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OVERALL SURVIVAL (OS) RESULTS OF A PHASE III RANDOMIZED TRIAL OF STANDARD OF CARE THERAPY WITH OR WITHOUT ENZALUTAMIDE FOR METASTATIC HORMONE SENSITIVE PROSTATE CANCER (mHSPC)

ENZAMET (ANZUP 1304):
AN ANZUP-LED INTERNATIONAL CO-OPERATIVE GROUP TRIAL
(NHMRC CTC, CCTG, CTI, DFCI)

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Metastatic Hormone Sensitive Prostate Cancer (mHSPC): History and Current State of the Art

- Until 2014 testosterone suppression ± standard nonsteroidal antiandrogen was the only therapy for mHSPC[1]
  - Patients with higher burden of mHSPC have shorter survival[2,3]
- Improvements in mHSPC overall survival (OS) from agents with survival benefits in castration-resistant prostate cancer (CRPC)
  - Docetaxel (a cytotoxic chemotherapy, microtubule spindle inhibitor) [4,5,6,7]
  - Abiraterone (a C17,20 lyase inhibitor, decreases extragonadal androgens) [8,9,10,11]
- Enzalutamide: potent direct AR inhibitor with OS benefit in CRPC[12,13]
  - Enzalutamide improves rPFS in mHSPC (± prior docetaxel) [ARCHES][14]
  - Apalutamide improves rPFS and OS in mHSPC (± prior docetaxel): [TITAN][15]

ENZAMET: first mHSPC trial to report OS data of enzalutamide + testosterone suppression and outcomes if patients also received <u>concurrent</u> docetaxel

[1]Huggins and Hodges Cancer Res 1941; [2]Tangen et al J. Urol, 2012; [3]Millikan et al J.Clin Oncol, 2008; [4]Tannock et al NEJM, 2004; [5]Petrylak et al NEJM, 2004; [6]Sweeney et al NEJM 2015;[7]James et al Lancet 2015; [8]Debono et al NEJM 2011, [9]Ryan et al Lancet Oncology 2015; [10]Fizazi et al NEJM 2017, [11]James et al NEJM 2017, [12]Scher et al NEJM 2012, [13]Beer et al NEJM 2014, [14]Armstrong et al GUASCO 2019; [15]Chi et al NEJM 2019

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The ENZAMET Hypothesis

- Enzalutamide added to testosterone suppression with greater inhibition of the androgen receptor
  - will prolong overall survival
  - as first line therapy for metastatic hormone sensitive prostate cancer
  - with or without concurrent docetaxel
  - more than the addition of a standard non-steroidal anti-androgen (first study to include as an active control)

[1]Huggins and Hodges Cancer Res 1941; [2]Tangen et al J. Urol, 2012; [3]Millikan et al J.Clin Oncol, 2008; [4]Tannock et al NEJM, 2004; [5]Petrylak et al NEJM, 2004; [6]Sweeney et al NEJM 2015;[7]James et al Lancet 2015; [8]Debono et al NEJM 2011, [9]Ryan et al Lancet Oncology 2015; [10]Fizazi et al NEJM 2017, [11]James et al NEJM 2017, [12]Scher et al NEJM 2012, [13]Beer et al NEJM 2014, [14]Armstrong et al GUASCO 2019; [15]Chi et al NEJM 2019

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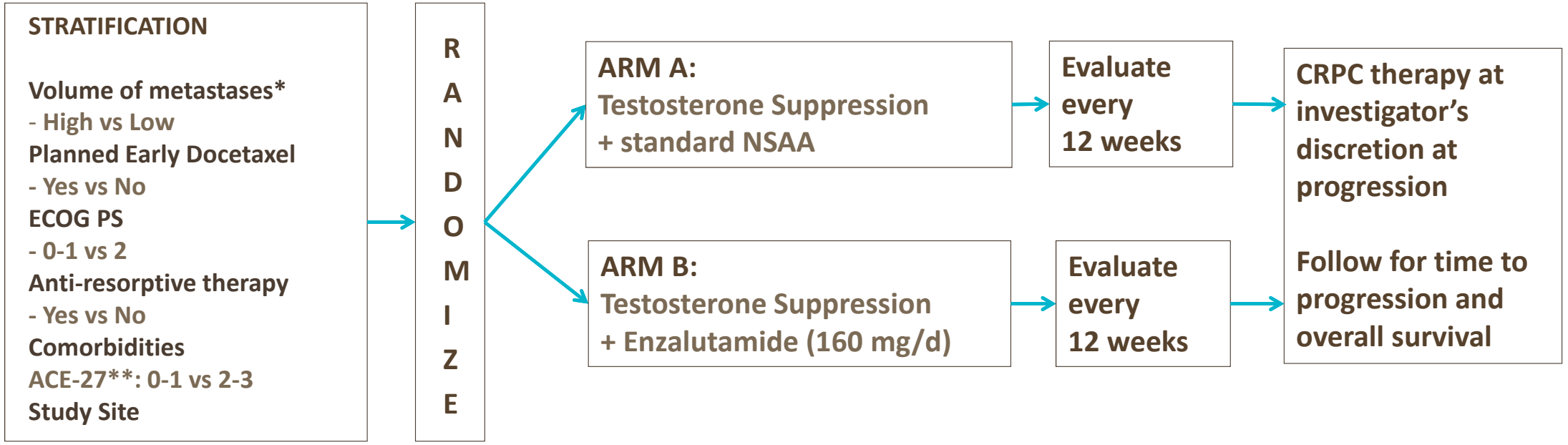
ENZAMET Treatment



- Prior to randomization testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed.
- Intermittent ADT and cyproterone were not allowed
- NSAA: bicalutamide; nilutamide; flutamide
- *High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)
- **Adult Co-morbidity Evaluation-27

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Study endpoints

- **Primary Endpoint**
  - **Overall survival**
- **Secondary Endpoints**
  - **Prostate specific antigen progression free survival (includes clinical progression if occurs first, PCWG2)**
  - **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)
  - Health outcomes relative to costs
  - Translational biological studies

PCWG2: Prostate Cancer Working Group Criteria version 2
CTCAE: NCI Common Terminology Criteria for Adverse Events

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Key eligibility criteria

- **Metastatic adenocarcinoma of the prostate**
  - Histology confirmed or
  - Clinical scenario c/w PrCa (PSA > 20 and rising and distribution of metastases)
- **Prior ADT limited to**
  - 12 weeks prior to randomization
  - Adjuvant Rx allowed if ≤24 months and completed >12 months prior
- **Organ function**
  - ECOG PS: 0-2 (2 only if due to PrCa)
  - CrCl > 30 mL/min; Bilirubin < 1.5 ULN
  - No major cardiovascular disease within prior 3 months
  - No prior seizures or conditions predisposing to seizures

Statistical Design and History of Amendments

Intent to treat analysis, 1,100 patients and 470 deaths; > 80% power to detect a 25% reduction in the hazard of death (HR 0.75), with a 2-sided type 1 error rate of 0.05 (with all versions)

	Version 1	Version 2	Version 3
Date	March 2014	November 2014	March 2018
Sample size	1,100	1,100	1,100
Purpose	IA with 67% of events	To allow early docetaxel*	Added IA with 50% and 80% of planned 470 events**
Enrollment	0	88	1,125 patients by March 2017 prior to any IA

IA: Interim Analyses

***Based on results of CHAARTED presented ASCO 2014** (Sweeney et al NEJM 2015)

****Based on results of abiraterone in mHSPC in 2017** (Fizazi et al NEJM 2017, James et al NEJM 2017)

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Results

- 1,125 men accrued
  - Planned interim analysis at 50% information (notification of 235 deaths), 28th Feb 2019 met pre-specified criteria for significance and release of data
  - (p-value of 0.0016 lower then 0.0031 rejection boundary*)
  - ASCO 2019 abstract; median follow-up 33 months for interim analysis

- Data to be presented based on survival sweep with 245 deaths
  - Median follow-up of 34 months
  - 143 deaths NSAA arm vs. 102 deaths enzalutamide arm

*Lan-DeMets alpha-spending function

Patient characteristics

	TS + NSAA (N=562)		TS + ENZA (N=563)	
	N	%	N	%
Age				
Median	69.0		69.2	
Interquartile Range	(63.6 to 74.5)		(63.2 to 74.5)	
Region				
Australia	321	57%	324	58%
Canada	107	19%	97	17%
United Kingdom	50	9%	63	11%
Ireland	43	8%	39	7%
United States*	22	4%	20	4%
New Zealand	19	3%	20	4%
ECOG PS				
0	405	72%	405	72%
1	151	27%	150	27%
2**	6	1%	8	1%

* Dana Farber Cancer Institute Only
** Limited to PrCa related PS 2

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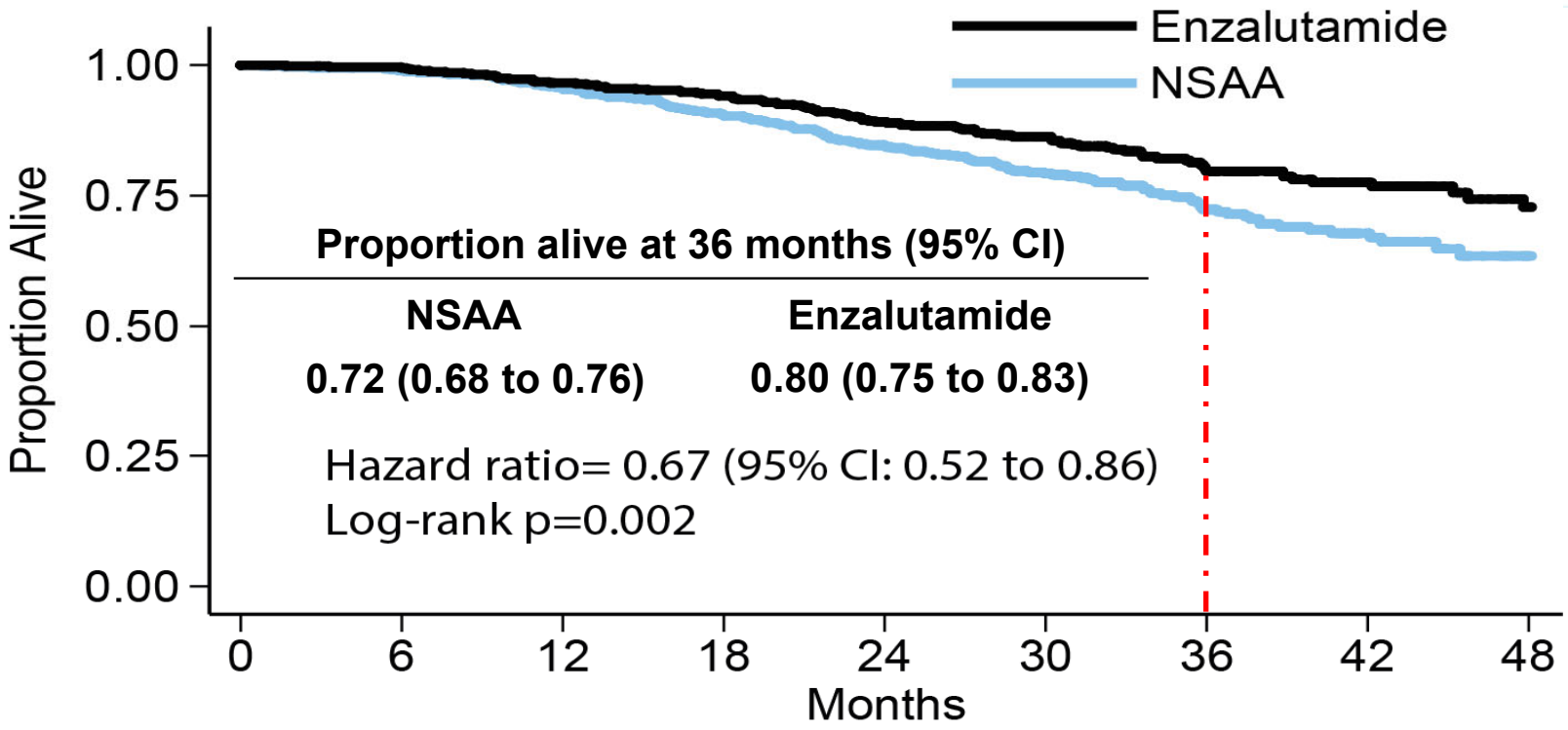
Patient characteristics

	TS + NSAA (N=562)		TS + Enzalutamide (N=563)	
	N	%	N	%
Planned Early Docetaxel				
Yes	249	44%	254	45%
No	313	56%	309	55%
Volume of Metastases				
High	297	53%	291	52%
Low	265	47%	272	48%
ACE-27 Stratum				
0-1	419	75%	422	75%
2-3	143	25%	141	25%
Prostate Cancer Related Therapies				
Planned SRE Rx	58	10%	55	10%
Prior Local Rx**	235	42%	238	42%
Prior Adjuvant ADT	40	7%	58	10%

- **Early docetaxel:**
  61% high volume; 27% of low volume
- ADT: androgen deprivation therapy
- ACE: Adult Co-morbidity Evaluation-27
- SRE Rx: Skeletal related event antiresorptive bone therapy
- **Prostatectomy or radiation

Primary endpoint: Overall survival

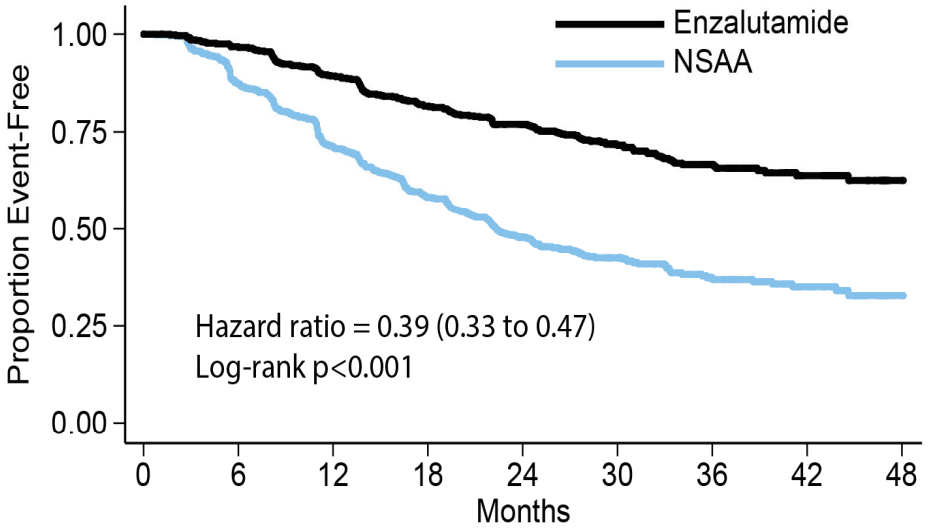


Number at risk

NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Secondary Endpoints: Progression–free survival (PCWG2)

Time to PSA rise, clinical progression or death

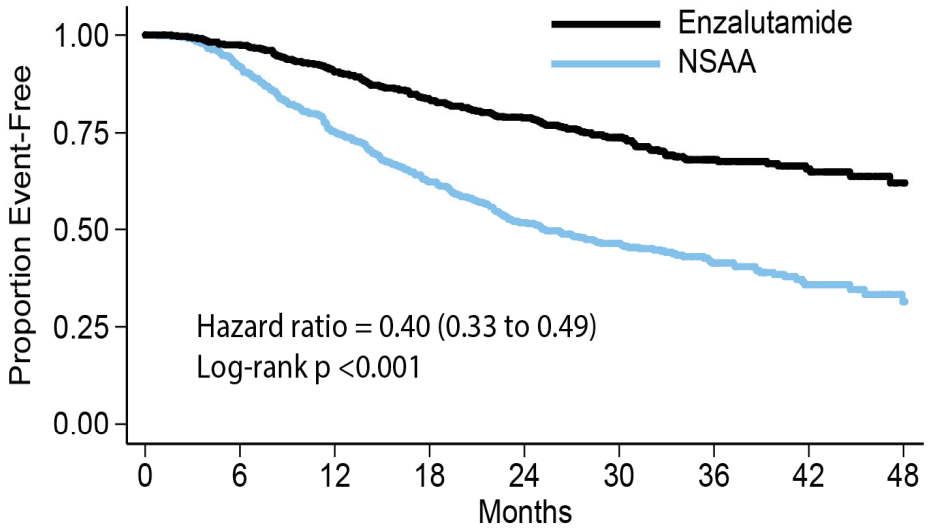


Number at risk

NSAA	562	486	395	322	249	161	78	44	17
Enzalutamide	563	543	500	455	411	269	146	77	34

Time to clinical progression

(imaging, symptoms, signs, change of therapy or death)



Number at risk

NSAA	562	512	418	346	272	182	96	50	17
Enzalutamide	563	547	507	468	424	284	156	84	36

Concurrent Docetaxel: Prespecified Subgroup of Interest (Biology and Treatment Implications)

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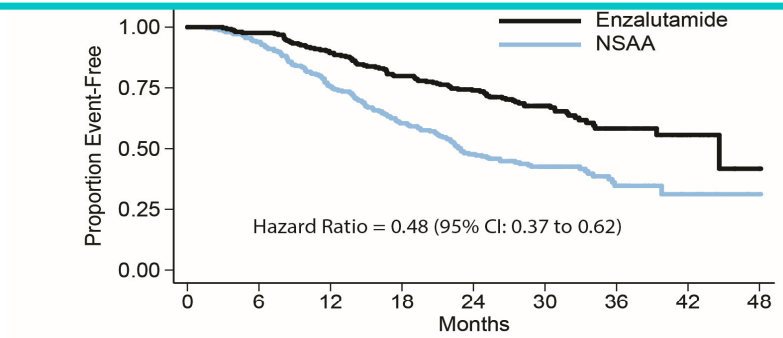
Clinical Progression-Free Survival

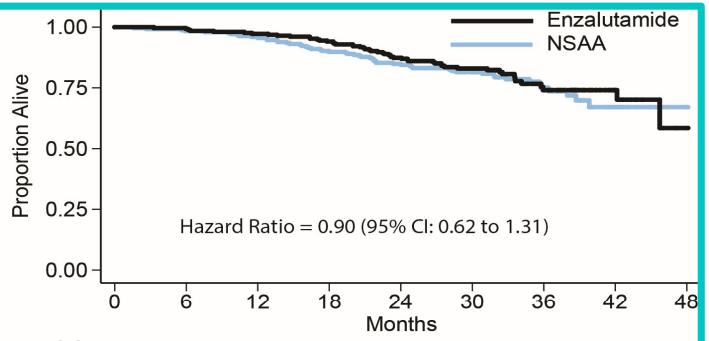
Overall Survival

Testosterone Suppression + Docetaxel N=503 (71% High Volume)



Number at risk

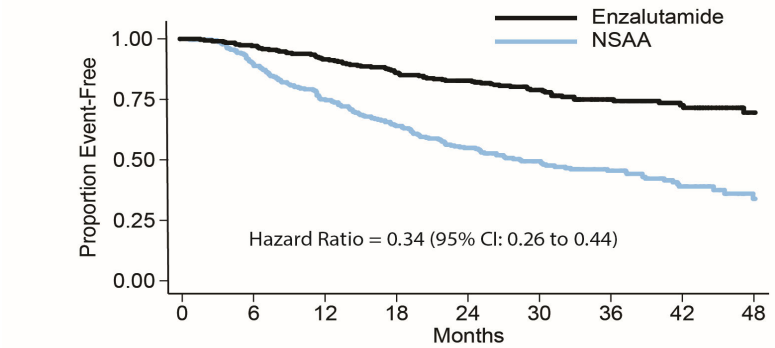
NSAA	249	230	185	148	112	73	21	6	1
Enzalutamide	254	248	226	202	178	109	35	12	2



Number at risk

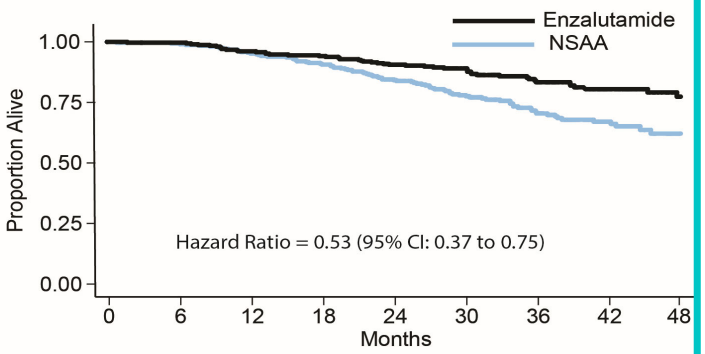
NSAA	249	241	235	220	203	135	56	13	2
Enzalutamide	254	252	246	238	210	139	54	19	3

Testosterone Suppression + No Docetaxel N=622 (37% High Volume)



Number at risk

NSAA	313	282	233	198	160	109	75	44	16
Enzalutamide	309	299	281	266	246	175	121	72	34



Number at risk

NSAA	313	310	296	281	249	176	118	73	30
Enzalutamide	309	306	295	289	270	201	135	87	42

3 year OS point-estimates in biologically and clinically relevant predefined subgroups

	TS + NSAA (N=562)		TS + Enzalutamide (N=563)	
	3 year OS (%)	95% CI	3 year OS (%)	95% CI
Early Docetaxel				
Yes	75	68 to 81	74	66 to 80
No	70	64 to 76	83	78 to 87
Volume of Metastases				
*High	64	58 to 70	71	64 to 76
Low	82	75 to 87	90	84 to 93

356 (61%) of 588 high volume patients received early docetaxel - OS is better than testosterone suppression alone in CHAARTED and LATITUDE: ~50% 3 year OS

Sweeney et al NEJM 2015, Fizazi et al NEJM 2017

Duration of study therapy and reasons for discontinuing

	TS + NSAA N=558	TS + ENZA N=563
6 cycles of early docetaxel*	76% of 238	65% of 243
Proportion on Rx at 36 months (95% CI)	0.34 (0.29 to 0.38)	0.62 (0.57 to 0.66)
Reasons for discontinuing	**N=356**	**N=201**
Discontinue due to adverse event	14 (4%)	33 (16%)
Imaging	144 (40%)	88 (44%)
Symptoms	55 (15%)	32 (16%)
New anti-cancer Rx	45 (13%)	7 (4%)
Clinician Preference	58 (16%)	13 (6%)
Death	7 (2%)	6 (3%)

*of those who received at least one cycle of docetaxel

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Selected adverse events (AE)*

All patients at anytime

	TS + NSAA N=558		TS + ENZA N=563	
Serious AE rate per yr of Rx exposure	0.33	95% CI: 0.28-0.39	0.34	95% CI: 0.29-0.40
AEs of Interest	**N**	**%**	**N**	**%**
Hypertension: Gde 3	24	4%	43	8%
Gde 2	30	5%	60	11%
Fatigue: Gde 3	4	1%	31	6%
Gde 2	80	14%	142	25%
Falls: Gde 3	2	<1%	6	1%
Gde 2	8	1%	28	5%
Syncope	7	1%	20	4%
Concentration Impairment: Gde 1/2	6	1%	24	4%
Any Seizure	0	0%	7	1%

*worst grade AE shown

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Selected docetaxel-relevant adverse events

Limited to First 6 months	TS + NSAA Docetaxel N=246	TS + ENZA Docetaxel N=254	TS + NSAA No Docetaxel N=312	TS + ENZA No Docetaxel N=309
Neutropenic Fever	32 (13%)	35 (14%)	0	1 (<1%)
Sensory neuropathy Gde 2	7 (3%)	24 (9%)	2 (<1%)	0
Gde 3	1 (<1%)	3 (1%)	0	0
Motor Neuropathy G2	1 (<1%)	4 (2%)	0	0
Gde 3	0	0	0	1 (<1%)
Nail discoloration	13 (5%)	25 (10%)	0	0
G1 or 2 Watery eyes	15 (6%)	52 (20%)	0	0
G2 fatigue	35 (14%)	52 (20%)	9 (3%)	32 (10%)

Total Treatment Exposure in Patients With Clinical Progression

	TS + NSAA (N=320)	TS + ENZA (N=167)
Docetaxel when starting testosterone suppression	139 (43%)	88 (53%)
One or more life prolonging CRPC therapy	271 (85%)	112 (67%)
Enzalutamide	141 (44%)	0 (0%)
Abiraterone	113 (35%)	46 (28%)
Docetaxel	69 (22%)	45 (27%)
Radium-223	22 (7%)	14 (8%)
Sipuleucel-T	2 (<1%)	0 (0%)
Cabazitaxel	64 (20%)	34 (20%)
Died without further CRPC therapy	13 (4%)** [3 pts early docetaxel]	28 (17%) [13 pts early docetaxel]

***10 of the 320 pts (4%) assigned early NSAA who progressed and died, did not receive additional life prolonging therapy (docetaxel for mHSPC or CRPC, or other life prolonging CRPC Rx*

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Conclusion

Early enzalutamide improved time to progression and overall survival when added to standard mHSPC therapy (testosterone suppression ± docetaxel).

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Clinical interpretation

- Enzalutamide added to testosterone suppression represents an appropriate option for men with metastatic prostate cancer commencing testosterone suppression
- Clear benefit in patients with low and high volume metastatic disease
  - Delays progression and improvement in overall survival
  - More expected toxicity was seen with enzalutamide alone
  - More docetaxel-related toxicity was reported with addition of enzalutamide
- For patients who are candidates for docetaxel when starting testosterone suppression, quality of life analyses and longer follow-up are needed to determine whether the delay in progression with concurrent enzalutamide
  - Results in a meaningful clinical benefit and / or
  - Is compounded by CRPC therapy and augments survival beyond 3 years

Acknowledgements

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In collaboration with:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

I.D. Davis, A.J. Martin, M.R. Stockler, S. Begbie, K.N. Chi, S. Chowdhury, X. Coskinas, M. Frydenberg, W.E. Hague, L.G. Horvath, A.M. Joshua, N.J. Lawrence, G. Marx, J. McCaffrey, R. McDermott, M. McJannett, S.A. North, F. Parnis, W. Parulekar, D.W. Pook, M.N. Reaume, S.K. Sandhu, A. Tan, T.H. Tan, A. Thomson, E. Tu, F. Vera-Badillo, S.G. Williams, S. Yip, A.Y. Zhang, R.R. Zielinski, and C.J. Sweeney, for the ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group*

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www.anzup.org.au/enzamet