Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test). Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug. AEs must be reported as AEs even if they do not meet SAE criteria.	An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below). Adverse events include the following: - All suspected adverse drug reactions - All reactions from drug– overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate) - Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses - Injury or accidents. - Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination) - Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test). Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug. AEs must be reported as AEs even if they do not meet SAE criteria. All .adverse events should be recorded and graded in the patient's medical record, and in the eCRF form associated with the relevant visit.	3.0
15	2.0	07-Nov-14	8.2 Reporting of Serious Adverse Events (including SUSARs)	31	Additional information	The investigator in all participating countries is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the NHMRC Clinical Trials Centre within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention. SAE reports should be submitted to the CTC as per the procedure documented in the Study Manual. The CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The CTC will be responsible for providing reports to the Lead HREC in Australia and New Zealand and the regional coordinating centres in the other regions. The investigator must notify the local HREC as required. The CTC will submit 'reportable safety events' to the TGA in Australia and Medsafe in NZ, and to the regional coordinating centre to provide to the regulatory authorities as required in other participating countries in which the study is being conducted within the requisite timeframes, with a copy to Astellas with a copy to Astellas. As per regulatory requirements, a SUSAR needs to be reported as soon as possible and not later than 7 days for a fatal or life threatening event and 15 days for a non-fatal or non- life threatening event. The following information will be recorded for each Serious Adverse Event: • Event description including classification according to CTCAE v4.03 • SAE criterion • Attribution to study intervention (enzalutamide) • Expectedness (listed in IB for enzalutamide) • Action taken with study intervention (enzalutamide), including rechallenge (if done) • Outcome of SAE including end date if resolved	The investigator in all participating countries is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the NHMRC Clinical Trials Centre within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention. SAE reports should be submitted to the CTC as per the procedure documented in the Study Manual. The CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The CTC will be responsible for providing reports to the Lead HREC in Australia and New Zealand and the regional coordinating centres in the other regions. The investigator must notify the local HREC as required. The CTC will submit 'reportable safety events' to the TGA in Australia and Medsafe in NZ, and to the regional coordinating centre to provide to the regulatory authorities as required in other participating countries in which the study is being conducted within the requisite timeframes, with a copy to Astellas with a copy to Astellas. As per regulatory requirements, a SUSAR needs to be reported as soon as possible and not later than 7 days for a fatal or life threatening event and 15 days for a non-fatal or non- life threatening event. The following information will be recorded for each Serious Adverse Event*: • Event description including classification according to CTCAE v4.03 • SAE criterion • Attribution to study intervention (enzalutamide) • Action taken with study intervention (enzalutamide), including rechallenge (if done) • Outcome of SAE including end date if resolved *Please note that site staff (investigators, data-managers, study nurses) should not complete the expectedness fields for SAE. Assessments of expectedness for SAE will be completed by the trial sponsor. Surgical/medical procedures that require an overnight admission as an inpatient should be reported as an SAE, but the diagnosis labelling the SAE should be the problem being treated, not the procedure being done. For example, if a patient is admitted for such an operation, then the SAE should be labelled with the diagnosis/problem for which the operation was done, not the operation itself. For example, overnight admission for excision of localised skin cancer should be reported as a new malignancy, not as an excision. This includes both planned (elective) and emergency procedures.	3.0
16	2.0	07-Nov-14	10.1.3 Study Drug Accountability	32	Additional information	The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate. Patients will be asked to return unused drug and empty drug containers at each return visit.	The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate. Patients will be asked to return unused drug and empty drug containers at each return visit. Drug accountability logs will be requested, as required, from each pharmacy for central review by each regional coordinating centre.	3.0
17	2.0	07-Nov-14	11.1 Sample size	33	Additional information	A trial comprising 1,100 participants that are followed until approximately 470 deaths are observed (e.g. over a 2 year recruitment with an additional follow-up of 3.5 years) provides over 80% power to detect a 25% reduction in the hazard of death with a 2-sided type 1 error of 0.05 assuming a 3-year survival rate of 65% amongst controls. A 25% reduction in the hazard of death is considered clinically plausible in light of the results of the AFFIRM trial of enzalutamide versus placebo in castration-resistant metastatic prostate cancer after chemotherapy, which showed a 37% reduction in the hazard of death, (11) and the PREVAIL trial of enzalutamide versus placebo for castration resistant metastatic prostate cancer before chemotherapy, which showed a 29% reduction in the hazard of death. (20) The design incorporates a formal interim analysis performed on overall survival once 2/3 of the required events are observed. The interim analysis allows for early rejection of the null hypothesis using an O'Brien-Fleming boundary. The critical value for |Zk| is 2.45 for the interim analysis and 2.00 for the final analysis. The conditional power of the study will also be calculated at the interim analysis.	A trial comprising 1,100 participants that are followed until approximately 470 deaths are observed (e.g. over a 2 year recruitment with an additional follow-up of 3.5 years) provides over 80% power to detect a 25% reduction in the hazard of death with a 2-sided type 1 error of 0.05 assuming a 3- year survival rate of 65% amongst controls. A 25% reduction in the hazard of death is considered clinically plausible in light of the results of the AFFIRM trial of enzalutamide versus placebo in castration-resistant metastatic prostate cancer after chemotherapy, which showed a 37% reduction in the hazard of death, (11) and the PREVAIL trial of enzalutamide versus placebo for castration resistant metastatic prostate cancer before chemotherapy, which showed a 29% reduction in the hazard of death. (20) The design incorporates formal interim analyses performed on overall survival using the Lan-DeMets O'Brien-Fleming spending function approach.	3.0
18	2.0	07-Nov-14	11.2.1 Timing of analyses	33	Updated timing of analyses transferred to new Section 11.4	11.2.1 An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Assuming the study is not terminated early, the final analysis is planned to be undertaken after the required number of deaths have occurred.	Please see new Section 11.4, below	3.0
19		07-Nov-14	11.2.2 Analysis of Efficacy Endpoints	33	Changed to 11.2.1 -Analysis of Efficacy Endpoints - additional information added	The primary analysis will be a comparison of overall survival (OS) in the two treatment arms using a log-rank test. Kaplan-Meier curves for OS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression. The sensitivity of treatment effect estimates to adjustment for baseline covariates, including stratification factors, will be explored. Other time-to-event endpoints will be analysed in a comparable fashion to the primary endpoint. The QoL scores collected longitudinally will be analysed using appropriate linear models for repeated measures data.	The primary analysis will be a comparison of overall survival (OS) in the two treatment arms using a log-rank test. Kaplan-Meier curves for OS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression. Other time-to-event endpoints will be analysed in a comparable fashion to the primary endpoint. The sensitivity of the treatment effect estimate on OS to adjustment for baseline covariates, including stratification factors, will be explored. Subgroup analyses will be performed for geographical region, volume of disease strata, and docetaxel strata (additional analyses may be specified in the statistical analysis plan). An evaluation of the treatment effect in the subgroup of high volume disease patients in the docetaxel stratum will also be performed. These subgroup analyses will be performed on OS, and repeated for PSA PFS and clinical PFS endpoints. The QoL scores collected longitudinally will be analysed using appropriate linear models for repeated measures data. Subgroup analyses on QoL endpoints will be performed by docetaxel strata and by symptom severity on baseline QoL.	3.0
20	2.0	07-Nov-14	11.2.3 Analysis of Safety Endpoints	34	Changed to 11.2.2 Analysis of Safety Endpoints	Section number change only	Section number change only	3.0
21	2.0	07-Nov-14	11.2.4 Analysis of Health Outcomes Relative to Costs	34	Changed to 11.2.3 Analysis of Health Outcomes Relative to Costs	Section number change only	Section number change only	3.0
22	2.0	07-Nov-14	11.3 Interim analyses	34	Clarification	An interim analysis on overall survival will be conducted when approximately 2/3 of the required number of deaths have occurred. Results of the interim analysis will be reviewed by the study Independent Data Safety Monitoring Committee (IDSMC) described in Section 12.2. The IDSMC will also monitor selected safety endpoints, accrual and event rates. Consideration will be given to altering aspects of the study if: • The results of the interim analyses yield clear evidence of benefit or harm based on the O'Brien-Fleming approach specified section 11.1. • The conditional power of the study (evaluated at the time of the interim analyses) is unacceptably low (e.g. <20%) • The accrual/event rate is insufficient to complete the study in a reasonable time frame. • The rate of serious AEs (grade 3 to 5) in the enzalutamide arm is unacceptably high compared to the control arm. • The rate of complicated neutropenia in those receiving early docetaxel is unacceptably high (see Section 11.2.3). • Medical or ethical reasons emerge affecting continued performance of the study.	Interim analyses on OS are planned as per Section 11.4. Interim results will be reviewed by the study Independent Data Safety Monitoring Committee (IDSMC) described in Section 12.2. The IDSMC will also monitor selected safety endpoints, accrual and event rates. Consideration will be given to altering aspects of the study if: • The results of the interim analyses on OS yield clear evidence of benefit or harm based on the Lan-DeMets O'Brien-Fleming spending function approach (Section 11.4). • The conditional power of the study (evaluated at the time of the interim analyses) is unacceptably low (e.g. <20%) • The accrual/event rate is insufficient to complete the study in a reasonable time frame. • The rate of serious AEs (grade 3 to 5) in the enzalutamide arm is unacceptably high compared to the control arm. • The rate of complicated neutropenia in those receiving early docetaxel is unacceptably high (see Section 11.2.2). • Medical or ethical reasons emerge affecting continued performance of the study.	3.0

23	2.0	07-Nov-14	11.4 Frequency and timing of Interim Analyses	34	Additional information		Versions 1 and 2 of the ENZAMET protocol specified an interim analysis on OS would be performed at 67% of the required events (i.e. 470 deaths, see Section 11.1). Following simultaneous publication in June 2017 of two randomized controlled trials, LATITUDE[24] and STAMPEDE[25], the ENZAMET Trial Management Committee decided to add two extra interim analyses at 50% and 80% of required events. No interim efficacy data from ENZAMET was considered or used to reach this decision. The Lan-DeMets O'Brien-Fleming spending function approach will be used, and remains the appropriate technique for evaluating these analysis results. LATITUDE and STAMPEDE evaluated abiraterone (a CYP17 inhibitor) in a similar clinical setting to ENZAMET. Both studies obtained estimated HRs for OS that were more impressive than had been hypothesised when these studies were designed. Abiraterone has a different mechanism of action to enzalutamide (i.e. inhibition of androgen synthesis versus blocking the androgen receptor), but both drugs target the androgen-signalling pathway. Abiraterone and enzalutamide have similar effects on survival time in castration-resistant prostate cancer.[6, 7] Thus the results of LATITUDE and STAMPEDE have major implications for informing the hypothesised effect that enzalutamide may have on OS in ENZAMET. However, the control event rate for ENZAMET is anticipated to be lower than for LATITUDE or STAMPEDE because those trials did not mandate the use of an NSAA in their control arms, or have provision for early docetaxel use. These factors could possibly also attenuate the observed effect of enzalutamide in ENZAMET relative to the observed effects of abiraterone in LATITUDE and STAMPEDE. Taking all these considerations into account, and without appraising any interim ENZAMET outcome results, the international ENZAMET Trial Management Committee concluded that a stronger treatment effect than originally hypothesized is plausible, and decided to conduct interim analyses at 50%, 67%, and 80% of the required events to minimize delays in the detection of such an effect.	3.0
24	2.0	07-Nov-14	12.1 Trial Steering Committee	35	Clarification	The international Trial Management Committee (TMC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). The international TMC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on interim analyses or other information. Each regional trial coordinating centre will identify a clinical lead and a coordinating centre lead who will represent the region on the international TMC.	The International Trial Steering Committee (ITSC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). The ITSC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on interim analyses or other information. Each regional trial coordinating centre will identify a clinical lead and a coordinating centre lead who will represent the region on the ITSC.	3.0
25	2.0	07-Nov-14	13.8 Publication Policy	37	Clarification	Authorship recognises the intellectual contributions of investigators and others to a study. It also identifies those who take public responsibility for the study. Authorship is defined as per ICMJE guidelines (www.icmje.org).The International Trial Management Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. The Writing Committee will develop a publication plan, including authorship, target journals, and expected dates of publication. The first publication will be the report of the full trial results based on the main protocol using the study group name with a list of specific contributions at the end. ANZUP and CTC will be acknowledged in all publications. All publications must receive prior written approval from the TMC prior to submission.	Authorship recognises the intellectual contributions of investigators and others to a study. It also identifies those who take public responsibility for the study. Authorship is defined as per ICMJE guidelines (www.icmje.org).The International Trial Steering Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. The Writing Committee will develop a publication plan, including authorship, target journals, and expected dates of publication. The first publication will be the report of the full trial results based on the main protocol using the study group name with a list of specific contributions at the end. ANZUP and CTC will be acknowledged in all publications. All publications must receive prior written approval from the International Trial Steering Committee prior to submission.	3.0
26	2.0	07-Nov-14	References	39	Addition of references 24 and 25		24. Fizazi, K., et al., Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. New England Journal of Medicine, 2017. 377(4): p. 352-360. 25. James, N.D., et al., Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. New England Journal of Medicine, 2017. 377(4): p. 338-351.	3.0

Minor administrative changes have also been made to formats and sub-section orders but these changes have not been documented above.

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: ENZAMET

Protocol number: ANZUP 1304
Protocol version: Version 3, 1 March 2018
Supersedes Version 2 (7 November, 2014)

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CONFIDENTIAL

The University of Sydney

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In addition to those listed on the previous page, the following individuals also made substantial contributions to this protocol:

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ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse events
AR	Androgen receptor
CT	Computed tomography (scan)
CRF	Case report form
CTC	NHMRC Clinical Trials Centre, University of Sydney
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DFCI	Dana Farber Cancer Institute
DRG	Diagnosis Related Groups
EBRT	External beam radiation therapy
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	Euroqol 5 item preference-based measure of health (5L)
FDHT	Fluoro dihydrotestosterone
GSA	Group Specific Appendix
HRQL	Health-Related Quality of Life
IC_{50}	50% maximal inhibitory concentration
ICER	Incremental cost effectiveness ratio
ICORG	All Ireland Cooperative Oncology Research Group
LHRHA	Luteinizing Hormone Releasing Hormone Analogue
MBS	Medicare Benefits Scheme (Australia)
NCIC CTG	Canadian NCIC Clinical Trials Group
NSAA	Non-steroidal anti androgen
OS	Overall survival
PBS	Pharmaceutical Benefits Scheme (Australia)
PCWG2	Prostate Cancer Working Group 2 (see Appendix 3)
PFS	Progression free survival
PR-25	EORTC Quality of Life Questionnaire for Prostate Cancer (25 items)
PSA	Prostate Specific Antigen
QLQ-C30	EORTC Core Quality of Life Questionnaire (30 items)
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
ULN	Upper limit of normal range
USYD	University of Sydney
WBBS	Whole Body Bone Scan

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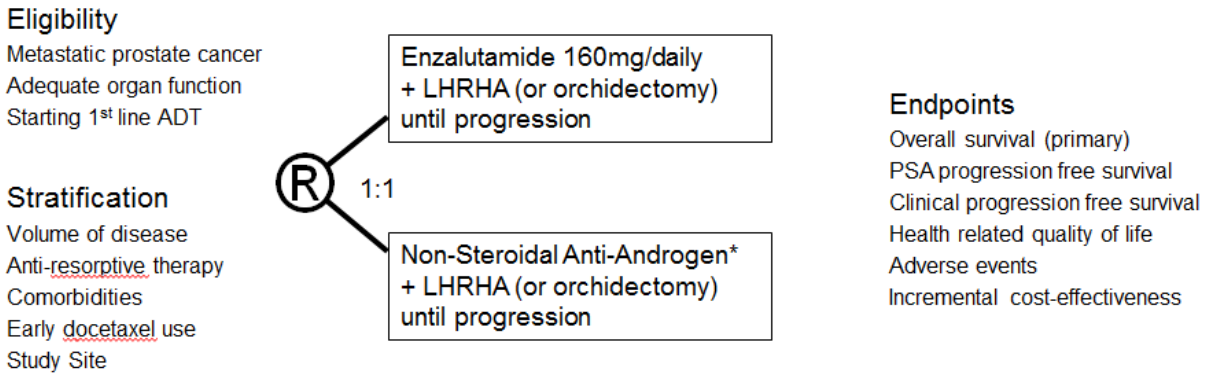
SYNOPSIS

Background	Combined androgen deprivation therapy (ADT) with a luteinising hormone releasing hormone analogue (LHRHA) or surgical castration, plus a conventional non-steroidal anti-androgen (NSAA: bicalutamide, nilutamide, or flutamide), is widely used as initial treatment for hormone-sensitive prostate cancer. Meta-analysis of RCTs showed a 3% absolute improvement in 5 year survival rates with the addition of a conventional NSAA to a LHRHA or surgical castration (1). Residual, low level androgen receptor AR signalling, or agonist activity from conventional NSAA, may provide a stimulatory signal to hormone-sensitive prostate cancer cells. We hypothesize that early use of enzalutamide, a more potent and effective androgen receptor blocker, will reduce residual androgen receptor signalling, and thereby improve outcomes.
General aim	To determine the effectiveness of enzalutamide, versus a conventional NSAA, when combined with a LHRHA or surgical castration, as first line androgen deprivation therapy (ADT).
Primary objective (endpoint)	To determine effects on: 1) Overall survival (death from any cause)
Secondary objectives (endpoints)	To determine effects on: 2) Prostate specific antigen progression free survival (PCGW2) 3) Clinical progression free survival (imaging, symptoms, signs) 4) Adverse events (CTCAE v4.03) 5) Health related quality of life (EORTC QLQ C-30, PR-25 and EQ-5D-5L) 6) Health outcomes relative to costs (incremental cost effectiveness ratio)
Tertiary/Correlative objectives	7) To identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes)
Design	Open label, randomised, 2-arm, multi-centre, phase 3 clinical trial, stratified for volume of disease, use of early docetaxel, antiresorptive therapy, study site, and comorbidities.
Population	The target population is men with metastatic prostate cancer commencing androgen deprivation therapy. Key eligibility criteria include metastatic prostate cancer, adequate organ function and ECOG performance status 0-2.
Study treatments	Participants randomised to: • Enzalutamide 160mg daily, by mouth, until disease progression or prohibitive toxicity (experimental group). OR • Conventional NSAA, by mouth, until disease progression or prohibitive toxicity (control group). All participants are treated with a LHRHA or surgical castration.

Assessments	Assessments at baseline, day 29, week 12, and then every 12 weeks from randomisation until evidence of clinical progression. Imaging with CT scan and whole body bone scan at baseline and at evidence of PSA or clinical progression (whichever occurs first). Blood tests for translational studies at baseline, day 29, week 24, and end of study treatment.
Statistical considerations	A trial of 1,100 participants followed until approximately 470 deaths are observed (e.g. 2 year recruitment plus 3.5 years follow-up) provides at least 80% power to detect a 25% reduction in the hazard of death with a logrank test evaluated at the 2-sided 5% level of significance assuming a 3-year survival rate of 65% amongst controls.

SCHEMA



1,100 participants
2 years accrual + 3.5 years minimum additional follow-up
80% power to detect 25% reduction in the hazard of death from any cause, assuming an OS rate at 3 years of 65% in the control group

*Conventional Non-Steroidal Anti-Androgens: bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg tid

1 BACKGROUND

Prostate cancer is often diagnosed when apparently localized to the prostate gland. However, metastatic disease can occur after surgery or radiation therapy given with curative intent or present as de novo metastatic disease. For cancer that has spread beyond the prostate, androgen suppression for hormone sensitive disease and then subsequent new generation hormonal therapies (enzalutamide, abiraterone), cytotoxic therapy and vaccine therapy for castration resistant prostate cancer (CRPC) can delay and/or cause cancer regression and increase the chance a man will live longer but are not able to cure metastatic prostate cancer. This protocol is based on the hypothesis that earlier use of a therapy shown to be effective in the more advanced state of castration resistant prostate cancer will prevent or delay the emergence of castration resistant disease and will prolong overall survival. As such this protocol aims to determine whether the potent second generation androgen receptor inhibitor, enzalutamide can enhance the ability of androgen suppression to increase the longevity of men commencing androgen suppression for newly metastatic prostate cancer.

The current treatment for patients commencing hormonal therapy for metastatic prostate cancer is androgen suppression either by LHRH analogue therapy or orchidectomy as monotherapy or in combination with an anti-androgen, also known as combined androgen deprivation therapy. Survival varies depending on the extent of disease at commencement of therapy. With the advent of the PSA test many patients are commenced on hormonal therapy at a very early stage (biochemical recurrence) and subjected to the long-term effects of androgen deprivation including osteoporosis. However, if patients with an asymptomatic rising PSA after definitive local therapy are observed until they develop overt metastatic disease (i.e. evident by imaging techniques), the median time from PSA relapse to clinical progression is approximately 8 years. In the pre-PSA era, studies relied upon bone scan and CT scans to document the presence of metastatic disease.

The median overall survival for men commencing androgen deprivation therapy with clinically evident metastatic disease (i.e. not PSA only disease) is about 30 months(1). This information is derived from a meta-analysis including 8,275 men in 27 randomized trials comparing castration alone (medical or surgical) versus combined androgen deprivation therapy including an oral, peripheral anti-androgen (previously known as maximal or combined androgen blockade). This individually updated patient-data meta-analysis showed that overall survival was not improved by the addition of a peripheral anti-androgen when all trials were analysed together. However, a planned subgroup analysis showed that overall survival at 5 years was approximately 3% higher (2p=0.005) in patients assigned combined androgen blockade including a Non-Steroidal Anti-Androgen (NSAA, nilutamide or flutamide) than control patients, and approximately 3% lower (2p=0.04) in patients assigned cyproterone compared with control patients.

The treatment of patients with newly diagnosed metastatic disease is heterogeneous. Some clinicians start treatment with castration alone, and only add a peripheral anti-androgen on progression, while others start treatment with combined androgen deprivation therapy. Both approaches are considered within the range of standard practice. Progression on combined androgen deprivation therapy eventually occurs in most patients, and is thought to be related to either residual low level AR signalling or to agonist activity from older anti-androgens. These may provide a survival signal or escape mechanism to metastatic hormone-sensitive prostate cancer cells. It is possible that a more effective and profound AR blockade with a more potent androgen receptor blocker like enzalutamide might therefore eliminate any such survival signal and improve progression free survival.

Phase 3 studies are ongoing or have recently been performed with the goal of improving the efficacy or tolerability of therapy for metastatic disease. Specifically, intermittent versus continuous dosing LHRH analogue suppression of testosterone in men who responded to therapy has been reported in a large randomized phase 3 SWOG trial (2). Specifically, in this study of 3040 men, 1535 achieved a PSA of < 4 in the induction phase and were randomized. The Hazard Ratio for death with intermittent dosing was 1.10; 90% CI - 0.99 to 1.23 and exceeded the upper boundary for non-inferiority (i.e. cannot rule out a 20% greater risk of death

with intermittent versus continuous therapy). However, there were too few events to rule out significant inferiority of intermittent therapy. A number of studies are comparing ADT plus docetaxel versus ADT alone in men commencing therapy for newly metastatic prostate cancer. The French study of 385 patients reported improvements in times to PSA and clinical progression but not overall survival (3). The US based ECOG E3805 CHAARTED study with 780 patients and the UK STAMPEDE study had not reported their outcomes by July of 2013. Studies of ADT with or without cytochrome P450 inhibitors (abiraterone and TAK700) with activity in CRPC were commenced in 2012 and 2013.

Once progression is documented with a testosterone less than 50ng/dL, the disease is referred to as castration resistant prostate cancer. Recent advances in our understanding of the molecular basis of CRPC have led to a growing number of innovative therapies that target these resistance mechanisms. Moreover, six agents prolong the longevity of a man with CRPC. These include two cytotoxic agents (docetaxel (4) and cabazitaxel (5)), two hormonal therapies (abiraterone (6) and enzalutamide (7)), an alpha-emitting radiopharmaceutical (radium-223 chloride(8)) and an immune therapy (sipuleucel-T (9)). Denosumab, a RANK-ligand inhibitor blocking NFκB mediated effects in the bone micro-environment, delays bone events, such as pathological fractures, more effectively than the bisphosphonate, zoledronic acid. (10) Unfortunately, none of these therapies cure CRPC.

A rational strategy to improve the efficacy of testosterone suppression for patients commencing therapy for metastatic prostate cancer would be to take agents which are proven to be effective in the metastatic setting and attempt to use them when starting therapy for metastatic disease. Enzalutamide has proven highly effective at reducing overall mortality in men with castrate-resistant metastatic prostate cancer and has a tolerable side-effect profile, making it an attractive candidate for testing in the up-front metastatic setting (11). Enzalutamide is a rationally-designed second generation androgen receptor (AR) inhibitor which competitively binds the AR with great potency. Additionally, enzalutamide inhibits nuclear translocation of activated AR and inhibits the association of activated AR with DNA (12).

Preclinical Data with Enzalutamide

Using the non-steroidal agonist RU59603 as the parent scaffold compound, Sawyers and colleagues identified two oral diarylthiohydantoins, RD162 and enzalutamide, from a screen of non-steroidal anti-androgens that retain anti-androgen activity in the setting of increased AR expression (12). Both compounds have enhanced affinity for the AR (5-8 fold) compared to the anti-androgen bicalutamide. Enzalutamide competitively binds the AR with an **IC_{50}** of 36 nM compared to 160 nM for bicalutamide. Additionally, enzalutamide inhibits nuclear translocation of activated AR, inhibits DNA binding to androgen response elements, and inhibits recruitment of co-activators, even in the setting of AR over expression and in prostate cancer cells resistant to anti-androgens. By contrast with bicalutamide, enzalutamide is a pure antagonist with no detectable agonist effects in LNCaP/AR prostate cells, which over express AR. The drug also induces regression of established LNCaP/AR xenograft tumours growing in castrated male mice, a model in which bicalutamide treatment only slows tumour growth.

Clinical Data with Enzalutamide

A phase I/II first in man study in patients with progressive, metastatic CRPC was initiated in July 2007 to assess safety, pharmacokinetics, tolerability, and antitumor activity (13). After administration of one dose, the drug was rapidly absorbed, and median time to Cmax was one hour (range 0.42 minutes – 4 hours). The t1/2 was about 1 week (range 3 – 10 days) and was not affected by dose. Full pharmacokinetic profiles were linear and consistent over the dose range study. Plasma concentrations reached steady state after one month of treatment. Once achievement of steady state, the Cmin in individual patients remained constant for several months, suggesting time-linear pharmacokinetics. Due to slow clearance from plasma, the daily fluctuation in steady-state enzalutamide concentrations was low. The mean Cmax/Cmin was 1.2 (range 1.14-1.3) indicating that the average difference between the peak and trough concentrations was ≤ 30%. AR binding was assessed in 22 patients at doses from 60-480 mg daily with FHDT-PET. All patients showed clear reduction of FDHT uptake (range 20-100%).

Fatigue was the most frequently reported adverse event, with dose-dependent increases of grade 3 fatigue (0% at 150 mg/day, 9% at 240 mg/day, 15% at 360 mg/day, and 20% at 480

mg/day). The dose of 240 mg/day was defined as the maximum tolerated dose. At doses of 240 mg and above, an increasing proportion of patients needed dose reductions for fatigue. Dose reductions were needed in 1 of 29 patients (3%) that received 240 mg/day, 3 of 28 patients (11%) that received 360 mg/day, and 5 of 22 patients (23%) that received 480 mg/day, and 0 of 58 patients that received 30, 60, or 150 mg/day. After dose reductions, the symptoms resolved. Only 1 patient discontinued treatment due to fatigue with an onset coinciding with PSA rise. Overall, the most common mild (grade 2) adverse events were fatigue (n = 38, 27.1%), nausea (n = 12, 8.6%), dyspnoea (n = 11, 7.9%), anorexia (n = 8, 5.7%), and back pain (n = 8, 5.7%). Fatigue, nausea, and anorexia were the only mild adverse events with an increasing incidence as the dose of enzalutamide was increased. None of the grade 2 events required dose modification or the discontinuation of treatment, apart from 1 patient treated at 480 mg/day who had nausea at baseline and stopped therapy after 7 weeks.

Two witnessed seizures occurred in patients receiving doses of 600 and 360 mg/day, and 1 possible seizure occurred at 480 mg/day. Both patients also had complicated medical problems that could have contributed to their seizures. Other causes of treatment discontinuation included rash in 1 patient that received 480 mg/day after 10 days and in 1 patient that received 600 mg/day after 3 days, and a myocardial infarction after 15 weeks of therapy in a patient with a history of diabetes, hypertension, and hypercholesterolemia that received 360 mg/day. All patients recovered without sequelae. No deaths and no other drug-related SAEs were reported.

In regard to efficacy, antitumor effects were noted at all doses including >50% declines in PSA in 78 (56%) patients, response in soft tissue in 13 (22%) of 59 patients, stabilized bone disease in 61 (56%) of 109 patients, and conversion from unfavourable to favourable circulating tumour cell (CTC) counts in 25 (49%) of 51 patients. Disease regression was dose dependent between daily doses of 30 mg and 150 mg, however no additional benefit was noted above this threshold.

Based on these results, two placebo-controlled, randomized phase 3 studies (AFFIRM and PREVAIL) were initiated to evaluate the efficacy and safety of enzalutamide in patient with advanced prostate cancer. The AFFIRM study evaluated the safety and efficacy of enzalutamide in 1,199 patients with CRPC after chemotherapy with docetaxel (11). Patients were randomized in a 2:1 ratio to receive oral enzalutamide at a dose of 160 mg per day or placebo. The primary endpoint was OS. The study was stopped after a planned interim analysis at the time of 520 deaths. The median OS was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR 0.63, 95% CI 0.53-0.75, p<0.001). The superiority of enzalutamide over placebo was shown with respect to all secondary endpoints: ≥50% PSA reduction (54% vs. 2%, p<0.001), soft-tissue response rate (29% vs. 4%, p<0.001), the quality-of-life response rate (43% vs. 18%, p<0.001), time to PSA progression (8.3 vs. 3.0 months, p<0.001), time to first SRE (16.7 vs. 13.3 months, p<0.001).

The rates of AEs between the enzalutamide and placebo group were similar. The enzalutamide group had a lower incidence of adverse events of grade 3 or above (45.3% vs. 53.1%). The median time to first AE was 12.6 months in the enzalutamide group compared to 4.2 months in the placebo group. There was a higher incidence of all grades of fatigue, diarrhoea, hot flushes, musculoskeletal pain, and headache in the enzalutamide group compared to placebo. Cardiac disorders were noted in 6% of patients receiving enzalutamide and in 8% of patients receiving placebo. Hypertension was observed in 6.6% of patients in the enzalutamide group compared to 3.3% in the placebo group. LFT abnormalities were reported as adverse events in 1% and 2% of the enzalutamide and placebo group, respectively. Five of the 800 patients in the enzalutamide group (0.6%) were reported to have seizures and no seizures were reported in the placebo group. One case of status epilepticus required medical intervention while the other four seizures were self-limited. There were potentially predisposing factors in several patients, including two patients who had brain metastases, one patient who had inadvertently been administered lidocaine intravenously, and one patient with brain atrophy in the context of heavy alcohol use and initiation of haloperidol. Based on the results of this trial, the FDA approved enzalutamide August 2012 for the treatment of patients with metastatic CRPC who have previously received docetaxel.

Results were recently released from the second interim analysis of PREVAIL, a double-blinded, randomized, placebo-controlled trial, investigating the effectiveness of 160mg daily enzalutamide in patients with metastatic CRPC who had not yet received chemotherapy. The trial was stopped early and unblinded at the recommendation of the independent data and safety monitoring committee because of a substantial benefit in OS that met the pre-specified stopping rule: hazard ratio for overall survival 0.70; 95% confidence interval, 0.59-0.83, p<0.0001, median survival 32 versus 30 months) and radiological PFS (hazard ratio for radiological PFS 0.19; 95% confidence interval, 0.15-0.23, p < 0.0001). (20)

"Early chemotherapy" refers to the combined use of ADT plus docetaxel as first line therapy for metastatic prostate cancer as tested in the CHAARTED trial (E3805).(21) In the CHAARTED trial, early chemotherapy consisted of docetaxel 75mg/m^2 given for 6 cycles and was commenced a median of 1 month from the start of ADT. This improved median OS from 44 months with ADT alone to 57 months with early chemotherapy (HR 0.61, 95% CI 0.48-0.82, P=0.0003) and a median time to clinical progression of 33 months versus 20 months (HR 0.49, 95% CI 0.37-0.65, p<0.0001). The survival benefit was most evident in patients with high volume disease: HR 0.62, 95% CI 0.46-0.83, 17 month improvement in median OS from 32 to 49 months. There was a trend of similar magnitude for a survival benefit in men with low volume disease (HR 0.58, 95% CI 0.31-1.08), but the smaller number of events meant this was still within the play of chance.

Early chemotherapy in GETUG15 did not result in a survival benefit. (23) However, the participants in GETUG15 were predominantly men with low volume disease (80% of study population) compared with CHAARTED where approximately one third of the participants had low volume disease. Despite no significant difference in OS, there were significant improvements in biochemical PFS and clinical PFS. Biochemical PFS in the group treated with ADT plus docetaxel was 23 months versus 13 months in the group treated with ADT alone (HR 0.72, 95% CI 0.57–0.91; p=0.005). Similarly, clinical PFS was significantly longer in the group treated with ADT and docetaxel than in the group given ADT alone (medians of 24 months versus 15 months, HR 0.75, 95% CI 0.59–0.94; p=0.015).

Use of early chemotherapy is likely to become standard of care for selected men with hormone-naïve, metastatic prostate cancer. Version 2 of the ENZAMET trial protocol anticipates this likely change in standard practice by allowing and stratifying for the use of early chemotherapy with docetaxel.

There are limited data about the use of docetaxel together with enzalutamide. A phase I trial showed no significant effect of enzalutamide on peak concentrations of docetaxel in men with castration-resistant, metastatic prostate cancer (Astellas; data on file). However, 4 of the 22 participants in this study experienced febrile neutropenia. More data are required to confirm the safety of using docetaxel together with enzalutamide.

The purpose of ENZAMET is to determine whether enzalutamide in combination with androgen suppression can increase the longevity of men commencing androgen suppression for newly diagnosed metastatic prostate cancer.

2 AIM AND OBJECTIVES

General aim	To determine the effectiveness of enzalutamide versus a conventional NSAA, when combined with a LHRHA or surgical castration, as first line androgen deprivation therapy (ADT).
Primary objective (endpoint)	To determine effects on: 1) Overall survival (death from any cause)
Secondary objectives (endpoints)	To determine effects on: 2) Prostate specific antigen progression free survival (PCGW2) 3) Clinical progression free survival (imaging, symptoms, signs) 4) Adverse events (CTCAE v4.03) 5) Health related quality of life (EORTC QLQ C-30, PR-25 and EQ-5D-5L) 6) Health outcomes relative to costs (incremental cost effectiveness ratio)
Tertiary/Correlative objectives	7) To identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes)

3 DESIGN

This is a multicentre, open label, randomised, phase 3 trial.

Participants will be allocated to treatment via a central randomisation system that stratifies for:

1. High volume disease (yes versus no), characterised as:
   - 4 or more bone metastases, one of which is outside the vertebral column and pelvis AND/OR
   - Visceral metastases (e.g. lung, pleura, liver, adrenal and others)

   Lymph node involvement or bladder invasion do NOT qualify as visceral disease.
2. Study site
3. Concomitant “anti-resorptive” therapy to delay skeletal related events when commencing ADT (denosumab, zoledronic acid or any other therapy at doses proven to prevent SRE. This does not include the use of these drugs at lower doses or frequencies for the treatment or prevention of osteoporosis).
4. Co-morbidities according to the Adult Co-morbidity Evaluation (ACE-27: 0-1 vs 2-3)
5. Early use of docetaxel defined as use of docetaxel in conjunction with initiation of ADT.

4 STUDY POPULATION

Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of randomisation. All enquiries about eligibility should be addressed by contacting the CTC prior to randomisation.

4.1 Target Population

Men starting first line androgen deprivation therapy for metastatic prostate cancer.

4.2 Inclusion criteria

1. Male aged 18 or older with metastatic adenocarcinoma of the prostate defined by
   - Documented histopathology or cytopathology of prostate adenocarcinoma from a biopsy of a metastatic site

     OR
   - Documented histopathology of prostate adenocarcinoma from a TRUS biopsy, radical prostatectomy, or TURP and metastatic disease consistent with prostate cancer.

     OR
   - Metastatic disease typical of prostate cancer (i.e. involving bone or pelvic lymph nodes or para-aortic lymph nodes) AND a serum concentration of PSA that is rising and >20ng/mL
2. Target or non-target lesions according to RECIST 1.1
3. Adequate bone marrow function: Hb ≥100g/L and WCC ≥ 4.0 x 10^9/L and platelets ≥100 x 10^9/L.
4. Adequate liver function: ALT < 2 x ULN and bilirubin < 1.5 x ULN, (or if bilirubin is between 1.5-2x ULN, they must have a normal conjugated bilirubin). If liver metastases are present ALT must be < 5xULN
5. Adequate renal function: calculated creatinine clearance > 30 ml/min (Cockroft-Gault, See Appendix 7)
6. ECOG performance status of 0-2. Patients with performance status 2 are only eligible if the decline in performance status is due to metastatic prostate cancer.
7. Study treatment both planned and able to start within 7 days after randomisation.
8. Willing and able to comply with all study requirements, including treatment and required assessments
9. Has completed baseline HRQL questionnaires UNLESS is unable to complete because of limited literacy or vision
10. Signed, written, informed consent

4.3 Exclusion criteria

1. Prostate cancer with significant sarcomatoid or spindle cell or neuroendocrine small cell components
2. History of
    a. seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma).
    b. loss of consciousness or transient ischemic attack within 12 months of randomization
    c. significant cardiovascular disease within the last 3 months including: myocardial infarction, unstable angina, congestive heart failure (NYHA functional capacity class II or greater, Refer to Appendix 6), ongoing arrhythmias of Grade >2 [CTCAE, version 4.03], thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism). Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed.
3. Life expectancy of less than 12 months.
4. History of another malignancy within 5 years prior to randomisation, except for either non-melanomatous carcinoma of the skin or, adequately treated, non-muscle-invasive urothelial carcinoma of the bladder (Tis, Ta and low grade T1 tumours).
5. Concurrent illness, including severe infection that might jeopardize the ability of the patient to undergo the procedures outlined in this protocol with reasonable safety
    a. HIV-infection is not an exclusion criterion if it is controlled with anti-retroviral drugs that are unaffected by concomitant enzalutamide.
6. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse;
7. Patients who are sexually active and not willing/able to use medically acceptable forms of barrier contraception.
8. Prior ADT for prostate cancer (including bilateral orchidectomy), except in the following settings:
    a. Started less than 12 weeks prior to randomisation AND PSA is stable or falling. The 12 weeks starts from whichever of the following occurs earliest: first dose of oral anti-androgen, LHRHA, or surgical castration.
    b. In the adjuvant setting, where the completion of adjuvant hormonal therapy was more than 12 months prior to randomisation AND the total duration of hormonal treatment did not exceed 24 months. For depot preparations, hormonal therapy is deemed to have started with the first dose and to have been completed when the next dose would otherwise have been due, e.g. 12 weeks after the last dose of depot goserelin 10.8mg.
9. Prior cytotoxic chemotherapy for prostate cancer, but up to 2 cycles of docetaxel chemotherapy for metastatic disease is permitted.as per section 5.3.2.4 is allowed.
10. Participation in other clinical trials of investigational agents for the treatment of prostate cancer or other diseases.

4.4 Screening

Written informed consent must be signed and dated by the participant, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed.

4.5 Randomisation

Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this study.

Prior to randomization, treating clinicians and participants must decide if early treatment with docetaxel is to be undertaken. Randomisation will be performed via a central randomization system that stratifies for volume of disease (high versus low), site, co-morbidities (ACE-27 0-1 versus 2-3), use of anti-resorptive therapy (denosumab, zoledronic acid or neither) at time of starting ADT, and planned use of docetaxel. The decisions regarding use of early docetaxel or of anti-resorptive therapy, must be made and documented prior to randomization.

Participants will be randomly allocated (1:1) to receive either enzalutamide OR NSAA in addition to their LHRHA (or surgical castration). Study treatment should be planned to start within 7 days after randomisation.

The instructions for the randomisation system provided in the Study Manual should be followed. Confirmation of each randomisation will be provided to the site.

Individuals may only be randomised once in this trial.

5 TREATMENT PLAN

Enzalutamide is the study intervention in this trial. Conventional NSAA are used only in the control group, as per an acceptable standard of care. Participants in both groups are treated with a LHRHA (or surgical castration), as per standard of care. Treatment with enzalutamide or NSAA will continue until evidence of clinical progression or prohibitive toxicity.

Androgen deprivation is to be given continuously in this trial. Intermittent androgen deprivation will be classified as a protocol violation.

5.1 Study Treatment

5.1.1 Study treatment: Enzalutamide (XTANDI® Astellas)

Enzalutamide is provided as 40 mg soft gelatine capsules administered as 160 mg (4 capsules) orally once daily until clinical disease progression or prohibitive toxicity.

Enzalutamide will be commenced within 7 days of randomisation. If a patient randomised to enzalutamide is already receiving a NSAA, then the NSAA will be stopped at randomisation and enzalutamide should be started within 7 days or randomisation.

Enzalutamide's potency is increased with the co-administration of strong CYP2C8 inhibitors e.g, gemfibrozil. In this trial, it is preferable that these medications are ceased prior to commencing enzalutamide. However if it is not possible for these medications to be ceased then participants will need to commence enzalutamide at 80mg daily. These participants will not be permitted to have their dose of enzalutamide increased to 160mg until they have ceased the co-administration of the strong CYP2C8 inhibitor.

5.1.2 Control Treatment: Non-Steroidal Anti-Androgen (NSAA)

Participants randomised to the control group will receive a conventional NSAA, i.e. bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg three times a day. The choice of NSAA is at the discretion of the treating clinician. Drug administration should be according to the product information. Cyproterone is NOT permitted.

The NSAA will be started within 7 days after randomisation, if not already started.

The NSAA will be continued until clinical disease progression or prohibitive toxicity.

5.1.3 Required background therapy in both arms

All participants are to receive standard background therapy with a LHRHA or surgical castration, as per standard of care. The choice of the LHRHA or surgical castration is at the discretion of the treating clinician.

Administration of the LHRHA should be according to the product information guide. Options include but are not restricted to: goserelin, leuprorelin, triptorelin, or degarelix. Use of a 3-monthly depot preparation is encouraged because its administration will often correspond with protocol assessments.

If an LHRHA is to be used, then it must be started no earlier than 12 weeks before randomization, and preferably within 2 weeks after starting enzalutamide or NSAA.

If surgical castration with bilateral orchidectomy is to be used instead of a LHRHA, then it must be performed less than 12 weeks before randomisation. Orchidectomy is permitted at any time after randomisation as long as ADT has been instituted already in accordance with protocol requirements.

5.1.4 Commencement of ADT prior to randomisation.

Patients who started androgen deprivation therapy less than 12 weeks prior to randomization for metastatic disease may be eligible for this trial. If a patient is on a LHRHA, this may continue as planned. If an eligible patient is on an oral non-steroidal anti-androgen prior to randomization, then the oral anti-androgen will be stopped at randomization. If the participant is randomly assigned experimental treatment, they will then start enzalutamide within 7 days of randomisation; if the participant is randomly assigned control treatment, then the a suitable NSAA will be started within 7 days of randomisation (or continued). ADT started before randomisation is deemed to have started on the earliest date that either an anti-androgen or a LHRHA was administered.

5.2 Dose modifications of study medications

Enzalutamide: Participants who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with study drug. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day). Treatment interruption and re-initiation should be discussed with the study chair or delegate.

The dose of enzalutamide can be reduced to 120 mg/day for chronic long term grade 2 adverse events (including but not limited to fatigue or cognitive impairment) at the site investigator's discretion. The dose reduction and justification must be documented in the patient's notes.
Dose modifications for other scenarios may be considered for the wellbeing of the participant, with the approval of the study sponsor and documentation in the medical record.

If enzalutamide is co-administered with a **strong** CYP2C8 inhibitor (e.g. gemfibrozil), then the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the **strong** CYP2C8 inhibitor is discontinued, then the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Conventional NSAA: should be used as per standard of care and according to the product information. NSAA should be stopped if significant abnormalities of liver function are observed during study treatment without a likely alternative explanation, e.g. the transaminases (AST or ALT) increase beyond 2-3 times the institutional upper limit of normal, or if the bilirubin increases above twice the upper limit of normal, as per the approved product information. Recommencement of NSAA may occur at the discretion of the investigator and with appropriate monitoring.

Background treatment with a LHRHA: There are no dose modifications for LHRHA. Intermittent hormonal therapy is not allowed.

5.3 Concomitant Medications/Treatments (including early docetaxel use)

5.3.1 Recommended

The following medications and treatments are standard of care for the prevention of osteoporosis during androgen deprivation therapy and should therefore be taken in this study:

- Calcium Carbonate: Patients will receive concomitant treatment with calcium carbonate at a dose of at least 500 mg orally per day every day, e.g., Caltrate™, Tums™. Calcium is best absorbed when taken with meals.

and

- Vitamin D: Patients will receive concomitant treatment with vitamin D by oral administration of at least 400 IU of vitamin D.

5.3.2 Permitted

The following medications and treatments are permitted in this study:

5.3.2.1 Treatment or Prevention of Osteoporosis

Treatment or prevention of **osteoporosis**

- zoledronic acid e.g. Aclasta ® (5mg every 12 months)
- denosumab e.g. Prolia® (60mg every 6 months)
- Other approved agents

5.3.2.2. Treatment of Bone Metastases

Treatment for **bone metastases** as per clinical guidelines, if commenced prior to randomization and on a stable dose:

- zoledronic acid or other bisphosphonates,
- denosumab or other RANK-ligand inhibitors
- Commencement of either of these classes of bone targeted therapy for metastatic bone disease beyond 6 weeks of commencing study treatment will be considered as evidence of disease progression.

5.3.2.3 Palliative Radiotherapy

Palliative radiation for sites of disease documented at time of randomisation is permissible if required within 6 weeks of commencing ADT. In this situation, the participant may continue on study treatments.

The requirement for palliative radiotherapy beyond 6 weeks of commencing study treatment should be deemed evidence of clinical progression and study treatment should be discontinued (see Section 5.5 Treatment discontinuation).

5.3.2.4 Early use of docetaxel

The decision to use early docetaxel must be made and specified prior to randomization and is at the discretion of the treating physician and patient.

Patients who have already commenced docetaxel prior to study entry are eligible for the ENZAMET trial if they are tolerating full doses of docetaxel (75mg/m^2) with ADT, and meet all eligibility criteria for the trial while receiving docetaxel, and have had no more than 2 cycles prior to randomisation.

For ENZAMET participants randomly allocated to the enzalutamide group who have not already started chemotherapy, the first dose of docetaxel should be given at least 4 weeks after starting enzalutamide, and no more than 6 weeks after randomisation.

For ENZAMET participants randomly allocated to receive standard NSAA who have not already started docetaxel, the first dose of docetaxel should be given at least 4 weeks after starting the standard NSAA and no more than 6 weeks after randomisation.

The minimum interval of 4 weeks is to establish that there is no evidence of significant hepatotoxicity that might increase the risk of docetaxel toxicity (serum ALT <3x ULN and serum bilirubin is either <ULN, or <1.5x ULN if the participant has Gilberts Syndrome). The maximum interval of 6 weeks after randomisation is to ensure that chemotherapy is completed by the week 24 follow-up visit. Participants unable to start docetaxel at 75mg/m^2 should not be treated with early docetaxel in this trial.

Docetaxel should be administered at 75mg/m^2 every 21 days for a total of 6 cycles with dose reductions and modifications as specified below. The number of cycles and dose reductions of docetaxel will be recorded in the eCRF.

5.3.2.4.1 Dose modifications for docetaxel:

No more than two dose reductions of docetaxel should be allowed for any patient. If a patient who has had 2 dose reductions has toxicities requiring further dose reductions, then docetaxel should be stopped and they should be treated with androgen deprivation and the assigned NSAA or enzalutamide. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. **All toxicities should be graded according to CTCAE version 4.03.**

Dose adjustments for toxicity should be made according to the following guidelines. If the dose level is reduced due to toxicity, then it will not be re-escalated in subsequent cycles. Treatment may be delayed no more than 3 weeks to allow recovery from toxicity. If treatment must be delayed longer than 3 weeks from the scheduled day of dosing, then docetaxel should be stopped and the patient should be treated with androgen deprivation alone.

Dose Level	Docetaxel (mg/m^2)
Level 0	75 mg/m^2
Level - 1	65 mg/m^2
Level - 2	55 mg/m^2

a) Myelosuppression

Dose modifications are to be made based on the granulocyte and/or platelet count drawn prior to planned treatment (can be done the day prior to planned dose):

Docetaxel	Neutrophils / 10^9/L Day 1 of treatment		Platelet / 10^9/L Day 1 of treatment
No change	≥ 1.5	and	≥100
Delay and reduce one dose level*	<1.5	or	<100

NOTE: If a dose reduction is made, maintain the lower dose for all subsequent cycles.

* If a dose is held due to myelosuppression, the patient will be retreated with a one level dose reduction once neutrophil count has recovered to at least 1.5 x 10^9/L and platelet count has recovered to at least 100 x 10^9/L.

* If planned day 1 dose must be delayed for three consecutive weeks, discontinue docetaxel and continue on ADT alone.

Delay and dose modification after complicated neutropenia. Patients with afebrile Grade 4 neutropenia ≥ 7 days, or Grade 3-4 neutropenia associated with fever (one reading of oral temperature > 38.5°C, or three readings of oral temperature >38.0°C in a 24-hour period) can be retreated with a 1-level dose reduction once the absolute neutrophil count has increased to 1.5 x 109/L. The fever must have resolved and if an infection is identified, it must be adequately treated and have clinically resolved before restarting therapy. If prior bacteremia, blood cultures must be negative on recheck. Patient can continue with chemotherapy dosing while on antibiotics. Use of growth factors is not required as the dose and schedule does not meet ASCO guidelines. If however, the investigator considers it in patients best interest growth factors can be used per investigator discretion.

b) Hepatic dysfunction

ALT and Bilirubin will be evaluated pre-study and Day 1 (may be evaluated within 24 hours of day 1) of cycles 1-6 of docetaxel:

Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Dose Modifications for Abnormal Liver Function

Bilirubin		**ALT/ SGPT**	**Action**
> ULN*	or	> 5 x ULN	Wait ≤ 3 weeks. If recovered**, reduce docetaxel dose by one dose level. If not, discontinue docetaxel.
≤ ULN*	and	> 3 x ULN	Reduce docetaxel by one dose level

* For patients with Gilbert's Syndrome, wait if the bilirubin level is >1.5 its baseline value

** Recovery is < 3X ULN for ALT/SGPT and WNL for bilirubin. For patients with Gilbert's Syndrome, recovery is defined as a bilirubin level <1.5 its baseline value. Dose modifications are based on ALT/ SGPT alone due to the lack of specificity of AST/SGOT.

c) Stomatitis

If stomatitis ≥ grade 2 is present on day 1 of any cycle, docetaxel should be held until stomatitis has resolved. If Grade 3/4 stomatitis occurs at any time, the dose of docetaxel will be reduced one dose level for all subsequent doses. If a second Grade 3/4 stomatitis event is incurred, docetaxel will be reduced one more dose level. If a third Grade 3/4 stomatitis event occurs, the docetaxel should be ceased.

d) Peripheral neuropathy

If ≥ Grade 3, the patient should discontinue docetaxel.

If Grade 2, the docetaxel should be held and the patient should be retreated upon recovery to a ≤ Grade 1 toxicity with a dose reduction of docetaxel by one level.

If Grade 2 or greater neurotoxicity persists for more than 3 weeks, the patient should discontinue docetaxel.

e) Hypersensitivity reactions for docetaxel

Docetaxel should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for docetaxel hypersensitivity reactions.

Grade 4 Hypersensitivity is defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion.

Patients with two episodes of Grade 3 hypersensitivity reactions or one Grade 4 hypersensitivty reaction should discontinue docetaxel.

f) Diarrhea

If patients experience >grade 2 diarrhea and concurrent grade 3 or 4 neutropenia, hold docetaxel until ANC>1000/mm^3 and diarrhea ≤ grade 2.

If patients experience significant diarrhea (>3 loose stools/24hrs over baseline), they should be treated prophylactically in subsequent cycles with loperamide or diphenoxylate. If patient experiences >grade 2 diarrhea despite prophylaxis, docetaxel should be reduced one dose level. If patients experience > grade 2 diarrhea despite prophylaxis AND dose reduction, they should discontinue docetaxel.

g) Other toxic effects possibly related to docetaxel:

If toxicities ≤ Grade 2, manage the patient symptomatically if possible, and retreat without dose reduction.

If toxicities ≥ Grade 3 and clinically significant (not mentioned above), docetaxel should be withheld (except for anemia as patients can be transfused) until resolution to ≤ Grade 1 or baseline and patients treated with a one dose level reduction.

h) Delay of therapy:

If docetaxel has to be delayed for more than 3 weeks from planned day of dosing because of any toxicity, then docetaxel should be stopped and the patient should be treated with LHRHA plus assigned NSAA or enzalutamide.

5.3.3 Use with caution

Some drugs affect the metabolism of enzalutamide. Enzalutamide is metabolised by the liver and the cytochrome P450 pathways 2C8 and 3A4 are responsible for the metabolism of enzalutamide. Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when

combining enzalutamide with drugs that are strong inducers or inhibitors of these CYP450 metabolic pathways. Where possible these drugs should be avoided. In settings where avoidance of these drugs is not possible, suggestions for dose reductions for enzalutamide are described in Section 5.2.

Enzalutamide affects the metabolism of some drugs. Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted utilizing local laboratories.
The 'Use with caution' medication list included in this protocol is not exhaustive. Please refer to the current approved enzalutamide Investigator Brochure.

5.3.4 Prohibited

The following should not be used during this study. Participants who require treatment with any of these agents will usually need to discontinue study treatment, and should be discussed with the Study Chair or delegate:

- Other investigational treatments
- St John's Wort
- Grapefruit juice

5.3.5 Concomitant medication reporting

Concomitant medications known to interact with the study medications will be recorded as well concomitant medications on development of SAEs.

5.4 Compliance

Participant medication compliance will be formally determined by a count of tablets performed at the time of clinic review and out of sight of the participant at 4 and 12 weeks after randomisation. The participant will be counselled appropriately if significant non-compliance is determined. Compliance at subsequent visits will be assessed at the time of clinic review by questioning the participant, recording if treatment has been taken as prescribed and, if not, the reasons and number of days of treatment missed.

5.5 Treatment discontinuation

Study treatment with enzalutamide or NSAA will be permanently discontinued for any of the reasons below

- Clinical progressive disease (PD) is documented by a site investigator. PSA progression alone does not constitute clinical progression i.e. if the participant has PSA progression alone they may remain on study drug until the criteria for clinical progression are met. See SECTION 7.3 for definition of clinical progression
- Delay of hormonal treatment for greater than 30 days due to treatment-related adverse events. Treatment interruptions and re-initiations should be discussed with the study chair or delegate.
- The investigator determines that continuation of treatment is not in the patient's best interest.
- Development of adverse events during the trial that would put the participant at risk if they continued study therapy e.g. seizures or liver toxicity, whilst on enzalutamide.
- The patient declines further study treatment, or withdraws their consent to participate in the study.

In addition, enzalutamide should be discontinued in the following circumstances:

- Required use of a concomitant treatment that is prohibited, as defined in section 5.3.4
- Failure to comply with the protocol, e.g. repeatedly failing to attend scheduled assessments. If a patient has failed to attend scheduled assessments in the study, the Investigator must determine the reasons.

The reasons for discontinuing study treatment will be documented in the participant's medical record and eCRF.

Follow up of participants who stop study treatment (enzalutamide or NSAA) should continue follow-up visits according to this protocol to allow collection of outcome data.

5.5.1 Subsequent treatment

Treatment after discontinuation of study treatment is at the discretion of the patient's clinician as per standard of care.

6 ASSESSMENT PLAN

6.1 Schedule of assessments

	Screening	Baseline[1]	On Study Treatment			After study treatment	
	Within 28 days prior to randomisation	Within 7 days prior to randomisation	Day 29[2] (±7 days)	Every 12 weeks (±1 week)[3] from randomisation until clinical progression[4]	At progression[5] (PSA and clinical) and end of treatment for reasons other than progression	30-42 days after the last dose of study treatment	Every 12 weeks (±2 weeks)
Informed consent	X						
Clinic assessment[6]	X	X	X	X	X	X	
Blood tests[7]:							
Haematology (CBE)	X	X	X				
Biochemistry (EUC, LFTs[8])	X	X	X	X	X		
PSA	X	X	X	X	X		
Fasting for glucose, HbA1C, lipids		X		X (wk 24 only)	X		
Fasting bloods for translational research		X		X (wk 24 only)	X (first progression only)		
Imaging[9]:							
CT/MRI of abdomen and pelvis	X				X		
CXR or CT chest	X				X		
Whole body bone scan (WBBS)	X				X		
Compliance[10]			X	X (wk 12 only)			
Concomitant medications			Drugs used at the time of SAEs, and drugs known to interact with enzalutamide[11]				
Adverse Events[12]			X	X	X	X	
Quality of life assessments (EORTC QLQ C-30 PR-25, EQ-5D)		X	X	X	X	X	
Resource use form[13]			X	X	X	X	
Patient status						X	X
Subsequent treatment for prostate cancer						X	X

Note: In the event that LHRHA or NSAA treatment was started within 12 weeks prior to randomisation, the pre-treatment PSA will be recorded as the baseline PSA, however the baseline CT and WBBS will still be required.

Footnotes:

1. If screening bloods were collected within 7 days prior to randomisation, baseline bloods do not need to be repeated.
2. Assessments on Day 29 is for adverse events and compliance.
3. 12-weekly assessments are intended to correspond with the 3 monthly depot of LHRHA if this is being administered at the trial site.
4. 12-weekly assessments are to continue until there is evidence of clinical progression. If PSA progression occurs without clinical progression, 12 weekly assessments continue.
5. PSA progression and clinical progression often occur at different times. If so, then these assessments must be recorded at both times. PSA progression is defined according to the PCWG2 criteria: first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later. Clinical progression is defined as evidence of progression or recurrence on imaging, clinical examination, development of cancer related symptoms, or initiation of other anticancer treatment for prostate cancer.
6. A clinical assessment should be done at each study visit. Clinical assessment includes history, physical examination, performance status, and weight.The waist circumference need only be done and recorded at the baseline visit (both in the eCRF and in the patient's medical records). All visits after baseline include a review of any **adverse events and physical examination as per standard of care** for a patient at this stage of their disease and treatment. The fact that the patient has been seen and examined at that assessment, along with any relevant findings, should be recorded in the patient's notes.
7. Bloods tests include,

   1) Haematology: complete blood examination (CBE): Haemoglobin concentration, white cell count, platelet count, white cell differential.

   2) Biochemistry: electrolytes, urea, creatinine (EUC);
   liver function tests (LFT): bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT)

   3) Fasting bloods for
   i) glucose, HbA1C, lipids (standard of care) and
   ii) storage for further metabolic research and biomarker studies for those participants consenting to translational research.

   Baseline samples can be drawn within 7 days **prior to start of randomised study treatment**. Week 24 and first progression samples should be drawn at the specified timepoint plus or minus 7 days. These samples must be taken after standard overnight fasting.
   Fasting bloods due at PSA progression should be taken **when PSA progression is confirmed** by a second value 3 or more weeks later (i.e. a confirmed rising trend). For translational research bloods - even if the patient has not fasted, proceed with collecting the bloods. Then record that the patient has not fasted in the translational research documentation and eCRF.

8. Clinical assessment, haematology and biochemistry tests should be performed prior to each cycle of docetaxel as per institutional standard of care. Liver function tests must be checked every 4 weeks from commencement of study drugs (LHRHA and assigned enzalutamide or NSAA) for the first 4 months. This does not require a clinic visit or other assessments.

9. Imaging at baseline must include a CT or MRI of the abdomen and pelvis, and a radio-isotope whole body bone scan (WBBS). Baseline scans are permitted up to **35 days before study treatment begins,** provided that the patient starts study medication within **7 days** after randomisation (window of 28 days before randomization + 7 days after randomization = 35 days in total). The chest can be imaged with either a plain x-ray, or a CT scan. However if lung nodules are identified on the CXR, then a CT scan of the chest must be performed. Scans at **EOT**, for any reason, should be done within 6 weeks. If PSA progression occurs within 6 weeks before EOT then the imaging (CT/MRI, CXR/CT chest and WBBS) does not need to be repeated. If the PSA progression occurs more than 6 weeks then the imaging does need to be repeated. If a patient subsequently commences other anticancer treatment within 6 weeks of the EOT scans, the scans do not need to be repeated, otherwise if > 6 weeks from the EOT scans, the scans should be repeated.
10. Formal count, in the clinic, of treatment tablets in experimental group (enzalutamide) and control group (NSAA tablets) at weeks 4 and 12. The enzalutamide bottles should be sent to pharmacy for drug reconciliation and destruction.
11. Only in the group assigned enzalutamide
12. Adverse events categorised and graded according to CTCAE v4.03 till the 30 day safety assessment visit, 30 days after the study treatment ends.
13. The following should be documented in the patient's medical notes: duration of any hospital stays, number of hospital visits, and number of office and clinic visits, since the last assessment. This includes review of correspondence from other sites confirming these hospital stays or visits. The outcome of this check should be recorded in the patient's notes. Note that admissions to hospital, or adverse events prolonging hospital stays, may constitute Serious Adverse Events.

6.2 Assessment phase definitions and special circumstances

6.2.1 Screening

All screening procedures must be performed within 28 days prior to randomisation, unless otherwise specified.

6.2.2 Baseline

All baseline procedures must be performed within 7 days prior to randomisation, and within 14 days prior to treatment commencement, unless otherwise specified.

6.2.3 On treatment

Assessments during treatment may be performed within 7 days of the specified timepoint, unless otherwise specified.

6.2.4 End of treatment and 30 day safety assessment

An end of treatment and safety assessment should be performed 30-42 days after the last dose of study treatment to include any adverse events occurring within 30 days after the last dose of study treatment.

6.2.5 Follow-up after completion of study treatment

Study-specific follow-up assessments should be completed at the specified timepoints (± 2 weeks).

Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol.

If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries.

Participants who discontinue protocol treatment (NSAA or enzalutamide) before clinical progression (for example stopped because of toxicity, patient or clinician preference, or PSA progression without clinical progression), should have the following assessments:

1. End of treatment assessments as per the protocol Schedule of Assessments 'At progression (PSA and clinical) and end of treatment for reasons other than progression' column.
2. A safety assessment performed 30-42 days after the last dose of study treatment
3. Continuing follow-up every 12 weeks until clinical progression, as per the "Every 12 weeks (±1 week) from randomisation until clinical progression" column of the Schedule of Assessments (underneath On Study Treatment). This is to ensure we have data about the time of any subsequent PSA and/or clinical progression. Translational bloods should be collected at the times of PSA and clinical progression, not when study treatment is stopped for other reasons.

7 OUTCOMES, ENDPOINTS AND OTHER MEASURES

7.1 Overall Survival

Overall survival is defined as the interval from the date of randomisation to date of death from any cause, or the date of last known follow-up alive.

7.2 PSA Progression Free Survival

PSA progression free survival (PFS) is defined as the interval from the date of randomisation to the date of first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last known follow-up without PSA progression.

PSA progression is defined as: a rise in PSA by more than 25% AND more than 2ng/mL

above the nadir (lowest PSA point). This needs to be confirmed by a repeat PSA performed at least 3 weeks later. (See Appendix 3 for more details on the PCWG2 criteria).

7.3 Clinical Progression Free Survival

Clinical progression free survival (PFS) is defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression.

Clinical progression is defined by progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions see Appendix 3 & 4), development of symptoms attributable to cancer progression, or initiation of other anticancer treatment for prostate cancer.

7.4 Safety (Adverse events worst grade according to NCI CTCAE *v4.03)*

The NCI Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.03) will be used to classify and grade the intensity of adverse events during study treatment.

7.5 Health Related Quality of Life

HRQL will be reported by participants using the EORTC core quality of life questionnaire (QLQ C-30) and prostate cancer specific module (PR-25). The EQ-5D-5L will be used to derive utility scores suitable for quality adjusted survival analyses. (See Appendix 1).

HRQL is a secondary outcome in this trial and the specific HRQL objective is to determine differential treatment effects by comparing scores between the randomly allocated groups. The underlying hypothesis is that there will be no important differences in HRQL between the two treatment groups.

The QLQ-C30 is a validated questionnaire developed to assess HRQL in cancer patients. It includes five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. The remaining single items assess additional symptoms commonly reported by cancer patients (dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea), as well as the perceived financial impact of the disease and treatment. (14)

The QLQ-PR25 is a 25 item module designed to assess HRQL in prostate cancer patients. It includes 5 multi-item scales assessing urinary symptoms, bowel symptoms, hormonal treatment-related symptoms, sexual activity, sexual function, and incontinence aids. (15)

The EQ-5D-5L is a standardised, self-rated measure of health status designed to provide a utility score suitable for use in health economic evaluations. It provides a descriptive classification based on self-assessment of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a 5 level rating scale of no problems, slight problems, moderate problems, severe problems and extreme problems. These scores are combined with a self-rating of health on a 20cm graduated, vertical, visual analogue scale from ‘the best health you can imagine’ to ‘the worst health you can imagine’.

7.6 Health Outcomes Relative to Costs

Information on the following areas of health-care resource usage will be collected: hospitalisations (for all participants by trial staff via a standard case record form (CRF), visits to health professionals (for Australian participants via Medicare benefits scheme (MBS) and for other regions as specified separately in their Group Specific Appendix (GSA), and medications (for Australian participants via Pharmaceutical Benefits Scheme (PBS) and for other regions as

separately specified in their GSA). Consent will be sought from Australian participants for access to their MBS and PBS records. Australian unit costs will be applied to the resource usage data (e.g. Diagnosis Related Groups (DRG) costs or similar for hospitalisations, and scheduled costs for medical visits and prescription items) to estimate the incremental cost of the addition of enzalutamide to standard treatment.

Quality-adjusted survival (QAS) time will be used to quantify the incremental effectiveness of adding enzalutamide to standard treatment. QAS will be calculated by applying utility weights for quality of life derived from the EQ5D to survival data using established methods. (16)

Economic evaluation in other regions will be undertaken at the discretion of the relevant regional trial coordinating centre.

7.7 Tertiary/Correlative Objectives

These will include exploratory studies of tissue and blood samples to identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment (associations of biomarkers with clinical outcomes). Studies may include, but are not limited to:

- investigating variants of the androgen receptor (AR) - a steroid receptor transcription factor, and changes in plasma profiles (or plasma signature) in understanding mechanisms of resistance to enzalutamide;
- investigations of how enzalutamide may work in people with prostate cancer;
- studies that may help to understand the course of this cancer and related diseases;
- biomarkers may be RNA-based (single entity or entire expressed genome, RNA, miRNA), DNA-based (single entity or whole genome, germ line or tumour related), protein-based or other entities and the consent form will allow patients to allow or limit use of specimens;

- Metabolic studies including glucose, HbA1C, lipids, insulin, and IGF

The treating doctor of the participant will be notified of any analytically or clinically valid findings that may emerge significant to the participant or their family regarding cancer;

Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment is a rapidly evolving research area, the definitive list of biomarkers remains to be determined.

8 SAFETY REPORTING

8.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

Adverse events include the following:

- All suspected adverse drug reactions
- All reactions from drug– overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical

intervention or further investigation (beyond ordering a repeat examination)

- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug.

AEs must be reported as AEs even if they do not meet SAE criteria. All adverse events should be recorded and graded in the patient's medical record, and in the eCRF form associated with the relevant visit.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the participant is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

(i) The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(ii) Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

AEs and SAEs will be recorded from the date of randomisation until 30 days after the last dose of study treatment.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Participant Information Sheet and Informed Consent Form or elsewhere in the protocol. (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010)).

An event is causally related if there is a reasonable possibility that the drug [intervention] caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010).

8.2 Reporting of Serious Adverse Events (including SUSARs)

The investigator in all participating countries is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the NHMRC Clinical Trials Centre within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention.

SAE reports should be submitted to the CTC as per the procedure documented in the Study Manual.

The CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The CTC will be responsible for

providing reports to the Lead HREC in Australia and New Zealand and the regional coordinating centres in the other regions.

The investigator must notify the local HREC as required.

The CTC will submit 'reportable safety events' to the TGA in Australia and Medsafe in NZ, and to the regional coordinating centre to provide to the regulatory authorities as required in other participating countries in which the study is being conducted within the requisite timeframes, with a copy to Astellas with a copy to Astellas.

As per regulatory requirements, a SUSAR needs to be reported as soon as possible and not later than 7 days for a fatal or life threatening event and 15 days for a non-fatal or non- life threatening event.

The following information will be recorded for each Serious Adverse Event***:**

- Event description including classification according to CTCAE v4.03
- SAE criterion
- Attribution to study intervention (enzalutamide)
- Action taken with study intervention (enzalutamide), including rechallenge (if done)
- Outcome of SAE including end date if resolved

*Please note that **site staff (investigators, data-managers, study nurses)** should not complete the ***expectedness*** fields for SAE. Assessments of expectedness for SAE will be completed by the trial sponsor.

Surgical/medical procedures that require an overnight admission as an inpatient should be reported as an SAE, but the diagnosis labelling the SAE should be the problem being treated, not the procedure being done. For example, if a patient is admitted for such an operation, then the SAE should be labelled with the diagnosis/problem for which the operation was done, not the operation itself. For example, overnight admission for excision of localised skin cancer should be reported as a new malignancy, not as an excision. This includes both planned (elective) and emergency procedures.

8.3 Pregnancy

Pregnancy occurring in the partner of a participant participating in the study and up to 90 days after the completion of the study drug should be reported to the investigator and the NHMRC Clinical Trials Centre. The investigator should counsel the participant; discuss the risks of continuing with the pregnancy and the possible effects on the foetus. The partner should be counselled and followed as described above. The coordinating centre must be notified within 1 working day using the SAE form and the participant followed during the entire course of the pregnancy and postpartum period. After obtaining participant and partner consent, parental and neonatal outcomes will be recorded even if they are completely normal.

9 CENTRAL REVIEW AND BIOSPECIMEN COLLECTION

9.1 Central Tissue Collection

Where available formalin-fixed paraffin-embedded (FFPE) tissue blocks of diagnostic tumour tissue will be collected for research (including potential future translational research relevant to this study). This diagnostic tissue may include biopsy of the primary tumour, biopsy or cytology of metastatic lesion. The tissue will be from archival tumour material – no additional biopsy of the participant is required. Tissue blocks will be collected at site and sent to a central lab for histology review. Patient consent will be sought for the conduct of translational studies (tertiary /correlative objectives) on these biospecimens. Refer to the Biological Sampling Handbook for the details

relating to central tissue collection.

9.2 Central Blood Collection

Patient consent will be sought for collection of blood at 3 timepoints: baseline, week 24 from randomisation and at first evidence of progression (PSA or clinical, whichever comes first). Whole blood will be collected, processed and stored frozen at each trial site. The frozen samples will be transported later to a central lab for translational studies (tertiary /correlative objectives). Refer to the Biological Sampling Handbook for collection and processing procedures.

10 TREATMENT INFORMATION

10.1 Enzalutamide (XTANDI® Astellas)

10.1.1 Description

Enzalutamide is an androgen receptor inhibitor. It is provided as liquid-filled soft gelatine capsules each containing 40 mg enzalutamide for oral administration. Each bottle contains 120 capsules. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatine, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

Bottles of enzalutamide should be stored at a room temperature between 20ºC to 25ºC (68ºF to 77ºF), in a dry place and kept with container tightly closed.

Full details on product handling information are provided in the Product information, Investigator Brochure and Pharmacy Manual.

10.1.2 Supply

Astellas is providing the study drug free of charge. Appropriately labelled enzalutamide will be distributed by a third party to each participating site from regional warehouses. Start-up supplies of enzalutamide will be dispatched once the institution has all requisite approvals in place.

Enzalutamide will be dispensed to study participants according to usual hospital practice at each participating institution.

Full details on drug ordering and supply is provided in the Pharmacy Manual

10.1.3 Study Drug Accountability

The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient and subsequent returns. The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate.

Patients will be asked to return unused drug and empty drug containers at each return visit. Drug accountability logs will be requested, as required, from each pharmacy for central review by each regional coordinating centre.

10.2 Non-steroidal anti-androgen (NSAA)

NSAA will be provided according to usual practice. Drug accountability will not be performed for NSAA.

10.3 LHRHA (e.g. Goserelin, Leuprorelin, Degarelix)

LHRHA will provided according to usual practice. Drug accountability will not be performed for LHRHA.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size

A trial comprising 1,100 participants that are followed until approximately 470 deaths are observed (e.g. over a 2 year recruitment with an additional follow-up of 3.5 years) provides over 80% power to detect a 25% reduction in the hazard of death with a 2-sided type 1 error of 0.05 assuming a 3-year survival rate of 65% amongst controls.

A 25% reduction in the hazard of death is considered clinically plausible in light of the results of the AFFIRM trial of enzalutamide versus placebo in castration-resistant metastatic prostate cancer after chemotherapy, which showed a 37% reduction in the hazard of death, (11) and the PREVAIL trial of enzalutamide versus placebo for castration resistant metastatic prostate cancer before chemotherapy, which showed a 29% reduction in the hazard of death. (20)

The design incorporates formal interim analyses performed on overall survival using the Lan-DeMets O'Brien-Fleming spending function approach.

11.2 Statistical Analysis

A statistical analysis plan will be prepared prior to data-lock, and contain additional detail on the methods described below.

All randomised participants will be eligible for inclusion in the full analysis set. Analysis of efficacy endpoints will be undertaken on participants in the full analysis set unless participants are deemed non-evaluable by the Trial Management Committee; all such decisions will be documented in the final study report. The safety population will comprise all randomised participants who received any study medication. Participants will be analysed according to the regimen they actually received for the purposes of the safety analysis.

11.2.1 Analysis of Efficacy Endpoints

The primary analysis will be a comparison of overall survival (OS) in the two treatment arms using a log-rank test. Kaplan-Meier curves for OS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression. Other time-to-event endpoints will be analysed in a comparable fashion to the primary endpoint.

The sensitivity of the treatment effect estimate on OS to adjustment for baseline covariates, including stratification factors, will be explored. Subgroup analyses will be performed for geographical region, volume of disease strata, and docetaxel strata (additional analyses may be specified in the statistical analysis plan). An evaluation of the treatment effect in the subgroup of high volume disease patients in the docetaxel stratum will also be performed. These subgroup analyses will be performed on OS, and repeated for PSA PFS and clinical PFS endpoints.

The QoL scores collected longitudinally will be analysed using appropriate linear models for repeated measures data. Subgroup analyses on QoL endpoints will be performed by docetaxel strata and by symptom severity on baseline QoL.

11.2.2 Analysis of Safety Endpoints

A descriptive analysis of the adverse events (AE) data will be prepared for participants in the safety population. The number and percentage of participants who experience AEs will be tabulated according to CTCAE term/category, grade, and seriousness. Safety will be monitored on an ongoing basis with regular review of Serious Adverse Events (SAE) by the Trial Management Committee.

The frequency of complicated neutropenia (febrile neutropenia or infection G3-4 with neutropenia G3-4) will be monitored in real time in the first 49 participants having early docetaxel in each of the 2 randomly allocated treatment groups. Consideration will be given to modifying the protocol if complicated neutropenia is observed in 8 or more of the first 49 participants allocated enzalutamide with early docetaxel, or in 8 or more of the first 49 participants in allocated NSAA with early docetaxel. These numbers are required to distinguish the observed rate (of complicated neutropenia in each treatment group) from a rate of 25% (unacceptably high, alternate hypothesis) versus an assumed rate of 8% (acceptably low, null hypothesis) using a one-sample binomial test with 1-sided type 1 and type 2 errors of 5%.

11.2.3 Analysis of Health Outcomes Relative to Costs

A within-trial estimate of the incremental cost-effectiveness of the addition of enzalutamide to standard treatment will be calculated in terms of Australian dollars per unit of quality adjusted survival (QAS) gained.

The incremental cost of the addition of enzalutamide to standard treatment will be estimated by applying Australian unit costs to the resource usage data (e.g. ANDRG costs for hospitalisations, and scheduled costs for MBS and PBS items). QAS will be calculated by applying utility weights for quality of life derived from the EQ-5D-5L to survival data using established methods. (16)

The feasibility of extrapolating beyond the within-trial estimate of cost-effectiveness using modelling methods will be explored.

11.3 Interim analyses

Interim analyses on OS are planned as per Section 11.4. Interim results will be reviewed by the study Independent Data Safety Monitoring Committee (IDSMC) described in Section 12.2. The IDSMC will also monitor selected safety endpoints, accrual and event rates. Consideration will be given to altering aspects of the study if:

- The results of the interim analyses on OS yield clear evidence of benefit or harm based on the Lan-DeMets O'Brien-Fleming spending function approach (Section 11.4).
- The conditional power of the study (evaluated at the time of the interim analyses) is unacceptably low (e.g. <20%)
- The accrual/event rate is insufficient to complete the study in a reasonable time frame.
- The rate of serious AEs (grade 3 to 5) in the enzalutamide arm is unacceptably high compared to the control arm.
- The rate of complicated neutropenia in those receiving early docetaxel is unacceptably high (see Section 11.2.2).
- Medical or ethical reasons emerge affecting continued performance of the study.

11.4 Frequency and timing of Interim Analyses

Versions 1 and 2 of the ENZAMET protocol specified an interim analysis on OS would be performed at 67% of the required events (i.e. 470 deaths, see Section 11.1). Following simultaneous publication in June 2017 of two randomized controlled trials, LATITUDE[24] and STAMPEDE[25], the ENZAMET Trial Management Committee decided to add two extra interim analyses at 50% and 80% of required events. No interim efficacy data from ENZAMET was considered or used to reach this decision. The

Lan-DeMets O'Brien-Fleming spending function approach will be used, and remains the appropriate technique for evaluating these analysis results.

LATITUDE and STAMPEDE evaluated abiraterone (a CYP17 inhibitor) in a similar clinical setting to ENZAMET. Both studies obtained estimated HRs for OS that were more impressive than had been hypothesised when these studies were designed. Abiraterone has a different mechanism of action to enzalutamide (i.e. inhibition of androgen synthesis versus blocking the androgen receptor), but both drugs target the androgen-signalling pathway. Abiraterone and enzalutamide have similar effects on survival time in castration-resistant prostate cancer.[6, 7] Thus the results of LATITUDE and STAMPEDE have major implications for informing the hypothesised effect that enzalutamide may have on OS in ENZAMET. However, the control event rate for ENZAMET is anticipated to be lower than for LATITUDE or STAMPEDE because those trials did not mandate the use of an NSAA in their control arms, or have provision for early docetaxel use. These factors could possibly also attenuate the observed effect of enzalutamide in ENZAMET relative to the observed effects of abiraterone in LATITUDE and STAMPEDE. Taking all these considerations into account, and without appraising any interim ENZAMET outcome results, the international ENZAMET Trial Management Committee concluded that a stronger treatment effect than originally hypothesized is plausible, and decided to conduct interim analyses at 50%, 67%, and 80% of the required events to minimize delays in the detection of such an effect.

12 ORGANISATION

The study is a collaboration between the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and the NHMRC Clinical Trials Centre, at the University of Sydney, which is the sponsor in Australia and New Zealand.

This international study will be conducted at a number of regional coordinating centres, each responsible for their own ethic and regulatory approvals, regional monitoring, medical oversight and facilitation of data collection and query resolution.

Overall study coordination, data acquisition and management and statistical analysis will be performed by the global coordinating centre, the NHMRC Clinical Trials Centre.

12.1 Trial Steering Committee

The International Trial Steering Committee (ITSC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).

The ITSC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on interim analyses or other information.

Each regional trial coordinating centre will identify a clinical lead and a coordinating centre lead who will represent the region on the ITSC.

12.2 Independent Safety and Data Monitoring Committee (ISDMC)

The ISDMC will provide an independent assessment of emerging evidence from interim analyses and sources external to the trial, and make recommendations to the international TMC about potential modifications to the trial protocol and conduct. An ISDMC charter will provide details on the composition of the committee, the roles and responsibilities of committee members, the format of meetings and methods of information transfer, statistical issues and relationships with other committees.

13 ADMINISTRATIVE ASPECTS

13.1 Ethics and regulatory compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations in other countries. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the CTC, study chair and HREC must be advised immediately.

13.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC Clinical Trials Centre, University of Sydney and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

13.3 Protocol amendments

Changes and amendments to the protocol can only be made by the international Trial Management Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

13.4 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

a. Participant's name, contact information and protocol identification.

b. The date that the participant entered the study, and participant number.

c. A statement that informed consent was obtained (including the date).

d. Relevant medical history

e. Dates of all participant visits and results of key trial parameters.

f. Occurrence and status of any adverse events.

g. The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.

Patient-reported outcome data such as health-related quality of life data entered into the CRF will be considered as source.

All study-related documentation at Australian and New Zealand sites will be maintained for 15 years following completion of the study.

13.5 Study Monitoring

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC Clinical Trials Centre (CTC) or their delegates. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during the study for source data verification, review of the investigator's site file and drug handling records. The CTC or regional coordinating centres will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the participant gives authorised CTC staff direct access to their medical records and the study data.

13.6 Audit and Inspection

This study may be subject to audit or inspection by representatives of the collaborative group, Astellas, CTC or representatives of regulatory bodies (e.g. Therapeutic Goods Administration (TGA), as well as regulatory authorities in each region such as FDA or EMEA).

13.7 Clinical Study Report

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued and form the basis of a manuscript for publication. The Clinical Study Report or summary thereof will be provided to the study investigators, ANZUP, Astellas and the ethics committees. A lay summary of results will be prepared for patients and other interested parties.

13.8 Publication Policy

Authorship recognises the intellectual contributions of investigators and others to a study. It also identifies those who take public responsibility for the study. Authorship is defined as per ICMJE guidelines (www.icmje.org).The International Trial Steering Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. The Writing Committee will develop a publication plan, including authorship, target journals, and expected dates of publication. The first publication will be the report of the full trial results based on the main protocol using the study group name with a list of specific contributions at the end. ANZUP and CTC will be acknowledged in all publications. All publications must receive prior written approval from the International Trial Steering Committee prior to submission.

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15 LIST OF APPENDICES

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15.1 Appendix 1: HRQL forms (EORTC QLQ C-30 & PR-25, EQ-5D-5L)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

During the last 4 weeks…	Not at all	A little	Quite a bit	Very much
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

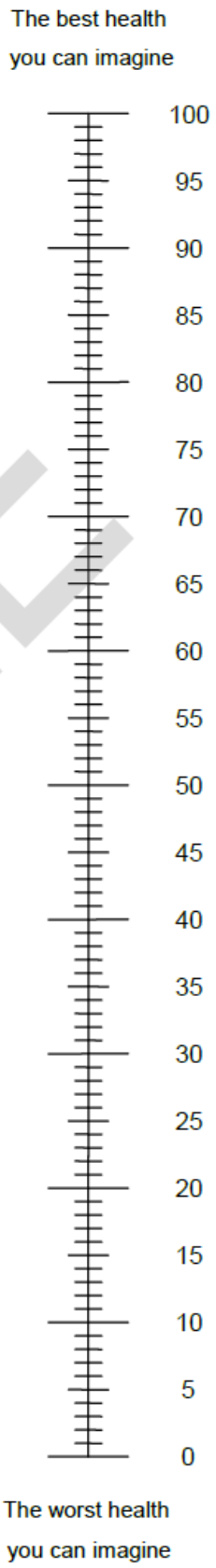
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



15.2 Appendix 2: ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol 1982. [1]

15.3 Appendix 3: Prostate Cancer Working Group 2 (PCWG2) Criteria

The sections that apply to this trial are the criteria for PSA response and progression, and the criteria for bone lesion "prevent/delay end points (progression).

Variable	PCWG2 (2007)
PSA	- Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug - Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression - Ignore early rises (prior to 12 weeks) in determining PSA response **Decline from baseline**: - Record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) **No decline from baseline:** - PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	**For control/relieve/eliminate end points:** Use RECIST with caveats: - Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline - Record changes in nodal and visceral soft tissue sites separately - Record complete elimination of disease at any site separately - Confirm favorable change with second scan - Record changes using waterfall plot **For delay/prevent end points:** - Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies) - Note that for some treatments, a lesion may increase in size before it decreases.
Bone	**For control/relieve eliminate end points:** - Record outcome as new lesions or no new lesions - First scheduled reassessment: o No new lesions: continue therapy o New lesions: perform a confirmatory scan 6 or more weeks later - Confirmatory scan: o No new lesions: continue therapy o Additional new lesions: progression - Subsequent scheduled reassessments: o No new lesions: continue o New lesions: progression **For prevent/delay end points (progression):** - The appearance of 2 or more new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions - The date of progression is the date of the first scan that shows the change
Symptoms	Consider independently of other outcome measures - Document pain and analgesia at entry with a lead in period and measure repeatedly at 3- to 4-week intervals - Perform serial assessments of global changes in HRQOL, urinary or bowel compromise, pain management, additional anticancer therapy - Ignore early changes (≤ 12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression - Confirm response or progression of pain or HRQOL end points ≥ 3 weeks later

See Scher et al 2008 [2] for more details.

15.4 Appendix 4: Response Evaluation Criteria in Solid Tumours (RECIST 1.1)

These instructions are based on the guidelines recommended by Eisenhauer et al. [3].
The sections that apply to this trial are the criteria for progression of soft tissue lesions.

1 Evaluable for response.

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below

2 Disease and lesion definitions

1.1 *Measurable Disease*. Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥10 mm with CT scan (assuming slice thickness of 5mm or less) or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres. Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

1.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

1.3 *Target Lesions*. When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions in total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological lymph nodes must meet the criterion of having a short axis of ≥ 15 mm by CT scan and only the *short* axis of these lymph nodes will contribute to the baseline sum. All other pathological lymph nodes (those with a short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of target lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions can not be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

1.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

Response Definitions

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of any specified tumour markers (no tumour markers for this trial). Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol. Confirmation of response is not required in this study.

Partial Response (PR): at least a 30% decrease in the sum of measures for target lesions (longest diameter for tumour lesions and short axis measure for target lymph nodes), taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol. Confirmation of response is not required in this study

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table: Integration of Target, non-Target and New lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of specified tumour markers, AND lymph nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks. from baseline [note, protocol may define; 6-8 weeks is recommended]
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of specified tumour markers AND lymph nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

2 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

3 Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment (or randomisation for randomized studies) until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

4 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent, unless the protocol specifies otherwise. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

4.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

4.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

4.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

4.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

4.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

4.6 *Tumour Markers*. Tumour markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. There are no specified tumour markers for this trial.

4.7 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

15.5 Appendix 5: TNM staging for prostate cancer

Pathologic staging

pT2	Organ confined.
pT2a	Unilateral, ≤½ of one side.
pT2b	Unilateral, involving >½ of side but not both sides.
pT2c	Bilateral disease.
pT3	Extraprostatic extension.
pT3a	Extraprostatic extension or microscopic invasion of bladder neck.[b]
pT3b	Seminal vesicle invasion.
pT4	Invasion of rectum, levator muscles, and/or pelvic wall.

p = Pathologic; T = Primary tumor.

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Stages

Stage	TNM	Description
I	T1a, N0, M0, G1	T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

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Stage	TNM	Description
IIA	T1a, N0, M0, G2–4	T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIA	T1b, N0, M0, any G	T1b = Tumor incidental histologic finding in >5% of tissue resected.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIA	T1c, N0, M0, any G	T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIB	T1, N0, M0, any G	T1 = Clinically inapparent tumor neither palpable nor visible by imaging.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
IIB	T2, N0, M0, any G	T2 = Tumor confined within prostate.[b]
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

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Stage	TNM	Description
III	T3, N0, M0, any G	T3 = Tumor extends through the prostate capsule.[c]
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade.

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Stage	TNM	Description
IV	T4, N0, M0, any G	T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).
	Any T, N1, M0, any G	TX = Primary tumor cannot be assessed.
		T0 = No evidence of primary tumor.
		T1 = Clinically inapparent tumor not palpable or visible by imaging.
		T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		T1b = Tumor incidental histologic finding in >5% of tissue resected.
		T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).
		T2 = Tumor confined within prostate.[b]
		T2a = Tumor involves ≤50% of one lobe.
		T2b = Tumor involves >50% of one lobe but not both lobes.
		T2c = Tumor involves both lobes.
		T3 = Tumor extends through the prostate capsule.[c]
		T3a = Extracapsular extension (unilateral or bilateral).
		T3b = Tumor invades seminal vesicle(s).
		T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as the bladder, external sphincter, rectum, levator muscles, and/or pelvic wall.
		N1 = Metastasis in regional lymph node(s).
		M0 = No distant metastasis.[a]
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

	Any T, any N, M1, any G	TX = Primary tumor cannot be assessed.
		T0 = No evidence of primary tumor.
		T1 = Clinically inapparent tumor not palpable or visible by imaging.
		T1a = Tumor incidental histologic finding in ≤5% of tissue resected.
		T1b = Tumor incidental histologic finding in >5% of tissue resected.
		T1c = Tumor identified by needle biopsy (e.g., because of elevated PSA).
		T2 = Tumor confined within prostate.[c]
		T2a = Tumor involves ≤50% of one lobe.
		T2b = Tumor involves >50% of one lobe but not both lobes.
		T2c = Tumor involves both lobes.
		T3 = Tumor extends through the prostate capsule.[c]
		T3a = Extracapsular extension (unilateral or bilateral).
		T3b = Tumor invades seminal vesicle(s).
		T4 = Tumor is fixed or invades adjacent structures other than seminal vesicles such as the bladder, external sphincter, rectum, levator muscles, and/or pelvic wall.
		NX = Regional lymph nodes were not assessed.
		pNX = Regional nodes not sampled.
		N0 = No regional lymph node metastasis.
		pN0 = No positive regional nodes.
		N1 = Metastasis in regional lymph node(s).
		pN1 = Metastases in regional node(s).
		M1 = Distant metastasis.[a]
		M1a = Nonregional lymph node(s).
		M1b = Bone(s).
		M1c = Other site(s) with or without bone disease.
		GX = Grade cannot be assessed.
		G1 = Well differentiated (slight anaplasia) (Gleason score of 2–4).
		G2 = Moderately differentiated (moderate anaplasia) (Gleason score of 5–6).
		G3–4 = Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10).

T = Primary tumor; N = Regional lymph nodes; M = Distant metastasis; G = Histopathologic grade; p = Pathologic.

Reprinted with permission from AJCC: Prostate. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 457-68.

[a] *When more than one site of metastasis is present, the most advanced category (pM1c) is used.*

[b] *Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.*

[c] *Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.*

15.6 Appendix 6: NYHA Heart Failure Classification

Reference: The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Criteria for use of the terms *minimal*, *moderately severe*, and *severe disease* cannot be defined precisely. Grading is based on the individual physician's judgment. The objective assessment of a patient with cardiac disease who has not had specific tests of cardiac structure or function is classified as undetermined.

The classification of patients according to cardiac functional capacity is only part of the information needed to plan the management of patients' activities. A prescription for physical activity should be based on information from many sources. Functional capacity is an estimate of what the patient's heart will allow the patient to do and should not be influenced by the character of the structural lesions or an opinion as to treatment or prognosis. A recommendation for physical activity is based not only on the amount of effort possible without discomfort but also on the nature and severity of the disease.

Following are examples of functional capacity and objective assessment classifications.

- A patient with minimal or no symptoms but a large pressure gradient across the aortic valve or severe obstruction of the left main coronary artery is classified: Functional Capacity I, Objective Assessment D
- A patient with a severe anginal syndrome but angiographically normal coronary arteries is classified: Functional Capacity IV, Objective Assessment A
- A patient with acute myocardial infarction, shock, reduced cardiac output, and elevated pulmonary artery wedge pressure is classified: Functional Capacity IV, Objective Assessment D
- A patient with mitral stenosis, moderate exertional dyspnea, and moderate reduction in mitral valve area is classified: Functional Capacity II or III, Objective Assessment C

Functional Capacity	**Objective Assessment**
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

15.7 Appendix 7: Adult Comorbidity Evalutation - 27

Adult Comorbidity Evaluation-27

Identify the important medical comorbidities and grade severity using the index.
Overall Comorbidity Score is defined according to the highest ranked single ailment, except in the case where two or more Grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score should be designated Grade 3.

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Cardiovascular System			
Myocardial Infarct	☐ MI ≤ 6 months	☐ MI > 6 months ago	☐ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	☐ Unstable angina	☐ Chronic exertional angina ☐ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) ☐ Recent (≤ 6 months) coronary stent	☐ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms ☐ Angina pectoris not requiring hospitalization ☐ CABG or PTCA (>6 mos.) ☐ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	☐ Hospitalized for CHF within past 6 months ☐ Ejection fraction < 20%	☐ Hospitalized for CHF >6 months prior ☐ CHF with dyspnea which limits activities	☐ CHF with dyspnea which has responded to treatment ☐ Exertional dyspnea ☐ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	☐ Ventricular arrhythmia ≤ 6 months	☐ Ventricular arrhythmia > 6 months ☐ Chronic atrial fibrillation or flutter ☐ Pacemaker	☐ Sick Sinus Syndrome ☐ Supraventricular tachycardia
Hypertension	☐ DBP≥130 mm Hg ☐ Severe malignant papilledema or other eye changes ☐ Encephalopathy	☐ DBP 115-129 mm Hg ☐ DBP 90-114 mm Hg while taking antihypertensive medications ☐ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	☐ DBP 90-114 mm Hg while not taking antihypertensive medications ☐ DBP <90 mm Hg while taking antihypertensive medications ☐ Hypertension, not otherwise specified
Venous Disease	☐ Recent PE (≤ 6 mos.) ☐ Use of venous filter for PE's	☐ DVT controlled with Coumadin or heparin ☐ Old PE > 6 months	☐ Old DVT no longer treated with Coumadin or Heparin
Peripheral Arterial Disease	☐ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago ☐ Untreated thoracic or abdominal aneurysm (≥6 cm)	☐ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago ☐ Chronic insufficiency	☐ Intermittent claudication ☐ Untreated thoracic or abdominal aneurysm (< 6 cm) ☐ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	☐ Marked pulmonary insufficiency ☐ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment ☐ Chronic supplemental O_2 ☐ CO_2 retention (pCO_2 > 50 torr) ☐ Baseline pO_2 < 50 torr ☐ FEV1 (< 50%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities ☐ FEV1 (51%-65%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment ☐ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	☐ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	☐ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	☐ Chronic hepatitis or cirrhosis without portal hypertension ☐ Acute hepatitis without cirrhosis ☐ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	☐ Recent ulcers(≤ 6 months ago) requiring blood transfusion	☐ Ulcers requiring surgery or transfusion > 6 months ago	☐ Diagnosis of ulcers treated with meds ☐ Chronic malabsorption syndrome ☐ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	☐ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	☐ Uncomplicated acute pancreatitis ☐ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	☐ Chronic pancreatitis w/o complications

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Renal System			
End-stage renal disease	☐ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis ☐ Acute dialysis	☐ Chronic Renal Insufficiency with creatinine >3 mg% ☐ Chronic dialysis	☐ Chronic Renal Insufficiency with creatinine 2-3 mg%.
Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	☐ Hospitalization ≤ 6 months for DKA ☐ Diabetes causing end-organ failure ☐ retinopathy ☐ neuropathy ☐ nephropathy* ☐ coronary disease* ☐ peripheral arterial disease*	☐ IDDM without complications ☐ Poorly controlled AODM with oral agents	☐ AODM controlled by oral agents only
Neurological System			
Stroke	☐ Acute stroke with significant neurologic deficit	☐ Old stroke with neurologic residual	☐ Stroke with no residual ☐ Past or recent TIA
Dementia	☐ Severe dementia requiring full support for activities of daily living	☐ Moderate dementia (not completely self-sufficient, needs supervising)	☐ Mild dementia (can take care of self)
Paralysis	☐ Paraplegia or hemiplegia requiring full support for activities of daily living	☐ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	☐ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	☐ Recent suicidal attempt ☐ Active schizophrenia	☐ Depression or bipolar disorder uncontrolled ☐ Schizophrenia controlled w/ meds	☐ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	☐ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	☐ Connective Tissue Disorder on steroids or immunosuppressant medications	☐ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	☐ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	☐ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	☐ Asymptomatic HIV+ patient. ☐ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	☐ Uncontrolled cancer ☐ Newly diagnosed but not yet treated ☐ Metastatic solid tumor	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago
Leukemia and Myeloma	☐ Relapse ☐ Disease out of control	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	☐ Relapse	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	☐ Delirium tremens	☐ Active alcohol abuse with social, behavioral, or medical complications	☐ H/o alcohol abuse but not presently drinking
Illicit Drugs	☐ Acute Withdrawal Syndrome	☐ Active substance abuse with social, behavioral, or medical complications	☐ H/o substance abuse but not presently using
Body Weight			
Obesity		☐ Morbid (i.e., BMI ≥ 38)	

OVERALL COMORBIDITY SCORE (Circle one.)	**0**	**1**	**2**	**3**	**9**
	None	**Mild**	**Moderate**	**Severe**	**Unknown**

15.8 Appendix 8: Cockroft-Gault formula

Renal function (GFR) may be estimated with the Cockcroft–Gault formula, as follows:

Male participants:

Creatinine clearance (ml/minute) = $\frac{(140 - age) * weight}{0.814 * SerumCr}$

Units:
Age in years
Weight in kilograms
Serum creatinine (SerumCr) in micromoles per litre

Female participants: Use above formula but multiply calculated Creatinine clearance by 0.85

1. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* American journal of clinical oncology, 1982. **5**(6): p. 649-656.
2. Scher, H.I., et al., *Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group.* Journal of Clinical Oncology, 2008. **26**(7): p. 1148-1159.
3. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

Summary of changes made to ENZAMET SAP from version 1.0 to version 2.0

Page 1: Protocol number added

Page 4: Additional detail added to censoring rules for PSA progression and clinical progression.

Page 4-5: Additional detail added to definition of analysis sets

Page 6: Clarified that analyses would use stratification data that was corrected post-randomisation, in the event it was incorrect at the time of randomisation.

Page 7: Subgroup analysis added for 'Prior local treatment Y vs N'

Page 8: Use of 'conditional mean-adjusted estimator' to explore effect of early rejection of null hypothesis on estimate hazard ratio.

Page 8-9, 13: Additional detail on derivation, and analysis, of quality of life endpoints data.

Page 9: Additional detail on derivation, and analysis, of quality-adjusted survival time.

Page 10: Use of Benjamini-Hochberg procedure to calculate p-values adjusted for multiple comparisons

Section 10.3 (Appendix): Minor edits to some table shells

Summary of changes made to ENZAMET SAP from version 2.0 to Addendum 1.1

The purpose of addendum v1.1 was to document the planned analyses of primary and secondary endpoints once N=470 deaths have occurred.

Addendum v1.1 differs from the SAP v2.0 in the following respects:

1. The number of deaths needed to trigger the analysis is N=470 (whereas SAP v2.0 had provision for earlier interim analyses).
2. The secondary objectives relating to Quality of Life and Resource Usage are out-of-scope.
3. "M0 disease at primary diagnosis (Y/N)" will be used in the subgroup analyses in place of "Local treatment (Y/N)" as a more accurate approach for distinguishing men who presented initially with non-metastatic disease and later developed metastatic hormone sensitive prostate cancer. The use of "Local treatment (Y/N)" was originally specified to identify this subgroup in order to align with the approach taken in the CHAARTED trial, however "Local treatment (Y/N)" in the ENZAMET database is an inaccurate marker of the clinical group of interest as men diagnosed with de novo metastatic disease may have received local therapy.
4. A section on efficacy estimand definition has been added.
5. References to a Per-Protocol Analysis set have been removed. All efficacy analyses will be performed on the full analysis set comprising all randomised patients (i.e. the ITT population).

6. Appendices (describing QoL scoring systems and output table shells) have been removed.

The following aspects in addendum 1 are unchanged from SAP v2.0:

1. Endpoint derivations
2. Analysis set definitions for the ITT and Safety Populations
3. Accounting for stratification factors
4. Approach to analyses of study endpoints and patient characteristics

NHMRC Clinical Trials Centre

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: ENZAMET

Statistical Analysis Plan

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Version: 1.0

Version date: 20180329

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29th March 2018

Contents

1 Introduction

The aim of the ENZAMET trial is to determine the effectiveness of enzalutamide versus conventional non-steroidal anti-androgen (NSAA) in men with metastatic prostate cancer.

The study is an open label phase III trial that randomises eligible patients to receive, until disease progression or prohibitive toxicity, either: oral enzalutamide 160mg daily or conventional oral NSAA treatment. All participants are treated with surgical castration or a Luteinizing Hormone-Releasing Hormone Analog (LHRHA)

The randomisation is performed in a 1:1 ratio and is stratified by volume of disease (high volume yes versus no), use of early docetaxel (yes versus no), antiresorptive therapy (yes versus no), comorbidities (Adult Co-morbidity Evaluation ACE-27 score: 0-1 vs 2-3), and treating institution (Study Site).

The target population is men with metastatic prostate cancer commencing androgen deprivation therapy. Key eligibility criteria include metastatic prostate cancer, adequate organ function and ECOG performance status 0-2.

The primary objective is to determine the effect of enzalutamide on overall survival (OS). The secondary objectives are to determine the effect of enzalutamide on: prostate specific antigen progression free survival (PCGW2), clinical progression free survival (imaging, symptoms, signs), adverse events (CTCAE v4.03), health related quality of life (EORTC QLQ C-30, PR-25 and EQ-5D-5L), and health outcomes relative to costs.

Correlative objectives include: to identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment. A separate analysis plan will be prepared to address these objectives.

The statisticians working on this study are aware of the importance treating any unblinded efficacy results as highly sensitive and taking reasonable measures to keep such information confidential, despite this being an open label study. DRAFT tabulations/analyses of efficacy endpoints should be prepared using dummy treatment allocations, or be pooled across randomised groups. Occasions where tabulations/analyses of efficacy endpoints are prepared by actual treatment allocation (for an interim analysis and/or the final analysis) will be documented. Access to the analysis programming environment will be restricted to authorised personnel.

2 Endpoint Derivation

A central clinical review will be performed on the results of the endpoint derivations specified below. A series of specific programmed endpoint checks are also performed, with any issues being centrally reviewed. Treatment allocation will not be included on the review outputs. Any instances

where the specifications below are overruled on the basis of the clinical review findings will be endorsed by the Clinical Lead (on behalf of the TMC) and documented in the study report.

2.1 Overall Survival (OS) (Primary Endpoint)

Overall survival is defined as the interval from the date of randomisation to date of death from any cause, or the date last known alive (at which point the observation is censored).

2.2 PSA Progression Free Survival (PSA PFS)

PSA progression free survival (PSA PFS) is defined as the interval from the date of randomisation to the date of first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last known follow-up without PSA progression (at which point the observation is censored).

2.3 Clinical Progression Free Survival (Clinical PFS)

Clinical progression free survival is defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression (at which point the observation is censored). Clinical progression is defined by progression on imaging, development of symptoms attributable to cancer progression, or initiation of other anticancer treatment for prostate cancer.

2.4 Safety

The NCI Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE) will be used to classify and grade the intensity of adverse events whilst on treatment, at progression, and 30-42 days after the last dose of study treatment.

2.5 Quality of Life (QoL)

The core EORTC QoL Questionnaire (QLQ-C30) will be used in conjunction with the disease specific module for prostate cancer (PR25). The EQ-5D will be used to obtain utility valuations on the health states experienced by participants. All instruments will be scored according to standard conventions (see Section 10.1 and 10.2).

2.6 Health Care Resource Usage

Information on the following areas of health-care resource usage will be collected: protocol therapy and hospitalisations (for all participants by trial staff via standard case record forms (CRFs), visits to health professionals (for Australian participants via Medicare benefits scheme (MBS) and for other regions as specified separately in their Group Specific Appendix (GSA), and non-protocol medications (for Australian participants via Pharmaceutical Benefits Scheme (PBS) and for other regions as separately specified in their GSA).

3 Analysis Sets

The intention-to-treat (ITT) population will comprise all randomised participants. The per-protocol population will comprise all randomised participants that are deemed eligible/evaluable on blinded central clinical review. The safety population will comprise all randomised participants that are deemed eligible/evaluable on blinded central clinical review who received at least one

administration of study medication. The reasons for any exclusions from analysis sets will be reviewed and endorsed by the Trial Executive Committee and documented in the final study report.

The primary analysis population used for the evaluation of enzalutamide on non-safety parameters will be the ITT population. The per-protocol population may be used in secondary analyses of non-safety parameters as part of a sensitivity analysis. Safety analyses will be performed using the safety population, and analysed according to allocated treatment (crossover is expected to be minimal during the period of planned study treatment).

4 Interim and Final Analyses

Assuming the study is not terminated early, the final analysis is planned to be undertaken after the required number of deaths have occurred (specified in sample size section of the protocol). The study design incorporates formal interim analyses performed on OS once 50%, 67%, and 80% of the required events are observed. The interim analysis allows for early rejection of the null hypothesis according to an alpha spending function with an O'Brien-Fleming boundary shape[1]. Indicative boundaries for these analyses are presented in the table below. The actual number of events observed at the time of the interim analyses would be used to construct the definitive rejection boundary. The conditional power (CP) of the study will also be calculated for OS at the interim analyses.[2] This procedure does not 'spend' any alpha associated with the test of the null hypothesis. The Independent Data Safety Monitoring Committee (IDSMC) may recommend altering aspects of the study (e.g. early termination on futility grounds) if the CP is unacceptably low. A CP <20% is suggested in the protocol as a guide for the IDSMC for defining 'an unacceptably low CP'. Refer to interim analysis section of the protocol for additional information on feasibility and safety monitoring overseen by the IDSMC.

Table 1: Indicative Boundary for Rejection of the Null Hypothesis

Stage	Proportion of Required Events	Z Score Boundary Rejection of the Null Hypothesis*	2-Sided P-value Corresponding to Boundary
1	0.5	+/-2.96	0.003
2	0.67	+/-2.53	0.011
3	0.8	+/-2.32	0.020
4	1	+/-2.03	0.042

* Calculated using following SAS code: PROC SEQDESIGN plots=boundary(hscale=samplesize) PSS(CREF=1) STOPPROB(CREF=1); ErrorSpendOBrienFleming: design nstages=4 method=ERRFUNCOBF ALPHA=0.05 BETA=0.133 INFO=CUM(0.50 0.67 0.80 1); run;

5 Type I Error (Alpha)

Unless otherwise specified (e.g. See Section 4 above), a two-sided alpha of 5% will be applied to interpret the results of hypothesis tests and to construct confidence intervals. P-values from

[1] Lan KKG, and DeMets DL. Discrete Sequential Boundaries for Clinical Trials. Biometrika 1983;70:659–663

[2] Lan KKG, Simon R and Halperin M. Stochastically curtailed tests in long–term clinical trials Sequential Analysis 1982;1:3:207-219

secondary analyses that are unadjusted for multiple comparisons, and/or early stopping of the trial, will be interpreted conservatively. For the many planned adjusted and subgroup analysis, this will involve grouping hypothesis tests into discrete families (sets), and evaluating the p-values within each family with due consideration of the family-wise type I error rate (See Section 0).

6 Accounting for Stratification Factors

Randomisation is stratified by 'volume of disease' (high volume yes versus no), 'use of early docetaxel' (yes versus no), 'use of antiresorptive therapy' (yes versus no), comorbidities (Adult Co-morbidity Evaluation ACE-27 score: 0-1 vs 2-3), and treating institution (Study Site). Sensitivity of conclusions when accounting for these factors will be explored in secondary analyses (See Section 0). Study sites will be grouped into geographical regions for these analyses. The regions are Europe (UK and Ireland), Australasia (Australia and New Zealand), and North America (USA and Canada).

7 Subgroups of Particular Interest

Consistency of the treatment effect on OS will be evaluated across prespecified subgroups defined by the stratification factors and the baseline characteristics shown below in Table 2. Consistency of the treatment effect on PSA PFS and clinical PFS will also be evaluated across these same subgroups. Study sites will be grouped into geographical regions for these analyses (See Section 6). The effects of enzalutamide in participants treated with early docetaxel, especially in participants with high volume disease treated with early docetaxel, are of particular clinical interest (see section 9).

Table 2: Subgroups Definitions

	Subgroup Definitions	**Subgroup Definitions from Other Trials (presented for reference)**		
Subgroups	**ENZAMET**	**STAMPEDE**	**LATITUDE**	**CHAARTED**
Gleason Score	≤7 vs 8-10	≤7 vs 8-10	≤7 vs 8-10	≤7 vs 8-10
Age	<70 vs ≥70	<70 vs ≥70	<65, ≥65, ≥75	<65, ≥65, ≥75
Performance Status	0 vs 1-2	0 vs 1-2	0 vs 1-2	
Visceral Disease	Yes vs No		Yes vs No	
High volume disease	Yes vs No			Yes vs No
Early docetaxel	Yes vs No			
Anti-resorptive threapy	Yes vs No			
ACE-27	0-1 vs 2-3			
Region	ANZ vs Europe vs North America			

8 Analysis of Study Endpoints and Patient Characteristics

See Section 10.3 for indicative mock-ups of the planned outputs for the analyses described below.

8.1 Subject Disposition

The number of patients in the analysis sets will be presented along with reasons for any exclusions. The Kaplan-Meier method will be used to summarise follow-up time for OS by treatment allocation with deaths being treated as censored observations. A CONSORT flow diagram will be prepared.

8.2 Baseline Demographic and Clinical Characteristics

Descriptive statistics will be prepared to summarise baseline characteristics of the study participants by treatment allocation. Variables to be summarised include: age, BMI, stratification factors, prostate cancer characteristics, and previous treatment for prostate cancer.

8.3 Exposure to Study Medication

The Kaplan-Meier method will be used to summarise time on study medication by treatment allocation, with any patients remaining on treatment being censored at the time the most recent dosing was recorded. Reasons for discontinuations will be tabulated by treatment group.

8.4 Other Treatments

The use of non-protocol anti-cancer treatment will be tabulated by treatment group.

A listing of other concomitant medications (and reasons for the concomitant medications) will be prepared.

8.5 Overall Survival (OS) – Primary Analysis of Primary Endpoint

Overall survival (OS) time for each treatment group will be quantified using the Kaplan-Meier method and compared using a log-rank test. A Cox PH model will be used to estimate the hazard ratio (with 95% CI). Section 4 and 9 provide detail on the interim, adjusted, and subgroup analyses that are planned to be conducted on OS.

8.6 PSA Progression Free Survival (PSA PFS)

PSA Progression Free Survival time for each treatment group will be quantified using the Kaplan-Meier method and compared using a log-rank test. A Cox PH model will be used to estimate the hazard ratio (with 95% CI).

8.7 Clinical Progression Free Survival (Clinical PFS)

Clinical Progression Free Survival will be analysed using the same approach as that described above for PSA PFS.

8.8 Safety Data Analysis

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be tabulated by treatment allocation and CTCAE criteria including system organ class, term, and (worst) grade.

8.9 Quality of life (QoL)

A descriptive analysis of QoL data over time will be undertaken. Scales for each QoL will be derived as per scoring manuals described in Sections 10.1 and 10.2. Scale scores from the QLQ-C30, PR25

and EQ5D will be summarised by treatment group over time, and are planned to be analysed using a mixed model for repeated measures (MMRM). The MMRM will include covariates for baseline, treatment arm, post-baseline time-point, and a treatment-by-time point interaction. A blinded analysis (of interim) QoL data will be used to refine the analysis method. This will include: (i) specifying the covariance structure after evaluation of various options (including compound symmetry and autoregressive) using the AIC statistic; and (ii) specifying the strategy for accommodating any highly skewed data (e.g. log transformation, or split at median or other logical value with analysis of the resultant categorical endpoint performed using a repeated measures generalised linear model with a logit link function).

8.10 Quality-Adjusted Survival (QAS)

Within-trial estimates of quality-adjusted survival (QAS) will be calculated for each randomised treatment group using the "quality-adjusted survival analysis with repeated measures" method[3]. This involves combining the QoL utility function estimated from the repeated measures analysis of the EQ-5D and the survival function estimated using the AUC of the Kaplan-Meier method. The QAS estimates will be truncated at the time point when either of the arms has <10% of patients at risk[4].

8.11 Analysis of Health Outcomes Relative to Costs

Australian unit costs will be applied to the resource usage data (See Section 2.6) to estimate the within-trial cost difference (in Australian dollars) between randomised arms. A within-trial estimate of the incremental cost-effectiveness of the addition of enzalutamide to standard treatment will be calculated in terms of the cost difference relative to the quality adjusted survival (QAS) difference.

The feasibility of extrapolating beyond the within-trial estimate of cost-effectiveness using modelling methods will be explored.

9 Adjusted and Subgroup Analyses

Sensitivity of conclusions from the primary analysis on OS to adjustment for stratification factors (See Section 6) will be investigated for the ITT population. A comparison between randomised groups will be undertaken using a stratified long-rank test. An adjusted hazard ratio (with 95% CI) will be obtained from a Cox PH model that includes the stratification factors as covariates. These analyses will be performed on the ITT population.

The consistency of the treatment effect on OS across the stratification factors and other pre-specified baseline characteristics (See Section 7) will be tested by fitting the relevant factor-by-treatment interaction term in a Cox regression model along with the associated main effects terms. The subgroup analyses will be repeated using PSA PFS and clinical PFS as the endpoints.

[3] Glasziou et al. Quality adjusted survival analysis with repeated quality of life measures. Stat Med. 1998 Jun 15;17(11):1215-29.
[4] Pocock et al. Survival plots of time-to-event outcomes in clinical trials: Good practice and pitfalls. Lancet. 2002;359:1686–9.

A clinical question of particular importance and interest is whether early docetaxel modifies the effect of enzalutamide in patients with high volume disease. The corresponding analysis will involve fitting a docetaxel-by-treatment interaction term, along with the associated main effects terms, in a Cox regression model applied to PSA PFS in the cohort of patients with high volume disease in the ITT population. Because that analysis will only include high disease volume patient, it will have less statistical power to detect effect modification than those subgroup analyses applied to the full ITT population.

The hypothesis tests from the planned adjusted and subgroup analysis described below will be considered as discrete sets (families) of secondary analyses: (1) a set of adjusted analyses; (2) a set of subgroup analyses on OS; (3) a set of subgroup analyses on PSA PFS; and (4) a set of subgroup analyses on clinical PFS. Due consideration will be given to the family-wise type I error rate when conservatively interpreting the p-values within each of family of tests.

10 Appendix

10.1 EORTC scoring

QLQ-C30					
	Scale	No. items	Range	Item number	High score
Global health status / QoL					
Global health status/QoL	QL2	2	6	29, 30	+ve
Functional scales					
Physical	PF2	5	3	1 - 5	+ve
Role	RF2	2	3	6, 7	+ve
Emotional	EF	4	3	21 - 24	+ve
Cognitive	CF	2	3	20, 25	+ve
Social	SF	2	3	26, 27	+ve
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	-ve
Nausea and vomiting	NV	2	3	14, 15	-ve
Pain	PA	2	3	9, 19	-ve
Dyspnoea	DY	1	3	8	-ve
Insomnia	SL	1	3	11	-ve
Appetite loss	AP	1	3	13	-ve
Constipation	CO	1	3	16	-ve
Diarrhoea	DI	1	3	17	-ve
Financial difficulties	FI	1	3	28	-ve
QLQ-PR25					
Symptom scales / items					
Urinary symptoms	PRURI	8	3	1 – 7,9	-ve
Bowel symptoms	PRBOW	4	3	10 – 13	-ve
Hormonal treatment-related symptoms	PRHTR	6	3	14 – 19	-ve
Incontinence aid	PRAID	1	3	8	-ve
Functional scales/items					
Sexual activity	PRSAC	2	3	20, 21	+ve
Sexual functioning	PRSFU	4	3	22-25	+ve

QLQ-PR25

The prostate cancer module is meant for use among patients with prostate cancer varying in disease stage and treatment modality (i.e. surgery, chemotherapy, radiotherapy, etc.). It should always be complemented by the QLQ-C30.

Remarks

- Items 20 and 21 can be completed by all patients

- Items 22-25 are conditional on being sexually active, and thus will only be completed by a subgroup of patients. **This will require reversing the response categories of questions 23-25 but not of 22**.

Definition:

In practical terms, if $I_1, I_2, \ldots, I_n$ are included in a scale, the procedure is as follows:

Calculate the raw score: $$RS = \frac{I_1 + I_2 + \cdots + I_n}{n}$$

Apply the linear transformation to 0-100 to obtain the score S:

Functional Scales: $$S = \{1 - \frac{(RS - 1)}{range}\} * 100$$

Symptom scales/items: $$S = \{\frac{(RS - 1)}{range}\} * 100$$

Global health status/QoL: $$S = \{\frac{(RS - 1)}{range}\} * 100$$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all the items in any scale take the same values. Therefore the range of RS equals the range of the items. Most items are scored 1 to 4 giving a *range* of 3. Exceptions are the items contributing to the global health status/QoL, which are 7-point questions with a *range* of 6.

Note a high score for a functional scale represents a *high/*healthy level of functioning, a high score for the global health status/QoL represents a *high QoL*, but a high score for a symptom/item scale represents a *high level of symptomatology/problems.*

Missing Items:

If at least half of the items from the scale have been answered, assume that the missing items have values equal to the average of those items which *are* present for that respondent.

Thus:

- Have at least half of the items from the scale been answered?
- If Yes, use all the items that were completed, and apply the standard equations for calculating the scale scores; ignore any items with missing values when making the calculations.
- If No, set scale score to missing.
- For single-item measures, set score to missing.

10.2 EQ5D-5L

a. 5 dimensions of QOL; generic (not tumor/cancer specific)
b. 5 possible answers to each dimension
c. transformed into a single index value
d. second part: visual analogue scale (0-100)

The EQ5D-5L is a standardised measure of health status developed by the EuroQol Group. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. This is designed to be self-completed by the respondents and has 5 questions (of five levels) and a visual analogue scale which takes few minutes to complete

The EQ5D-5L to be scored as per UK health states, as this is the health state deemed the most similar to the Australian population.

The EQ-5D index will need to be computed for each patient/each time point.

10.3 Table Shells

10.3.1 Subject Disposition

Analysis Set	Conventional NSAA	Enzalutamide	Both Groups
ITT	x	x	x
PP	x	x	x
Safety	x	x	x

Place holder for CONSORT flow diagram

10.3.2 Baseline Demographic and Clinical Characteristics

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
Age (Years)-Mean(SD)		x (x)	x (x)	x (x)
Age <=70 yrs		x (x%)	x (x%)	x (x%)
Age >70 yrs		x (x%)	x (x%)	x (x%)
Height-Mean(SD)		x (x)	x (x)	x (x)
Weight-Mean(SD)		x (x)	x (x)	x (x)
BMI-Mean(SD)		x (x)	x (x)	x (x)
BSA-Mean(SD)		x (x)	x (x)	x (x)
Site Country	Australia	x (x%)	x (x%)	x (x%)
	Canada	x (x%)	x (x%)	x (x%)
	Ireland	x (x%)	x (x%)	x (x%)
	New Zealand	x (x%)	x (x%)	x (x%)
	UK	x (x%)	x (x%)	x (x%)
	United States	x (x%)	x (x%)	x (x%)
Docetaxel chemotherapy strata	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Volume of disease strata	High	x (x%)	x (x%)	x (x%)
	Low	x (x%)	x (x%)	x (x%)
Anti-resorptive therapy strata	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
ACE-27 strata	0-1	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
	2-3	x (x%)	x (x%)	x (x%)
Visceral metastases	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Site of visceral metastases				
Lung		x (x%)	x (x%)	x (x%)
Liver		x (x%)	x (x%)	x (x%)
Other		x (x%)	x (x%)	x (x%)
T Stage	Missing	x (x%)	x (x%)	x (x%)
	T0: No evidence of primary tumor	x (x%)	x (x%)	x (x%)
	T1: Clinically inapparent tumor not palpable or visible by imaging	x (x%)	x (x%)	x (x%)
	T2: Tumor confined within prostate	x (x%)	x (x%)	x (x%)
	T3: Tumor extends through the prostate capsule	x (x%)	x (x%)	x (x%)
	T4: Tumor is fixed or invades adjacent structures other than seminal vesicles	x (x%)	x (x%)	x (x%)
	TX: Primary tumor cannot be assessed	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)
N Stage	Missing	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
	N0: No regional lymph node metastasis	x (x%)	x (x%)	x (x%)
	N1: Metastasis in regional lymph node(s)	x (x%)	x (x%)	x (x%)
	NX: Regional lymph nodes cannot be assessed	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)
M Stage	M0: No distant metastasis	x (x%)	x (x%)	x (x%)
	M1: Distant metastasis	x (x%)	x (x%)	x (x%)
	MX: Distant metastasis cannot be assessed	x (x%)	x (x%)	x (x%)
	Missing	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)
Gleason score	06 or less	x (x%)	x (x%)	x (x%)
	07 (3+4)	x (x%)	x (x%)	x (x%)
	07 (4+3)	x (x%)	x (x%)	x (x%)
	08	x (x%)	x (x%)	x (x%)
	09 (4+5)	x (x%)	x (x%)	x (x%)
	09 (5+4)	x (x%)	x (x%)	x (x%)
	10	x (x%)	x (x%)	x (x%)
	Missing	x (x%)	x (x%)	x (x%)
Group staging	Missing	x (x%)	x (x%)	x (x%)
	Stage I	x (x%)	x (x%)	x (x%)
	Stage IIA	x (x%)	x (x%)	x (x%)
	Stage IIB	x (x%)	x (x%)	x (x%)
	Stage III	x (x%)	x (x%)	x (x%)
	Stage IV	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
Local disease Prostate	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Local disease Bladder invasion	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Regional lymph node involvement	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient had any prior cytotoxic chemotherapy? This includes adjuvant chemotherapy, but does NOT include docetaxel chemotherapy for metastatic prostate cancer	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient received docetaxel for metastatic disease prior to randomisation?	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Is the patient currently receiving any anti-resorptive therapy? (including up to 6 weeks after commencing study treatment)	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient had any prior androgen deprivation therapy? This includes adjuvant	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
ADT, but does NOT include ADT for metastatic disease started within 12 weeks prior to randomisation or bilateral orchidectomy	Yes	x (x%)	x (x%)	x (x%)
Has the patient received an NSAA for metastatic disease within 12 weeks prior to randomisation?	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient received an LHRHA for metastatic disease within 12 weeks prior to randomisation?	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Prior local treatment?	Missing/NA	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient had any prior surgery related to the primary tumour? This includes all prostate-related surgeries and biopsies	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Previous radical prostatectomy	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient had any prior radiotherapy? This includes adjuvant radiotherapy, radiotherapy started prior to randomisation or up to 6 weeks after commencing study treatment	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Previous local radiotherapy	Missing/NA	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
	Yes	x (x%)	x (x%)	x (x%)
Previous radiotherapy to bone metastases within the vertebral column and pelvis	Missing/NA	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Previous radiotherapy to bone metastases outside the vertebral column and pelvis	Missing/NA	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)

10.3.3 Exposure to Study Medication

Characteristic		Conventional NSAA	Enzalutamide	Both Groups
Has patient ceased anti-androgen treatment?	Missing	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Reason for permanently ceasing anti-androgen treatment*	Missing	x (x%)	x (x%)	x (x%)
	Adverse event	x (x%)	x (x%)	x (x%)
	Clinical Progression (Anti-cancer Rx)	x (x%)	x (x%)	x (x%)
	Clinical Progression (Radiological)	x (x%)	x (x%)	x (x%)
	Clinical Progression (Symptoms)	x (x%)	x (x%)	x (x%)
	Clinical Progression OTHER	x (x%)	x (x%)	x (x%)
	Clinician preference	x (x%)	x (x%)	x (x%)
	Death	x (x%)	x (x%)	x (x%)
	Other	x (x%)	x (x%)	x (x%)
	Patient preference	x (x%)	x (x%)	x (x%)
Wk 4 proportion of days patient took Enzalutamide/NSAA	Missing	32 (5.7%)	8 (1.4%)	40 (3.6%)
	90% - 100%	529 (94.1%)	546 (97.0%)	1075 (95.6%)
	80% - 89%		8 (1.4%)	8 (0.7%)
	<80%	1 (0.2%)	1 (0.2%)	2 (0.2%)
Wk 12 proportion of days patient took Enzalutamide/NSAA	Missing	50 (8.9%)	24 (4.3%)	74 (6.6%)
	90% - 100%	506 (90.0%)	521 (92.5%)	1027 (91.3%)
	80% - 89%	2 (0.4%)	11 (2.0%)	13 (1.2%)
	<80%	4 (0.7%)	7 (1.2%)	11 (1.0%)

*Note: Investigators allowed to select more than one criterion for clinical progression, however only one criterion is shown in the table with sequence for attribution being: (1) radiological, (3) anti-cancer Rx, (3) symptoms

Place holder for Kaplan-Meier plot showing duration of treatment

Percentile	Conventional NSAA	Enzalutamide	Both Groups
25th	x (95% CI: x to x)	x (95% CI: x to x)	x (95% CI: x to x)
50th (Median)	x (95% CI: x to x)	x (95% CI: x to x)	x (95% CI: x to x)
75th	x (95% CI: x to x)	x (95% CI: x to x)	x (95% CI: x to x)

10.3.4 Non-protocol anti-cancer treatments

Non-protocol anti-cancer treatments	Conventional NSAA	Enzalutamide	Both groups
<treatment 1>	x (x%)	x (x%)	x (x%)
<treatment 2>	x (x%)	x (x%)	x (x%)
<treatment 3>	x (x%)	x (x%)	x (x%)
<etc>	x (x%)	x (x%)	x (x%)

10.3.5 Overall Survival

Place holder for Kaplan-Meier plot

Median Time to Event		HR	Log-rank Test	Proportional Hazards Test*
Conventional NSAA	Enzalutamide			
x (95% CI: x to x)	x (95% CI: x to x)	x (95% CI: x to x; p= x.xx)	p=x.xx	p=x.xx

p-values < 0.05 suggest violation of the proportional hazards assumption

10.3.6 PSA Progression Free Survival

As per 0

10.3.7 Clinical Progression Free Survival

As per 0

10.3.8 Safety Tables

A selection of the key tables for (S)AEs are illustrated below.

10.3.8.1 Serious Adverse Events

	Conventional NSAA (N=x)	Enzalutamide (N= x)	Both groups (N= x)
Number of Patients with at least 1 SAE	x	x	x
Cumulative number of SAEs	x	x	x

10.3.8.2 Number of AEs by Category and Grade

System Organ Class/CTCAE Term		Treatment Arm						
		Conventional NSAA			Enzalutamide			
		Grade			Grade			GRAND
		1-2	3-5	N	1-2	3-5	N	TOTAL
<Class1>	TOTAL	x	x	x	x	x	x	x
	<Term 1>	x	x	x	x	x	x	x
	<Term 2>	x	x	x	x	x	x	x
	<Term 3>	x	x	x	x	x	x	x
	<etc.>	x	x	x	x	x	x	x
<Class2>	TOTAL	x	x	x	x	x	x	x
	<Term 1>	x	x	x	x	x	x	x
	<Term 2>	x	x	x	x	x	x	x
	<Term 3>	x	x	x	x	x	x	x
	<etc.>	x	x	x	x	x	x	x

<NOTE: a version of this table with each grade desegregated will be also prepared>

10.3.8.3 AE Terms by Worst Grade* (Excluding Grade 1-2 AEs)

		Treatment Arm								
		Conventional NSAA				Enzalutamide				
		Worst grade				Worst grade				GRAND
		3	4	5	TOTAL	3	4	5	TOTAL	TOTAL
<Class1>	*Total***	26	10	1	37	30	6	_	36	73
	<Term 1>	2	1	_	3	1	_	_	1	4
	<Term 2>	1	1	1	3	_	_	_	_	3
	<Term 3>	23	8	_	31	29	6	_	35	66
<Class2>	*Total***	9	2	1	12	12	_	1	13	25
	<Term 1>	9	2	1	12	12	_	1	13	25
	<Term 2>	9	2	1	12	12	_	1	13	25
	<Term 3>	9	2	1	12	12	_	1	13	25

*If a patient had multiple events within a particular term, that with the worst grade is shown.

**The worst grade events are summed within a system organ class to form row totals

<NOTE: a version of this table including grade 1-2 AEs will be also prepared>

10.3.9 Quality of life

10.3.9.1 Analysis of QoL Scales over Time

Scale	Time Point	NSAA		Enzalutamide		Modelled Difference*
		Descriptive Statistics	Modelled Estimates*	Descriptive Statistics	Modelled Estimates*	
<Scale 1>	Baseline	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)		N=x Missing=x Mean=x STD=x Median=x (min, max: x x)		
<Scale 1>	<time 1>	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	Mean=x StdErr=x (95%CI: x to x; p=x)
<Scale 1>	<time 2>	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	Mean=x StdErr=x (95%CI: x to x; p=x)
<Scale 1>	<etc.>	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	Mean=x StdErr=x (95%CI: x to x; p=x)
<etc.>	<etc.>	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)		N=x Missing=x Mean=x STD=x Median=x (min, max: x x)		

* Mixed model for repeated measures with fixed effect terms for treatment allocation, time point, a time point-by-treatment allocation interaction, and the baseline assessment.

10.3.9.2 Quality-Adjusted Survival (QAS)

QAS	Conventional NSAA mean (95%CI)	Enzalutamide mean (95%CI)	Difference mean (95%CI)
Within-trial (truncated)	x (x)	x (x)	x (x) p=x
Extrapolated – Scenario 1	x (x)	x (x)	
Extrapolated – Scenario 1	x (x)	x (x)	
Extrapolated – Scenario <etc>	x (x)	x (x)	

10.3.9.3 Analysis of Health Outcomes Relative to Costs

	Conventional NSAA Estimate (plausible range)	Enzalutamide Estimate (plausible range)	Difference (plausible range)
Costs			
Within Trial	x (x-x)	x (x-x)	x (x-x)
Category <1>	x (x-x)	x (x-x)	x (x-x)
Category <2>	x (x-x)	x (x-x)	x (x-x)
Category <etc>	x (x-x)	x (x-x)	x (x-x)
Total			
Extrapolated	x (x-x)	x (x-x)	x (x-x)
Scenario 1	x (x-x)	x (x-x)	x (x-x)
Scenario 2	x (x-x)	x (x-x)	x (x-x)
Scenario <etc>			
ICER			
Within Trial	-	-	x (x-x)
Extrapolated	-	-	x (x-x)
Scenario 1	-	-	x (x-x)
Scenario 2	-	-	x (x-x)
Scenario <etc>	-	-	x (x-x)

10.3.9.4 Adjusted and Subgroup Analyses

Covariate	Individual Covariate and Treatment Fitted as Main Effects	
	HR for Covariate (95% CI)	Stratified Log-Rank p-value
Treatment	x (x to x; p=0.xxx)	p=0.xxx
<Covariate 1>		-
<level 1 vs level 2>	x (x to x; p=0.xxx)	
<Covariate 2>		-
<level 1 vs level 2>	x (x to x; p=0.xxx)	
Etc.	Etc.	-

Place holder for forest plot showing within subgroup estimates (of HRs; 95% CIs; p-values) and p-values from test of interaction

THE UNIVERSITY OF SYDNEY

ANZUP Cancer Trials Group Limited

NHMRC Clinical Trials Centre

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: ENZAMET

Protocol number: ANZUP 1304

Statistical Analysis Plan

Prepared by: Andrew Martin
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Version: 2.0

Version date: 20190210

Approved by: Val Gebski
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Signature:

Date: 15/02/19

NHMRC Clinical Trials Centre

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: ENZAMET

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Statistical Analysis Plan

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Contents

1 Introduction

The aim of the ENZAMET trial is to determine the effectiveness of enzalutamide versus conventional non-steroidal anti-androgen (NSAA) in men with metastatic prostate cancer.

The study is an open label phase III trial that randomises eligible patients to receive, until disease progression or prohibitive toxicity, either: oral enzalutamide 160mg daily or conventional oral NSAA treatment. All participants are treated with surgical castration or a Luteinizing Hormone-Releasing Hormone Analog (LHRHA)

The randomisation is performed in a 1:1 ratio and is stratified by volume of disease (high volume yes versus no), use of early docetaxel (yes versus no), antiresorptive therapy (yes versus no), comorbidities (Adult Co-morbidity Evaluation ACE-27 score: 0-1 vs 2-3), and treating institution (Study Site).

The target population is men with metastatic prostate cancer commencing androgen deprivation therapy. Key eligibility criteria include metastatic prostate cancer, adequate organ function and ECOG performance status 0-2.

The primary objective is to determine the effect of enzalutamide on overall survival (OS). The secondary objectives are to determine the effect of enzalutamide on: prostate specific antigen progression free survival (PCGW2), clinical progression free survival (imaging, symptoms, signs), adverse events (CTCAE v4.03), health related quality of life (EORTC QLQ C-30, PR-25 and EQ-5D-5L), and health outcomes relative to costs.

Correlative objectives include: to identify biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment. A separate analysis plan will be prepared to address these objectives.

The statisticians working on this study are aware of the importance treating any unblinded efficacy results as highly sensitive and taking reasonable measures to keep such information confidential, despite this being an open label study. DRAFT tabulations/analyses of efficacy endpoints should be prepared using dummy treatment allocations, or be pooled across randomised groups. Occasions where tabulations/analyses of efficacy endpoints are prepared by actual treatment allocation (for an interim analysis and/or the final analysis) will be documented. Access to the analysis programming environment will be restricted to authorised personnel.

2 Endpoint Derivation

A central clinical review will be performed on the results of the endpoint derivations specified below. A series of specific programmed endpoint checks are also performed, with any issues being centrally reviewed. Treatment allocation will not be included on the review outputs. Any instances where the specifications below are overruled on the basis of the clinical review findings will be endorsed by the Clinical Lead (on behalf of the TMC) and documented in the study report.

2.1 Overall Survival (OS) (Primary Endpoint)

Overall survival is defined as the interval from the date of randomisation to date of death from any cause, or the date last known alive (at which point the observation is censored).

2.2 PSA Progression Free Survival (PSA PFS)

PSA progression free survival (PSA PFS) is defined as the interval from the date of randomisation to the date of first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last PSA test without PSA progression (at which point the observation is censored).

2.3 Clinical Progression Free Survival (Clinical PFS)

Clinical progression free survival is defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression (at which point the observation is censored). The censoring date will be the latest of the following: the date of the patient's last assessment during the 'on treatment' phase where clinical progression status is recorded as 'no'; and, the maximum date the patient is last known not to have progressed collected during the 'post-treatment follow-up' phase. Clinical progression is defined by progression on imaging, development of symptoms attributable to cancer progression, or initiation of other anticancer treatment for prostate cancer.

2.4 Safety

The NCI Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE) will be used to classify and grade the intensity of adverse events whilst on treatment, at progression, and 30-42 days after the last dose of study treatment.

2.5 Quality of Life (QoL)

The core EORTC QoL Questionnaire (QLQ-C30) will be used in conjunction with the disease specific module for prostate cancer (PR25). The EQ-5D will be used to obtain utility valuations on the health states experienced by participants. All instruments will be scored according to standard conventions (see Section 10.1 and 10.2).

2.6 Health Care Resource Usage

Information on the following areas of health-care resource usage will be collected: protocol therapy and hospitalisations (for all participants by trial staff via standard case record forms (CRFs), visits to health professionals (for Australian participants via Medicare benefits scheme (MBS) and for other regions as specified separately in their Group Specific Appendix (GSA), and non-protocol medications (for Australian participants via Pharmaceutical Benefits Scheme (PBS) and for other regions as separately specified in their GSA).

3 Analysis Sets

All randomised participants will be eligible for inclusion in the full analysis set in accordance with the intention-to-treat analysis principle. The full analysis set thus comprises the intention-to-treat (ITT) population. The per-protocol population will comprise all randomised participants that are deemed eligible/evaluable on blinded central clinical review. Patients are classified according to study

medication assigned at the time of randomisation. The safety population will comprise all randomised participants who received at least one administration of study medication.
If a patient receives at least one dose of enzalutamide (irrespective of randomised allocation) in the period between randomisation and cessation of study treatment, they will be included in the enzalutamide arm of the safety population. If that condition does not apply, and the patient receives a least one dose of NSAA (irrespective of randomised allocation) in the period between randomisation and cessation of study treatment, they will be included in the NSAA arm of the safety population. If neither of the above criteria apply, the patient will be excluded from the safety population.

The reasons for any exclusions from analysis sets will be reviewed and endorsed by the Trial Executive Committee and documented in the final study report.

The primary analysis population used for the evaluation of enzalutamide on non-safety parameters will be the ITT population. The per-protocol population may be used in secondary analyses of non-safety parameters as part of a sensitivity analysis. Safety analyses will be performed using the safety population.

4 Interim and Final Analyses

Assuming the study is not terminated early, the final analysis is planned to be undertaken after the required number of deaths have occurred (i.e. N=470, see sample size section of the protocol). The study design incorporates formal interim analyses performed on OS once 50%, 67%, and 80% of the required events are observed. The interim analysis allows for early rejection of the null hypothesis according to an alpha spending function with an O'Brien-Fleming boundary shape[1]. Indicative boundaries for these analyses are presented in the table below. The actual number of events observed at the time of the interim analyses would be used to construct the definitive rejection boundary. The conditional power (CP) of the study will also be calculated for OS at the interim analyses.[2] This procedure does not 'spend' any alpha associated with the test of the null hypothesis. The Independent Data Safety Monitoring Committee (IDSMC) may recommend altering aspects of the study (e.g. early termination on futility grounds) if the CP is unacceptably low. A CP <20% is suggested in the protocol as a guide for the IDSMC for defining 'an unacceptably low CP'. Refer to interim analysis section of the protocol for additional information on feasibility and safety monitoring overseen by the IDSMC.

[1] Lan KKG, and DeMets DL. Discrete Sequential Boundaries for Clinical Trials. Biometrika 1983;70:659–663

[2] Lan KKG, Simon R and Halperin M. Stochastically curtailed tests in long–term clinical trials Sequential Analysis 1982;1:3:207-219

Table 1: Indicative Boundary for Rejection of the Null Hypothesis

Stage	Proportion of Required Events	Z Score Boundary Rejection of the Null Hypothesis*	2-Sided P-value Corresponding to Boundary
1	0.5	+/-2.96	0.003
2	0.67	+/-2.53	0.011
3	0.8	+/-2.32	0.020
4	1	+/-2.03	0.042

* Calculated using following SAS code: PROC SEQDESIGN plots=boundary(hscale=samplesize) PSS(CREF=1) STOPPROB(CREF=1); ErrorSpendOBrienFleming: design nstages=4 method=ERRFUNCOBF ALPHA=0.05 BETA=0.133 INFO=CUM(0.50 0.67 0.80 1); run;

5 Type I Error (Alpha)

Unless otherwise specified (e.g. See Section 4 above), a two-sided alpha of 5% will be applied to interpret the results of hypothesis tests and to construct confidence intervals. P-values from secondary analyses that are unadjusted for multiple comparisons, and/or early stopping of the trial, will be interpreted conservatively. For the many planned adjusted and subgroup analysis, this will involve grouping hypothesis tests into discrete families (sets), and evaluating the p-values within each family with due consideration of the family-wise type I error rate (See Section 9).

6 Accounting for Stratification Factors

Randomisation is stratified by 'volume of disease' (high volume yes versus no), 'use of early docetaxel' (yes versus no), 'use of antiresorptive therapy' (yes versus no), comorbidities (Adult Co-morbidity Evaluation ACE-27 score: 0-1 vs 2-3), and treating institution (Study Site). Sensitivity of conclusions when accounting for these factors will be explored in secondary analyses (See Section 9). Study sites will be grouped into geographical regions for these analyses. The regions are Europe (UK and Ireland), Australasia (Australia and New Zealand), and North America (USA and Canada). If stratification data were incorrectly collected and reported at the time of randomisation, data that are corrected by site after the randomisation process will be used in analysis.

7 Subgroups of Particular Interest

Consistency of the treatment effect on OS will be evaluated across pre-specified subgroups defined by the stratification factors and the baseline characteristics shown below in Table 2. Consistency of the treatment effect on PSA PFS and clinical PFS will also be evaluated across these same subgroups. Study sites will be grouped into geographical regions for these analyses (See Section 6). The effects of enzalutamide in participants treated with early docetaxel, especially in participants with high volume disease treated with early docetaxel, are of particular clinical interest (see section 9).

Table 2: Subgroups Definitions

	Subgroup Definitions	**Subgroup Definitions from Other Trials (presented for reference)**		
Subgroups	**ENZAMET**	**STAMPEDE**	**LATITUDE**	**CHAARTED**
Gleason Score	≤7 vs 8-10	≤7 vs 8-10	≤7 vs 8-10	≤7 vs 8-10
Age	<70 vs ≥70	<70 vs ≥70	<65, ≥65, ≥75	<65, ≥65, ≥75
Performance Status	0 vs 1-2	0 vs 1-2	0 vs 1-2	
Visceral Disease	Yes vs No		Yes vs No	
Prior local treatment	Yes vs No			Yes vs No
High volume disease	Yes vs No			Yes vs No
Early docetaxel	Yes vs No			
Anti-resorptive therapy	Yes vs No			
ACE-27	0-1 vs 2-3			
Region	ANZ vs Europe vs North America			

8 Analysis of Study Endpoints and Patient Characteristics

See Section 10.3 for indicative mock-ups of the planned outputs for the analyses described below.

8.1 Subject Disposition

The number of patients in the analysis sets will be presented along with reasons for any exclusions. The Kaplan-Meier method will be used to summarise follow-up time for OS by treatment allocation with deaths being treated as censored observations. A CONSORT flow diagram will be prepared.

8.2 Baseline Demographic and Clinical Characteristics

Descriptive statistics will be prepared to summarise baseline characteristics of the study participants by treatment allocation. Variables to be summarised include: age, BMI, stratification factors, other prostate cancer characteristics, and previous treatment for prostate cancer.

8.3 Exposure to Study Medication

The Kaplan-Meier method will be used to summarise time on study medication by treatment allocation, with any patients remaining on treatment being censored at the time the most recent dosing was recorded. Reasons for discontinuations will be tabulated by treatment group.

8.4 Other Treatments

The use of non-protocol anti-cancer treatment will be tabulated by treatment group.

A listing of other concomitant medications (and reasons for the concomitant medications) will be prepared.

8.5 Overall Survival (OS) – Primary Analysis of Primary Endpoint

Overall survival (OS) time for each treatment group will be quantified using the Kaplan-Meier method and compared using an unstratified log-rank test. An unadjusted Cox PH model will be used to estimate the hazard ratio (with 95% CI). In addition, if early stopping is triggered by rejection of the null hypothesis at an interim analysis (see Section 4), the conditional mean-adjusted estimator will be used to obtain an estimate of hazard ratio for OS corrected for early stopping and a 95% confidence interval for the estimate will be obtained using bootstrapping[3]. This will be presented along with the conventional HR and confidence interval for reference purposes. Section 4 and 9 provide detail on the interim, adjusted, and subgroup analyses that are planned to be conducted on OS.

8.6 PSA Progression Free Survival (PSA PFS)

PSA Progression Free Survival time for each treatment group will be quantified using the Kaplan-Meier method and compared using an unstratified log-rank test. An unadjusted Cox PH model will be used to estimate the hazard ratio (with 95% CI). Section 9 provide detail on the subgroup analyses that are planned to be conducted on PSA PSF.

8.7 Clinical Progression Free Survival (Clinical PFS)

Clinical Progression Free Survival will be analysed using the same approach as that described above for PSA PFS. Section 9 provide detail on the subgroup analyses that are planned to be conducted on clinical PSF

8.8 Safety Data Analysis

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be tabulated by treatment received (see Section 3) and CTCAE criteria including system organ class, term, and (worst) grade.

8.9 Quality of life (QoL)

The QoL analyses will comprise a primary and a secondary set of approaches (next described).

8.9.1 Primary Approach: Deterioration-Free Survival

A deterioration-free survival (DetFS) endpoint will be constructed as a marker of overall net-benefit over the on-treatment period. This is defined as the time from randomisation to the first of the following events: a 10-point or more deterioration in health status from baseline (without subsequent 10-point or more improvement compared with baseline), clinical progression, death, or treatment discontinuation. If a patient experiences none of these events, they will be censored. The censoring date will be the latest of the following: the date of the patient's last QoL assessment; the date of the patient's last assessment during the 'on treatment' phase where clinical progression status is recorded as 'no'; and, the maximum date the patient is last known not to have progressed collected during the 'post-treatment follow-up' phase. Two DFS endpoints will be derived using different markers of health status deterioration based on the EORTC QLQ-C30: one used the Physical

[3] Shimura M. Comparison of conditional bias-adjusted estimators for interim analysis in clinical trials with survival data. Statistics in medicine 2017;36(13):2067

Function Scale ($DetFS_{PF}$), and the other used the General Health Scale ($DetFS_{GHS}$). The treatment groups will be compared on $DetFS_{PF}$ and DFS_{GHS} using an unstratified log-rank test. Kaplan-Meier curves will be prepared and used to estimate median DetFS with 95% confidence intervals. An estimate of the hazard ratio for the treatment effect will be obtained using a Cox proportional hazard regression model without stratification factors.

8.9.2 Secondary Approach: Mixed Model for Repeated Measures

Scale scores from the QLQ-C30, PR25 and EQ5D will be summarised by treatment group over time, and are planned to be analysed using a mixed model for repeated measures (MMRM). The MMRM will include covariates for baseline, treatment arm, post-baseline time-point, and a treatment-by-time point interaction. A blinded analysis (of interim) QoL data will be used to refine the analysis method. This will include: (i) specifying the covariance structure after evaluation of various options (including compound symmetry and autoregressive) using the AIC statistic; and (ii) specifying the strategy for accommodating any highly skewed data (e.g. log transformation, or split at median or other logical value with analysis of the resultant categorical endpoint performed using a repeated measures generalised linear model with a logit link function).

8.10 Quality-Adjusted Survival (QAS)

Within-trial estimates of quality-adjusted survival (QAS) will be calculated for each randomised treatment group[4]. This will involve combining the QoL utility function estimated from the repeated measures analysis of the EQ-5D collected up to treatment cessation with the time-to-treatment-cessation function estimated using the Kaplan-Meier method; and, combining post treatment cessation QoL estimate(s) (from external sources) with the survival-post-treatment-cessation function estimated using the Kaplan-Meier method. The QAS estimates will be truncated at the time point when either of the arms has <10% of patients at risk[5]. Confidence intervals will be constructed using bootstrapping. The applicability of approaches for deriving utilities from the EORTC QLQ-C30, to use as an alternative to the EQ-5D, may also be explored in sensitivity analyses.

8.11 Analysis of Health Outcomes Relative to Costs

Australian unit costs will be applied to the resource usage data (See Section 2.6) to estimate the within-trial cost difference (in Australian dollars) between randomised arms. A within-trial estimate of the incremental cost-effectiveness of the addition of enzalutamide to standard treatment will be calculated in terms of the cost difference relative to the quality-adjusted survival (QAS) difference.

The feasibility of extrapolating beyond the within-trial estimate of cost-effectiveness using modelling methods will be explored.

9 Adjusted and Subgroup Analyses

Sensitivity of conclusions from the primary analysis on OS to adjustment for stratification factors (See Section 6) will be investigated for the ITT population. A comparison between randomised

[4] Glasziou et al. Quality adjusted survival analysis with repeated quality of life measures. Stat Med. 1998 Jun 15;17(11):1215-29.

[5] Pocock et al. Survival plots of time-to-event outcomes in clinical trials: Good practice and pitfalls. Lancet. 2002;359:1686–9.

groups will be undertaken using a stratified long-rank test. An adjusted hazard ratio (with 95% CI) will be obtained from a Cox PH model that includes the stratification factors as covariates. These analyses will be performed on the ITT population.

The consistency of the treatment effect on OS across the stratification factors and other pre-specified baseline characteristics (See Section 9) will be tested by fitting the relevant factor-by-treatment interaction term in a Cox regression model along with the associated main effects terms. The subgroup analyses will be repeated using PSA PFS and clinical PFS as the endpoints.

A clinical question of particular importance and interest is whether early docetaxel modifies the effect of enzalutamide in patients with high volume disease. The corresponding analysis will involve fitting a docetaxel-by-treatment interaction term, along with the associated main effects terms, in a Cox regression model applied to PSA PFS in the cohort of patients with high volume disease in the ITT population. Because that analysis will only include high disease volume patient, it will have less statistical power to detect effect modification than those subgroup analyses applied to the full ITT population. Note that exposure to docetaxel is not randomised.

The hypothesis tests from the planned adjusted and subgroup analysis described above will be considered within the following discrete families: (1) a set of adjusted analyses on OS; (2) a set of subgroup analyses on OS; (3) a set of subgroup analyses on PSA PFS; and (4) a set of subgroup analyses on clinical PFS. Due consideration will be given to the family-wise type I error rate when conservatively interpreting the p-values within each of family of tests, and the Benjamini-Hochberg procedure[6] will be used to calculate adjusted p-values with the family-wise type I error being set to 5%.

[6] Huque M. F. Validity of the Hochberg procedure revisited for clinical trial applications. Stat Med 2016;35:5-20

10 Appendix

10.1 EORTC scoring

Instrument/Scale/Item					
	Scale	**No. items**	**Range**	**Item number**	**High score**
QLQ-C30					
Global health status/QoL	QL2	2	6	29, 30	+ve
Functional scales					
Physical	PF2	5	3	1 - 5	+ve
Role	RF2	2	3	6, 7	+ve
Emotional	EF	4	3	21 - 24	+ve
Cognitive	CF	2	3	20, 25	+ve
Social	SF	2	3	26, 27	+ve
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	-ve
Nausea and vomiting	NV	2	3	14, 15	-ve
Pain	PA	2	3	9, 19	-ve
Dyspnoea	DY	1	3	8	-ve
Insomnia	SL	1	3	11	-ve
Appetite loss	AP	1	3	13	-ve
Constipation	CO	1	3	16	-ve
Diarrhoea	DI	1	3	17	-ve
Financial difficulties	FI	1	3	28	-ve
QLQ-PR25					
Symptom scales / items					
Urinary symptoms	PRURI	8	3	1 – 7,9	-ve
Bowel symptoms	PRBOW	4	3	10 – 13	-ve
Hormonal treatment-related symptoms	PRHTR	6	3	14 – 19	-ve
Incontinence aid	PRAID	1	3	8	-ve
Functional scales/items					
Sexual activity	PRSAC	2	3	20, 21	+ve
Sexual functioning	PRSFU	4	3	22-25	+ve

QLQ-PR25

The prostate cancer module is meant for use among patients with prostate cancer varying in disease stage and treatment modality (i.e. surgery, chemotherapy, radiotherapy, etc.). It should always be complemented by the QLQ-C30.

Remarks

- Items 20 and 21 can be completed by all patients

- Items 22-25 are conditional on being sexually active, and thus will only be completed by a subgroup of patients. **This will require reversing the response categories of questions 23-25 but not of 22**.

Definition:

In practical terms, if $I_1, I_2, \ldots, I_n$ are included in a scale, the procedure is as follows:

Calculate the raw score: $$RS = \frac{I_1 + I_2 + \cdots + I_n}{n}$$

Apply the linear transformation to 0-100 to obtain the score S:

Functional Scales: $$S = \{1 - \frac{(RS - 1)}{range}\} * 100$$

Symptom scales/items: $$S = \{\frac{(RS - 1)}{range}\} * 100$$

Global health status/QoL: $$S = \{\frac{(RS - 1)}{range}\} * 100$$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all the items in any scale take the same values. Therefore the range of RS equals the range of the items. Most items are scored 1 to 4 giving a *range* of 3. Exceptions are the items contributing to the global health status/QoL, which are 7-point questions with a *range* of 6.

Note a high score for a functional scale represents a *high/*healthy level of functioning, a high score for the global health status/QoL represents a *high QoL*, but a high score for a symptom/item scale represents a *high level of symptomatology/problems.*

Missing Items:

If at least half of the items from the scale have been answered, assume that the missing items have values equal to the average of those items which *are* present for that respondent.

Thus:

- Have at least half of the items from the scale been answered?
- If Yes, use all the items that were completed, and apply the standard equations for calculating the scale scores; ignore any items with missing values when making the calculations.
- If No, set scale score to missing.
- For single-item measures, set score to missing.

10.2 EQ5D-5L

The EQ5D-5L comprises the following items:

1. Mobility (5 response levels)
2. Personal Care (5 response levels)
3. Usual Activity (5 response levels)
4. Pain/Discomfort (5 response levels)
5. Anxiety/Depression (5 response levels)
6. a visual analogue scale assessing overall health (0-100)

Items 1 to 5 collectively define 5^5=3,125 health profiles. The UK utilities for these profiles will be applied. These weights are available from the EQ5D website (accessed 02FEB19): https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/

10.3 Table Shells

Indicative mock-ups of the planned outputs are presented below. The numbering shown does not necessarily correspond the numbering that will be applied to the definitive tables.

10.3.1 Subject Disposition

Analysis Population	Conventional NSAA	Enzalutamide	Both Groups
ITT	x	x	x
PP	x	x	x
Safety	x	x	x

Place holder for CONSORT flow diagram

10.3.2 Baseline Demographic and Clinical Characteristics

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
Age (Years)-Mean(SD)		x (x)	x (x)	x (x)
Age <=70 yrs		x (x%)	x (x%)	x (x%)
Age >70 yrs		x (x%)	x (x%)	x (x%)
Height-Mean(SD)		x (x)	x (x)	x (x)
Weight-Mean(SD)		x (x)	x (x)	x (x)
BMI-Mean(SD)		x (x)	x (x)	x (x)
BSA-Mean(SD)		x (x)	x (x)	x (x)
Site Country	Australia	x (x%)	x (x%)	x (x%)
	Canada	x (x%)	x (x%)	x (x%)
	Ireland	x (x%)	x (x%)	x (x%)
	New Zealand	x (x%)	x (x%)	x (x%)
	UK	x (x%)	x (x%)	x (x%)
	United States	x (x%)	x (x%)	x (x%)
Docetaxel chemotherapy strata	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Volume of disease strata	High	x (x%)	x (x%)	x (x%)
	Low	x (x%)	x (x%)	x (x%)
Anti-resorptive therapy strata	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
ACE-27 strata	0-1	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
	2-3	x (x%)	x (x%)	x (x%)
Visceral metastases	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Site of visceral metastases				
Lung		x (x%)	x (x%)	x (x%)
Liver		x (x%)	x (x%)	x (x%)
Other		x (x%)	x (x%)	x (x%)
T Stage	Missing	x (x%)	x (x%)	x (x%)
	T0: No evidence of primary tumor	x (x%)	x (x%)	x (x%)
	T1: Clinically inapparent tumor not palpable or visible by imaging	x (x%)	x (x%)	x (x%)
	T2: Tumor confined within prostate	x (x%)	x (x%)	x (x%)
	T3: Tumor extends through the prostate capsule	x (x%)	x (x%)	x (x%)
	T4: Tumor is fixed or invades adjacent structures other than seminal vesicles	x (x%)	x (x%)	x (x%)
	TX: Primary tumor cannot be assessed	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)
N Stage	Missing	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
	N0: No regional lymph node metastasis	x (x%)	x (x%)	x (x%)
	N1: Metastasis in regional lymph node(s)	x (x%)	x (x%)	x (x%)
	NX: Regional lymph nodes cannot be assessed	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)
M Stage	M0: No distant metastasis	x (x%)	x (x%)	x (x%)
	M1: Distant metastasis	x (x%)	x (x%)	x (x%)
	MX: Distant metastasis cannot be assessed	x (x%)	x (x%)	x (x%)
	Missing	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)
Gleason score	06 or less	x (x%)	x (x%)	x (x%)
	07 (3+4)	x (x%)	x (x%)	x (x%)
	07 (4+3)	x (x%)	x (x%)	x (x%)
	08	x (x%)	x (x%)	x (x%)
	09 (4+5)	x (x%)	x (x%)	x (x%)
	09 (5+4)	x (x%)	x (x%)	x (x%)
	10	x (x%)	x (x%)	x (x%)
	Missing	x (x%)	x (x%)	x (x%)
Group staging	Missing	x (x%)	x (x%)	x (x%)
	Stage I	x (x%)	x (x%)	x (x%)
	Stage IIA	x (x%)	x (x%)	x (x%)
	Stage IIB	x (x%)	x (x%)	x (x%)
	Stage III	x (x%)	x (x%)	x (x%)
	Stage IV	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
Local disease Prostate	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Local disease Bladder invasion	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Regional lymph node involvement	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Unknown	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient had any prior cytotoxic chemotherapy? This includes adjuvant chemotherapy, but does NOT include docetaxel chemotherapy for metastatic prostate cancer	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient received docetaxel for metastatic disease prior to randomisation?	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Is the patient currently receiving any anti-resorptive therapy? (including up to 6 weeks after commencing study treatment)	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient had any prior androgen deprivation therapy? This includes adjuvant	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
ADT, but does NOT include ADT for metastatic disease started within 12 weeks prior to randomisation or bilateral orchidectomy	Yes	x (x%)	x (x%)	x (x%)
Has the patient received an NSAA for metastatic disease within 12 weeks prior to randomisation?	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient received an LHRHA for metastatic disease within 12 weeks prior to randomisation?	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has a bilateral orchidectomy been performed?	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Prior local treatment?	Missing/NA	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient had any prior surgery related to the primary tumour? This includes all prostate-related surgeries and biopsies	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Previous radical prostatectomy	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Has the patient had any prior radiotherapy? This includes adjuvant radiotherapy, radiotherapy	Missing	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)

Characteristic	Level	Conventional NSAA	Enzalutamide	Both groups
started prior to randomisation or up to 6 weeks after commencing study treatment	Yes	x (x%)	x (x%)	x (x%)
Previous local radiotherapy	Missing/NA	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Previous radiotherapy to bone metastases within the vertebral column and pelvis	Missing/NA	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Previous radiotherapy to bone metastases outside the vertebral column and pelvis	Missing/NA	x (x%)	x (x%)	x (x%)
	No	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)

10.3.3 Exposure to Study Medication

Characteristic		Conventional NSAA	Enzalutamide	Both Groups
Has patient ceased anti-androgen treatment?	Missing	x (x%)	x (x%)	x (x%)
	Yes	x (x%)	x (x%)	x (x%)
Reason for permanently ceasing anti-androgen treatment*	Missing	x (x%)	x (x%)	x (x%)
	Clinical Progression (Imaging)	x (x%)	x (x%)	x (x%)
	Clinical Progression (Symptoms)	x (x%)	x (x%)	x (x%)
	Clinical Progression (Anti-cancer Rx)	x (x%)	x (x%)	x (x%)
	Clinical Progression OTHER	x (x%)	x (x%)	x (x%)
	Adverse event	x (x%)	x (x%)	x (x%)
	Clinician preference	x (x%)	x (x%)	x (x%)
	Death	x (x%)	x (x%)	x (x%)
	Other	x (x%)	x (x%)	x (x%)
	Patient preference	x (x%)	x (x%)	x (x%)
Wk 4 proportion of days patient took Enzalutamide/NSAA	Missing	x (x%)	x (x%)	x (x%)
	90% - 100%	x (x%)	x (x%)	x (x%)
	80% - 89%	x (x%)	x (x%)	x (x%)
	<80%	x (x%)	x (x%)	x (x%)
Wk 12 proportion of days patient took Enzalutamide/NSAA	Missing	x (x%)	x (x%)	x (x%)
	90% - 100%	x (x%)	x (x%)	x (x%)
	80% - 89%	x (x%)	x (x%)	x (x%)
	<80%	x (x%)	x (x%)	x (x%)

*Note: Investigators allowed to select more than one criterion for clinical progression, however only one criterion is shown in the table with sequence for attribution being: (1) imaging, (2) symptoms, (3) anti-cancer Rx, (4) Other

Place holder for Kaplan-Meier plot showing duration of treatment

Percentile	Conventional NSAA	Enzalutamide	Both Groups
25th	x (95% CI: x to x)	x (95% CI: x to x)	x (95% CI: x to x)
50th (Median)	x (95% CI: x to x)	x (95% CI: x to x)	x (95% CI: x to x)
75th	x (95% CI: x to x)	x (95% CI: x to x)	x (95% CI: x to x)

10.3.4 Non-protocol anti-cancer treatments

Non-protocol anti-cancer treatments	Conventional NSAA	Enzalutamide	Both groups
Goserelin	x (x%)	x (x%)	x (x%)
Leuprorelin	x (x%)	x (x%)	x (x%)
Triptorelin	x (x%)	x (x%)	x (x%)
Degarelix	x (x%)	x (x%)	x (x%)
Nilutamide	x (x%)	x (x%)	x (x%)
Flutamide	x (x%)	x (x%)	x (x%)
Bicalutamide	x (x%)	x (x%)	x (x%)
Cyproterone	x (x%)	x (x%)	x (x%)
Enzalutamide	x (x%)	x (x%)	x (x%)
Abiraterone and prednisolone	x (x%)	x (x%)	x (x%)
Orteronel	x (x%)	x (x%)	x (x%)
Sipuleucel-T	x (x%)	x (x%)	x (x%)
Radium 223 (Alpharadin)	x (x%)	x (x%)	x (x%)
Radiotherapy	x (x%)	x (x%)	x (x%)
Docetaxel	x (x%)	x (x%)	x (x%)
Cabazitaxel	x (x%)	x (x%)	x (x%)
Mitoxantrone	x (x%)	x (x%)	x (x%)
Steroids alone	x (x%)	x (x%)	x (x%)
Other	x (x%)	x (x%)	x (x%)

10.3.5 Overall Survival

Place holder for Kaplan-Meier plot

Median Time to Event		HR	Log-rank Test	Proportional Hazards Test*
Conventional NSAA	Enzalutamide			
x (95% CI: x to x)	x (95% CI: x to x)	x (95% CI: x to x; p= x.xx)	p=x.xx	p=x.xx

p-values < 0.05 suggest violation of the proportional hazards assumption

10.3.6 PSA Progression Free Survival

As per overall survival

10.3.7 Clinical Progression Free Survival

As per overall survival

10.3.8 Safety Tables

A selection of the key tables for (S)AEs are illustrated below.

10.3.8.1 Serious Adverse Events

	Conventional NSAA (N=x)	Enzalutamide (N= x)	Both groups (N= x)
Number of Patients with at least 1 SAE	x	x	x
Cumulative number of SAEs	x	x	x

10.3.8.2 Number of AEs by Category and Grade

System Organ Class/CTCAE Term		Treatment Arm						
		Conventional NSAA			Enzalutamide			
		Grade			Grade			GRAND
		1-2	3-5	N	1-2	3-5	N	TOTAL
<Class1>	TOTAL	x	x	x	x	x	x	x
	<Term 1>	x	x	x	x	x	x	x
	<Term 2>	x	x	x	x	x	x	x
	<Term 3>	x	x	x	x	x	x	x
	<etc.>	x	x	x	x	x	x	x
<Class2>	TOTAL	x	x	x	x	x	x	x
	<Term 1>	x	x	x	x	x	x	x
	<Term 2>	x	x	x	x	x	x	x
	<Term 3>	x	x	x	x	x	x	x
	<etc.>	x	x	x	x	x	x	x

<NOTE: a version of this table with each grade desegregated will be also prepared>

10.3.8.3 AE Terms by Worst Grade* (Excluding Grade 1-2 AEs)

		Treatment Arm								
		Conventional NSAA				Enzalutamide				
		Worst grade				Worst grade				GRAND
		3	4	5	TOTAL	3	4	5	TOTAL	TOTAL
<Class1>	*Total***	26	10	1	37	30	6	_	36	73
	<Term 1>	2	1	_	3	1	_	_	1	4
	<Term 2>	1	1	1	3	_	_	_	_	3
	<Term 3>	23	8	_	31	29	6	_	35	66
<Class2>	*Total***	9	2	1	12	12	_	1	13	25
	<Term 1>	9	2	1	12	12	_	1	13	25
	<Term 2>	9	2	1	12	12	_	1	13	25
	<Term 3>	9	2	1	12	12	_	1	13	25

*If a patient had multiple events within a particular term, that with the worst grade is shown.

**The worst grade events are summed within a system organ class to form row totals

<NOTE: a version of this table including grade 1-2 AEs will be also prepared>

10.3.9 Quality of life

10.3.9.1 Analysis of QoL Scales over Time

Scale	Time Point	Conventional NSAA		Enzalutamide		Modelled Difference*
		Descriptive Statistics	Modelled Estimates*	Descriptive Statistics	Modelled Estimates*	
<Scale 1>	Baseline	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)		N=x Missing=x Mean=x STD=x Median=x (min, max: x x)		
<Scale 1>	<time 1>	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	Mean=x StdErr=x (95%CI: x to x; p=x)
<Scale 1>	<time 2>	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	Mean=x StdErr=x (95%CI: x to x; p=x)
<Scale 1>	<etc.>	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	N=x Missing=x Mean=x STD=x Median=x (min, max: x x)	Mean=x StdErr=x (95%CI: x to x)	Mean=x StdErr=x (95%CI: x to x; p=x)
<etc.>	<etc.>	<etc.>	<etc.>	<etc.>	<etc.>	<etc.>

* Mixed model for repeated measures with fixed effect terms for treatment allocation, time point, a time point-by-treatment allocation interaction, and the baseline assessment.

10.3.9.2 Quality-Adjusted Survival (QAS)

QAS	Conventional NSAA mean (95% CI)	Enzalutamide mean (95% CI)	Difference mean (95% CI)
Within-trial (truncated)	x (x)	x (x)	x (x)
<Extrapolation/Sensitivity Analysis 1>	x (x)	x (x)	x (x)
<Extrapolation/Sensitivity Analysis 2>	x (x)	x (x)	x (x)
<etc.>	<etc.>	<etc.>	<etc.>

10.3.9.3 Analysis of Health Outcomes Relative to Costs

	Conventional NSAA Estimate (plausible range)	Enzalutamide Estimate (plausible range)	Difference (plausible range)
Costs			
Within Trial	x (x-x)	x (x-x)	x (x-x)
Category <1>	x (x-x)	x (x-x)	x (x-x)
Category <2>	x (x-x)	x (x-x)	x (x-x)
<etc.>	<etc.>	<etc.>	<etc.>
Total	x (x-x)	x (x-x)	x (x-x)
Extrapolated	x (x-x)	x (x-x)	x (x-x)
Scenario 1	x (x-x)	x (x-x)	x (x-x)
Scenario 2	x (x-x)	x (x-x)	x (x-x)
<etc.>	<etc.>	<etc.>	<etc.>
ICER			
Within Trial	-	-	x (x-x)
Extrapolated	-	-	x (x-x)
Scenario 1	-	-	x (x-x)
Scenario 2	-	-	x (x-x)
<etc>	-	-	<etc>

10.3.9.4 Adjusted and Subgroup Analyses

Covariate	Individual Covariate and Treatment Fitted as Main Effects		
	HR for Covariate (95% CI)	HR for Treatment (95% CI)	Stratified Log-Rank p-value for treatment
<Covariate 1>			p=x.xx
<level 1 vs level 2>	x (x to x; p=x.xx)	x (x to x; p=x.xx)	
<Covariate 2>			p=x.xx
<level 1 vs level 2>	x (x to x; p=x.xx)	x (x to x; p=x.xx)	
<etc>	<etc>	<etc>	<etc>

Place holder for forest plot showing within subgroup estimates (of HRs; 95% CIs; p-values) and p-values from test of interaction

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: ENZAMET

Protocol number: ANZUP 1304

Statistical Analysis Plan Addendum 1.1

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Version: 1.1

Version date: 28MAY21

Approved by: _____ (Name)

_____ (Designation)

_____ (Signature)

_____ (Date)

Ian Marschner

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Contents

1 Introduction

The aim of the ENZAMET trial is to determine the effectiveness of enzalutamide versus conventional non-steroidal anti-androgen (NSAA) in men with metastatic prostate cancer. The study is an open label phase III trial that randomised N=1,125 eligible patients to receive, until disease progression or prohibitive toxicity, either: oral enzalutamide 160mg daily or conventional oral NSAA treatment. The primary endpoint is overall survival (OS).

The final analysis for ENZAMET was planned to occur after N=470 deaths (see sample size section of the protocol), however interim analyses were pre-specified at 50%, 67%, and 80% of the 470 events for exclusive review by the Independent Data Monitoring Committee (IDMC). The null hypothesis of no effect on OS was rejected at the first of these planned interim analyses (i.e. at 50% of the 470 events amongst the N=1125 randomised participants). The IDSMC advised the ENZAMET executive committee of this, and recommended that the results be disclosed. Under direction from the ENZAMET executive committee, an analysis of all primary and secondary endpoints was performed following the specifications in the Statistical Analysis Plan (SAP) v2.0, and the ENZAMET trial has continued to treat/follow-up participants and accumulate endpoint data.

This document is an addendum (v1.1) to the ENZAMET SAP v2.0. Its purpose is to document the planned analyses of primary and secondary endpoints once N=470 deaths have occurred.

Addendum v1.1 differs from the SAP v2.0 in the following respects:

1. The number of deaths needed to trigger the analysis is N=470 (whereas SAP v2.0 had provision for earlier interim analyses).
2. The secondary objectives relating to Quality of Life and Resource Usage are out-of-scope.
3. "M0 disease at primary diagnosis (Y/N)" will be used in the subgroup analyses in place of "Local treatment (Y/N)" as a more accurate approach for distinguishing men who presented initially with non-metastatic disease and later developed metastatic hormone sensitive prostate cancer. The use of "Local treatment (Y/N)" was originally specified to identify this subgroup in order to align with the approach taken in the CHAARTED trial, however "Local treatment (Y/N)" in the ENZAMET database is an inaccurate marker of the clinical group of interest as men diagnosed with de novo metastatic disease may have received local therapy.
4. A section on efficacy estimand definition has been added.
5. References to a Per-Protocol Analysis set have been removed. All efficacy analyses will be performed on the full analysis set comprising all randomised patients (i.e. the ITT population).
6. Appendices (describing QoL scoring systems and output table shells) have been removed.

The following aspects in addendum 1 are unchanged from SAP v2.0:

1. Endpoint derivations
2. Analysis set definitions for the ITT and Safety Populations
3. Accounting for stratification factors
4. Approach to analyses of study endpoints and patient characteristics

2 Objectives

The objectives being addressed by this SAP addendum are to determine effect of enzalutamide on:

1. Overall survival (primary)
2. PSA Progression-Free Survival (PSA PFS)
3. Clinical Progression-Free Survival (Clinical PFS)
4. Safety

3 Efficacy Estimand Definition

As per ICH E9(R1)[1], a precise definition of the relevant estimand for each of the efficacy objectives requires the specification of: (1) the treatment; (2) population of interest; (3) the endpoint; (4) handling of other intercurrent events; and, (5) the population-level summary measure used to compare treatments.

The standard estimand definition for the efficacy objectives is based on the following specifications:

1. the treatment conditions of interest are randomisation to enzalutamide or conventional NSAA;
2. the population of interest is that defined by the protocol inclusion/exclusion criteria;
3. the endpoints are as per the definitions in Section 4;
4. a 'treatment policy' approach will be used to account for intercurrent events; and,
5. the population-level summary measures used to compare treatments are as per the definitions in Section 0.

4 Endpoint Derivation

Endpoint derivations are the same as those specified in SAP v2.0.

4.1 Overall Survival (OS) (Primary Endpoint)

Overall survival is defined as the interval from the date of randomisation to date of death from any cause, or the date last known alive (at which point the observation is censored).

4.2 PSA Progression Free Survival (PSA PFS)

PSA progression free survival (PSA PFS) is defined as the interval from the date of randomisation to the date of first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last PSA test without PSA progression (at which point the observation is censored).

4.3 Clinical Progression Free Survival (Clinical PFS)

Clinical progression free survival is defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression (at which point the observation is censored). The censoring date will be the latest of the following: the date of the patient's last assessment during the 'on treatment' phase where clinical progression status is recorded as 'no'; and, the maximum date the patient is last known not to have progressed collected during the 'post-treatment follow-up' phase. Clinical progression is defined by progression on imaging, development

of symptoms attributable to cancer progression, or initiation of other anticancer treatment for prostate cancer.

4.4 Safety

The NCI Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE) will be used to classify and grade the intensity of adverse events whilst on treatment, at progression, and 30-42 days after the last dose of study treatment.

5 Analysis Sets

Analysis set definitions for the ITT and Safety Populations are the same as those specified in SAP v2.0.

All randomised participants will be eligible for inclusion in the full analysis set in accordance with the intention-to-treat analysis principle. The full analysis set thus comprises the intention-to-treat (ITT) population. Patients are classified according to study medication assigned at the time of randomisation. The safety population will comprise all randomised participants who received at least one administration of study medication. If a patient receives at least one dose of enzalutamide (irrespective of randomised allocation) in the period between randomisation and cessation of study treatment, they will be included in the enzalutamide arm of the safety population. If that condition does not apply, and the patient receives a least one dose of NSAA (irrespective of randomised allocation) in the period between randomisation and cessation of study treatment, they will be included in the NSAA arm of the safety population. If neither of the above criteria apply, the patient will be excluded from the safety population.

The reasons for any exclusions from analysis sets will be reviewed and endorsed by the Trial Executive Committee and documented in the final study report.

The primary analysis population used for the evaluation of enzalutamide on non-safety parameters will be the ITT population. Safety analyses will be performed using the safety population.

6 Analyses Timing

The analysis is planned to be undertaken after N=470 deaths have occurred (see sample size section of the protocol).

7 Type I Error (Alpha)

Unless otherwise specified, a two-sided alpha of 5% will be applied to interpret the results of hypothesis tests and to construct confidence intervals. P-values from secondary analyses that are unadjusted for multiple comparisons will be interpreted conservatively. For the many planned subgroup analysis, this will involve grouping hypothesis tests into discrete families (sets), and evaluating the p-values within each family with due consideration of the family-wise type I error rate (See Section 11).

8 Accounting for Stratification Factors

The approach for accounting for stratification factors are the same as those specified in SAP v2.0.

Randomisation is stratified by 'volume of disease' (high volume yes versus no), 'use of early docetaxel' (yes versus no), 'use of antiresorptive therapy' (yes versus no), comorbidities (Adult Co-morbidity Evaluation ACE-27 score: 0-1 vs 2-3), and treating institution (Study Site). Sensitivity of conclusions when accounting for these factors will be explored in secondary analyses (See Section 11). Study sites will be grouped into geographical regions for these analyses. The regions are Europe (UK and Ireland), Australasia (Australia and New Zealand), and North America (USA and Canada). If stratification data were incorrectly collected and reported at the time of randomisation, data that are corrected by site after the randomisation process will be used in analysis.

9 Subgroups of Particular Interest

Consistency of the treatment effect on OS will be evaluated across pre-specified subgroups defined by the stratification factors and the baseline characteristics shown below in Table 1. Consistency of the treatment effect on PSA PFS and clinical PFS will also be evaluated across these same subgroups. Study sites will be grouped into geographical regions for these analyses (See Section 8). The effects of enzalutamide in participants treated with early docetaxel, especially in participants with high volume disease treated with early docetaxel, are of particular clinical interest (see section 11).

Table 1: Subgroups Definitions

	Subgroup Definitions	**Subgroup Definitions from Other Trials (presented for reference)**		
Subgroups	**ENZAMET**	**STAMPEDE**	**LATITUDE**	**CHAARTED**
Gleason Score	≤7 vs 8-10	≤7 vs 8-10	≤7 vs 8-10	≤7 vs 8-10
Age	<70 vs ≥70	<70 vs ≥70	<65, ≥65, ≥75	<70, ≥70
Performance Status	0 vs 1-2	0 vs 1-2	0 vs 1-2	0-1 vs 2
Visceral Disease	Yes vs No		Yes vs No	
M0 Disease at Original Diagnosis	Yes vs No			Prior Local Treatment Used
High volume disease	Yes vs No			Yes vs No
Early docetaxel	Yes vs No			
Anti-resorptive therapy	Yes vs No			Yes vs No
ACE-27	0-1 vs 2-3			
Region	ANZ vs Europe vs North America			

10 Analysis of Study Endpoints and Patient Characteristics

The methods to analyses study endpoints and patient characteristics are the same as those specified in SAP v2.0.

10.1 Subject Disposition

The number of patients in the analysis sets will be presented along with reasons for any exclusions. The Kaplan-Meier method will be used to summarise follow-up time for OS by treatment allocation with deaths being treated as censored observations. A CONSORT flow diagram will be prepared.

10.2 Baseline Demographic and Clinical Characteristics

Descriptive statistics will be prepared to summarise baseline characteristics of the study participants by treatment allocation. Variables to be summarised include: age, BMI, stratification factors, other prostate cancer characteristics, and previous treatment for prostate cancer.

10.3 Exposure to Study Medication

The Kaplan-Meier method will be used to summarise time on study medication by treatment allocation, with any patients remaining on treatment being censored at the time the most recent dosing was recorded. Reasons for discontinuations will be tabulated by treatment group.

10.4 Other Treatments

The use of non-protocol anti-cancer treatment will be tabulated by treatment group.

10.5 Overall Survival (OS) – Primary Analysis of Primary Endpoint

Overall survival (OS) time for each treatment group will be quantified using the Kaplan-Meier method and compared using an unstratified log-rank test. An unadjusted Cox PH model will be used to estimate the hazard ratio (with 95% CI). The population-level summary measure used to compare treatments will be the HR from this model. Section 8 and 11 provide detail on adjusted, and subgroup analyses that are planned to be conducted on OS.

10.6 PSA Progression Free Survival (PSA PFS)

PSA Progression Free Survival time for each treatment group will be quantified using the Kaplan-Meier method and compared using an unstratified log-rank test. An unadjusted Cox PH model will be used to estimate the hazard ratio (with 95% CI). The population-level summary measure used to compare treatments will be the HR from this model. Section 11 provide detail on the subgroup analyses that are planned to be conducted on PSA PFS.

10.7 Clinical Progression Free Survival (Clinical PFS)

Clinical Progression Free Survival will be analysed using the same approach as that described above for PSA PFS. Section 11 provide detail on the subgroup analyses that are planned to be conducted on clinical PFS.

10.8 Safety Data Analysis

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be tabulated by treatment received (see Section 5) and CTCAE criteria including system organ class, term, and (worst) grade.

11 Adjusted and Subgroup Analyses

Sensitivity of conclusions from the primary analysis of OS to adjustment for stratification factors (See Section 8) will be investigated for the ITT population. A comparison between randomised groups will be undertaken using a stratified log-rank test. An adjusted hazard ratio (with 95% CI) will be obtained from a Cox PH model that includes the stratification factors as covariates. These analyses will be performed on the ITT population.

The consistency of the treatment effect across the individual stratification factors and other pre-specified baseline characteristics (See Section 9) will be tested by fitting the relevant factor-by-treatment interaction term in a Cox regression model along with the associated main effects terms. The subgroup analyses will be performed on the primary endpoint of OS as repeated for the secondary endpoints of PSA PFS and clinical PFS.

It is furthermore of clinical and biological interest to investigate whether the effect of enzalutamide is consistent across combinations of covariates which represent subgroups with distinct outcomes when managed with testosterone suppression alone. Two specific clinical hypotheses will be tested and an exploratory analysis will be performed. The two specific clinical hypotheses are:

Hypothesis 1: enzalutamide will be effective within the subset of patients with high volume disease in the early docetaxel stratum. The log-rank p-value for the effect of enzalutamide in subset of patients with high volume disease in the early docetaxel stratum will be used to test hypothesis 1.

Hypothesis 2: For those NOT in the early docetaxel stratum, there will be no statistically significant heterogeneity of enzalutamide effect across the volume of disease subgroups (high versus low). The p-value for the test of heterogeneity (i.e. interaction) across the volume of disease subgroups (high versus low) for those in NOT in the early docetaxel stratum will be used to test hypothesis 2.

The hypothesis tests from the planned subgroup analysis will be grouped into sets. Three of these sets will comprise the tests involving individual covariates with OS, PSA PFS, and clinical PFS. A fourth set will comprise the tests associated with hypothesis 1 and 2 described above. Due consideration will be given to the family-wise type I error rate when conservatively interpreting the p-values within each set of tests. The Benjamini-Hochberg procedure[1] will be used to calculate adjusted p-values.

The exploratory analysis will evaluate whether the effect of enzalutamide is modified by a combination of prognostic grouping and docetaxel stratum status. Two binary factors will be used to construct the prognostic groups. One factor is M1 staging at initial diagnosis (i.e. denovo metastatic disease). The other factor is high volume of disease at entry to ENZAMET. The three prognostic groups are defined as follows:

- Poor prognosis = both prognostic factors present (i.e. M1 at initial diagnosis AND high volume disease at baseline)

[1] Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society Series B (Methodological) 1995; 57(1): 289-300.

- Intermediate prognosis = only one prognostic-factor present (i.e. M1 at initial diagnosis with low volume disease at baseline, OR M0 at initial diagnosis with high volume disease at baseline)
- Good prognosis = no prognostic factor present (i.e. M0 at initial diagnosis with low volume disease at baseline)

The exploratory analysis will involve fitting a second-order interaction (prognostic group-by-docetaxel stratum-by-randomised group) to a Cox proportional hazards model (along with the relevant first-order interactions and main effect terms). If that second-order interaction is non-significant at the 5% level, the first-order interactions of interest will be tested and the Benjamini-Hochberg procedure will be used to calculate adjusted p-values.