A randomised phase II trial of ^{177}Lu-PSMA-617 (Lu-PSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: Initial results

TheraP (ANZUP 1603)

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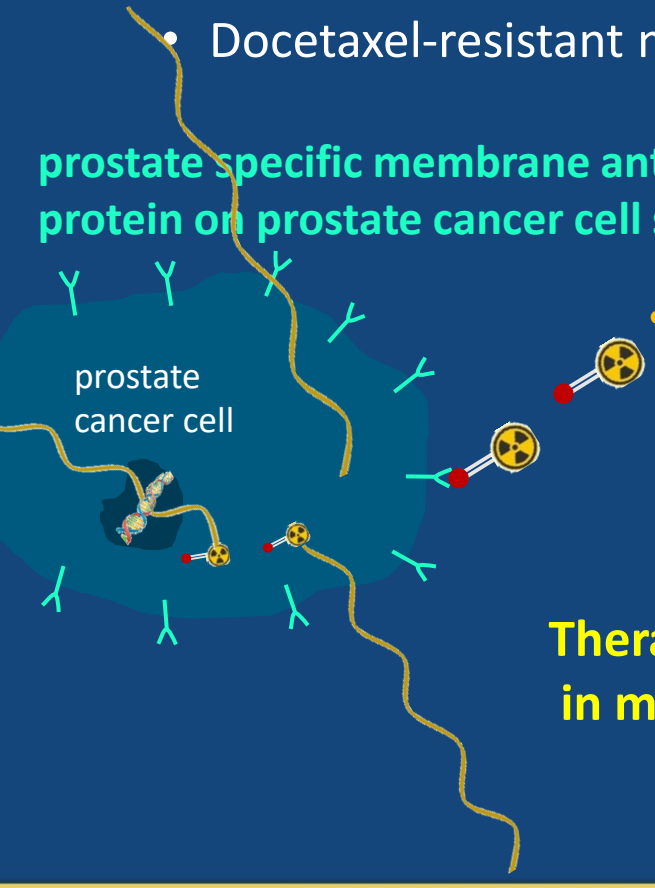
ANZUP® Cancer Trials Group Limited

Metastatic Castration Resistant Prostate Cancer (mCRPC): History and Current State of the Art

- **mCRPC: a lethal disease and novel treatments are needed to improve outcomes[1]**
  - Life prolonging therapies include docetaxel[1], abiraterone[2], enzalutamide[3], sipuleucel-T[4] and ^{223}Ra[5]
  - Docetaxel-resistant mCRPC: cabazitaxel ↑OS compared to mitoxantrone[7] and 2nd line novel anti-androgen[8]

prostate specific membrane antigen (PSMA): protein on prostate cancer cell surface



- **^{177}Lu-PSMA-617 (Lu-PSMA): radiolabelled small molecule binds to PSMA**
  - Delivers therapeutic β-radiation to mCRPC
  - Encouraging efficacy and safety in non-randomised trials of mCRPC[9-11]
  - Phase II study: PSA ≥ 50% in 64% of men with low toxicity[12-13]

TheraP: first randomised trial comparing Lu-PSMA to an active therapy (cabazitaxel) in men with mCRPC progressing after docetaxel

[1]Gillessen S *Eur Urol* 2020;77(4) [2]Tannock IF *NEJM* 2004;351(15) [3]de Bono JS *NEJM* 2011;364(21)
[4]Scher HI *NEJM* 2012;367(13) [5]Kantoff PW *NEJM* 2010;353(5) [6]Parker C et *NEJM* 2013;369(3)
[7]de Bono JS *Lancet* 2010;376(9747) [8]de Wit R *NEJM* 2019;381(26)
[9]Kratochwil C *Eur J Nucl Med Mol Imaging* 2015;42(6)
[10]Rahbar K *J Nucl Med* 2017;58(1) [11]Heck MM *Eur Urol* 2019;75(6)
[12]Hofman MS *Lancet Oncol* 2018;19(8) [13]Violet J *J Nucl Med* 2019;Nov 15 epub

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PRESENTED BY: Michael Hofman, MBBS @DrMHofman

Aim: to determine the activity and safety of Lu-PSMA vs cabazitaxel

KEY ELIGIBILITY

- mCRPC post docetaxel suitable for cabazitaxel
- Progressive disease with rising PSA and PSA ≥ 20 ng/mL
- Adequate renal, haematologic and liver function
- ECOG performance status 0-2

↓

^{68}Ga-PSMA + ^{18}F-FDG PET/CT

- PSMA SUVmax > 20 at any site
- Measurable sites SUVmax > 10
- No FDG positive/PSMA negative sites of disease
- Centrally reviewed

R

^{177}Lu-PSMA-617

8.5 GBq IV q6 weekly
↓ 0.5GBq each cycle
Up to 6 cycles

SPECT/CT @ 24 hours

suspend Rx if exceptional response; recommence upon progression

200 men 1:1 randomisation
11 sites in Australia

Stratified by:

- Disease burden (>20 sites vs ≤ 20 sites)
- Prior enzalutamide or abiraterone
- Study site

CABAZITAXEL

20mg/m^2 IV q3 weekly,
Up to 10 cycles

80% power to detect a true absolute difference of 20% in the PSA response rate (from 40% to 60%), with a 2-sided type 1 error of 5% and allowance of 3% for missing data.

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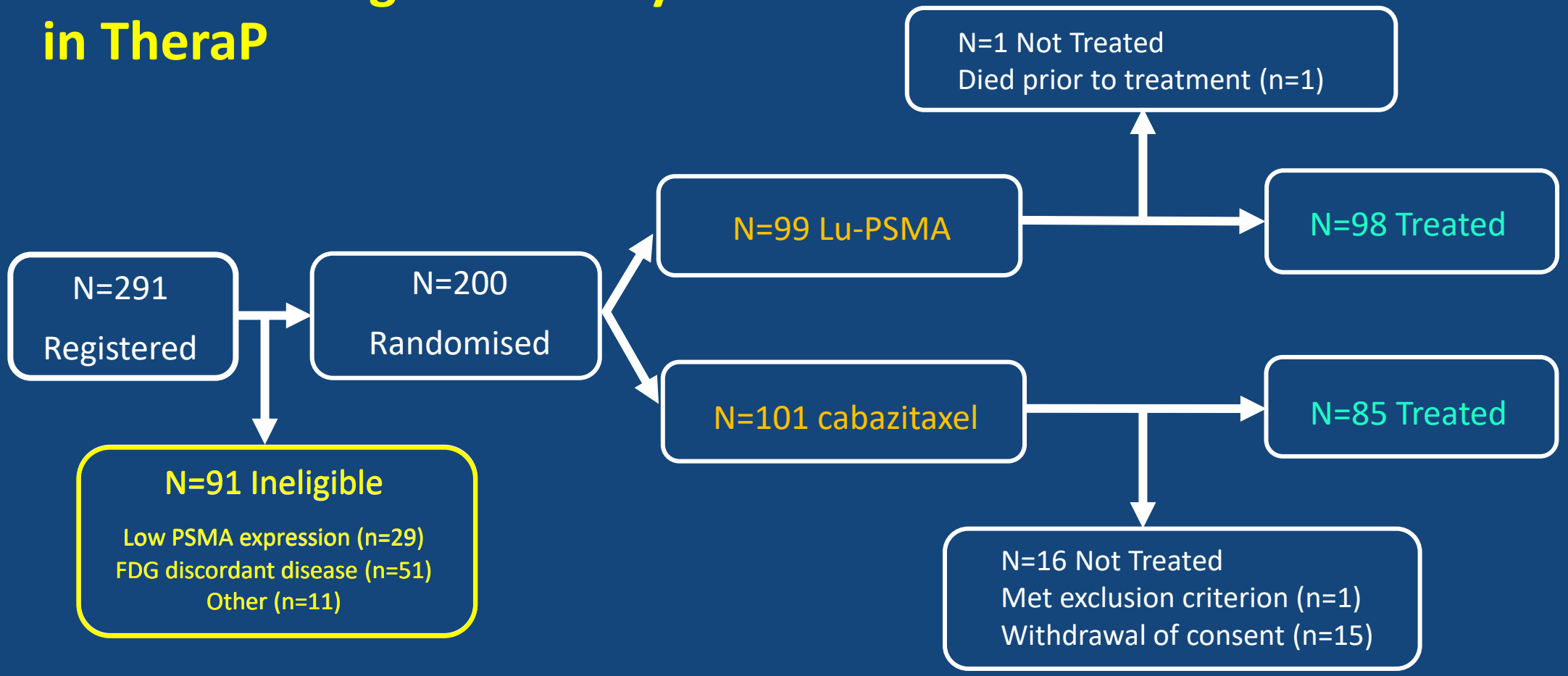
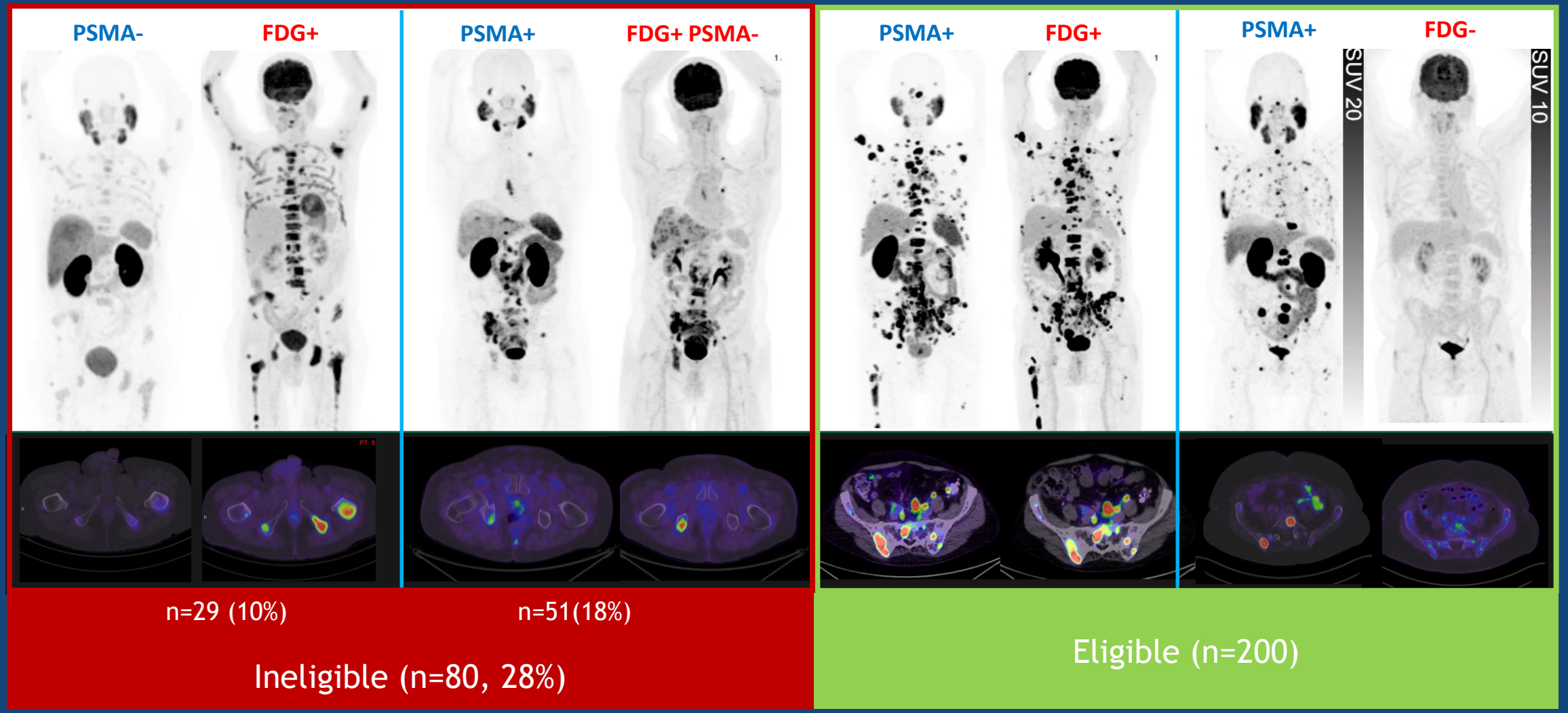
Protocol paper: Hofman MS *BJUI Int* 2019;124(S1)

CONSORT Diagram for Key Details in TheraP



Intention-to-treat (ITT) analysis + sensitivity analysis for per-protocol analysis

Patient selection: PSMA and FDG PET/CT



TheraP Endpoints

- **Primary Endpoint**
  - PSA response, defined by PSA reduction of ≥ 50% from baseline (PSA50-RR) (PCWG3)

- **Secondary Endpoints**
  - PSA progression-free survival (PFS) (PCWG3)
  - Adverse events (CTCAE v4.03)

  - Objective tumour response (RECIST v1.1)
  - Pain response (McGill-Melzack Present pain intensity (PPI) scale and analgesic score)
  - Radiographic PFS (PCWG3 criteria for bone lesions and RECIST 1.1 for soft tissue lesions)
  - Pain PFS
  - Overall PFS (time to PSA progression, pain progression, radiographic progression or death)
  - Health related quality of life (EORTC Core Quality of Life Questionnaire C30 [QLQ-C30], PDF)
  - Overall survival

Not reported in this analysis; further follow-up pending

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PCWG3: Prostate Cancer Working Group Criteria version 3
CTCAE: NCI Common Terminology Criteria for Adverse Events
PDF: Patient disease and Treatment Assessment Form

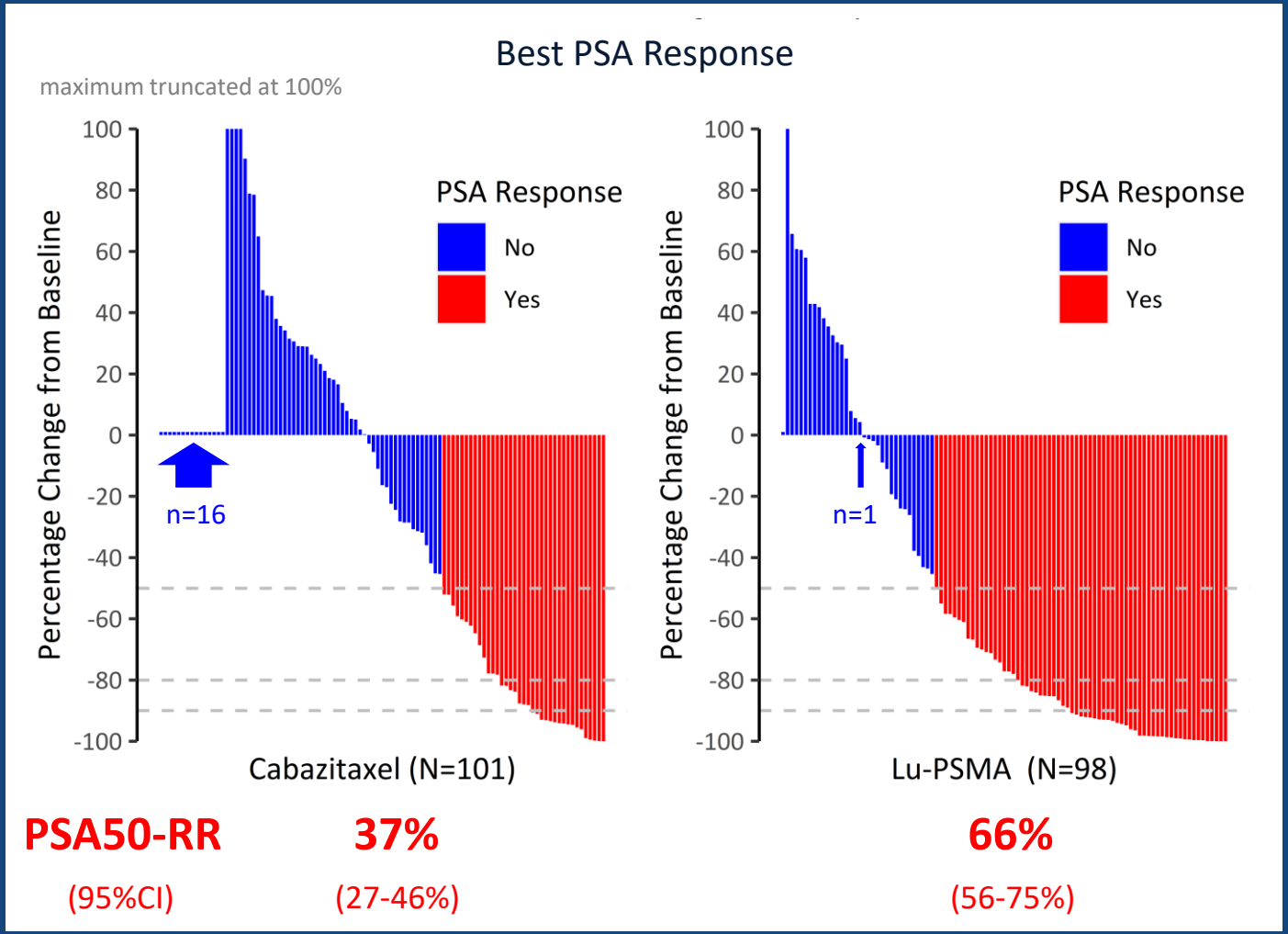
Results: patient characteristics

	Cabazitaxel (N=101)	Lu-PSMA (n=99)
Age (Years): Median (IQR)	72 (67 to 77)	72 (67 to 77)
Prior enzalutamide or abiraterone	91	91
Disease burden (> 20 sites)	79	77
ECOG performance status		
0	44	42
1	52	53
2	4	4
unknown	1	
PSA: Median (IQR)	110 (64 to 245)	94 (44 to 219)
ALP: Median (IQR)	130 (79 to 187)	111 (83 to 199)
Gleason Score at diagnosis		
≤ 7	35	25
≥ 8	50	53
unknown	16	21

- **Updated dataset[1] with cut-off 31 MAR 2020**
- **Median follow-up of 13.3 months (IQR: 9.5 to 17.7) months**

[1]Updated compared to ASCO abstract first analysis cut-off 31 DEC 2019

Primary endpoint: PSA ≥ 50% response (PSA50-RR)



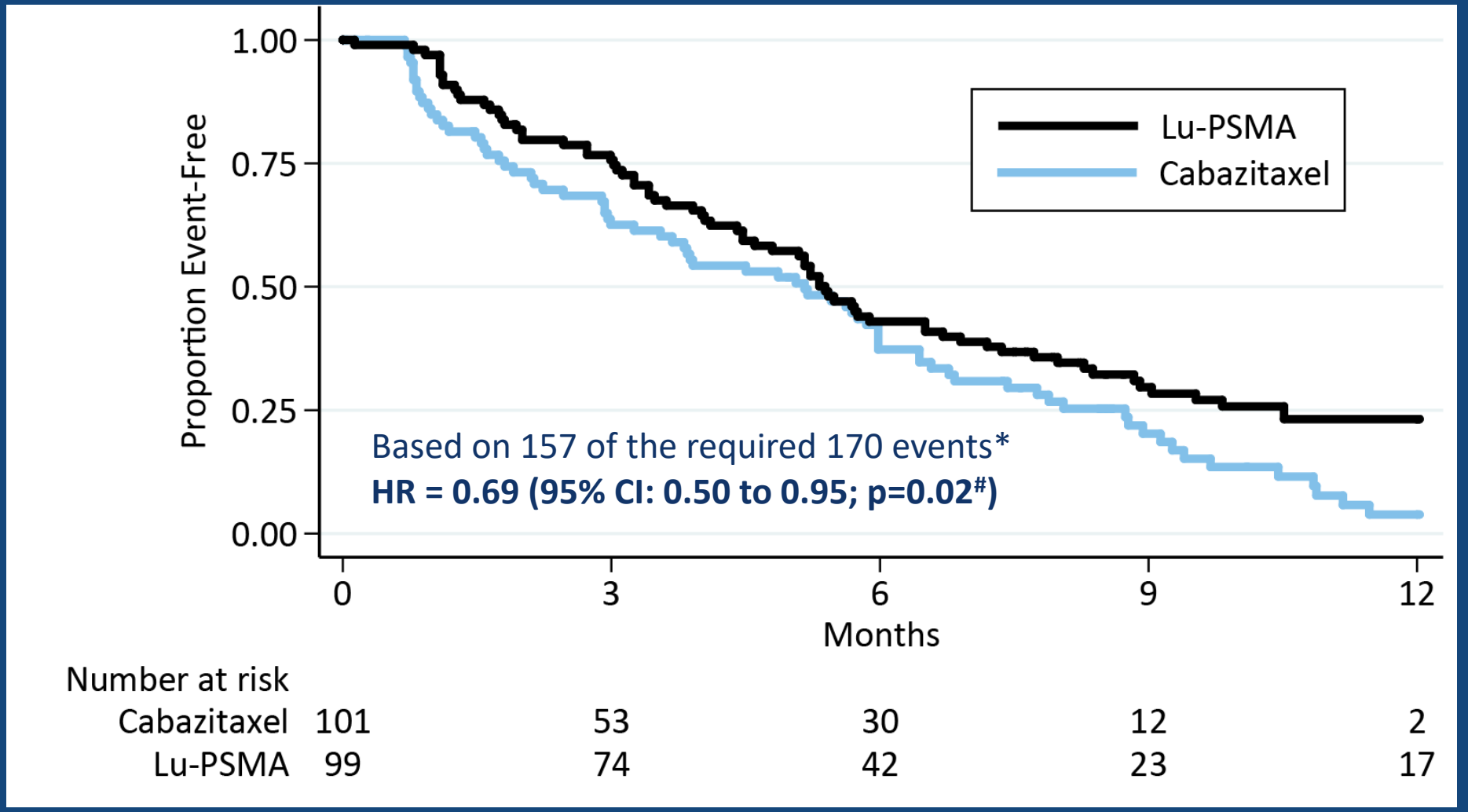
PSA50-RR **37%** (95%CI) (27-46%)

66% (56-75%)

Lu-PSMA: 29% absolute (95% CI 16%-42%; p<0.0001) greater PSA50-RR compared to cabazitaxel

For sensitivity analysis per-protocol, the difference was 23% (95% CI 9%-37%; p=0.0016)

Secondary endpoint: PSA PFS (preliminary)



* Primary analysis at 170 events (as per SAP)
# p<0.0027 is required to trigger rejection of null hypothesis prior to planned primary analysis at 170 events (as per SAP)
There have been 71 deaths in total.

Safety: Selected Adverse Events by Worst Grade

Term	Cabazitaxel (N=85)		Lu-PSMA (N=98)	
	G1-2	G3-4	G1-2	G3-4
	%	%	%	%
Neutropenia (+/- fever)	5	**13**	6	4
Thrombocytopaenia	4	0	**17**	**11**
Dry mouth	21	0	**59**	0
Diarrhea	**52**	**5**	18	1
Dry eye	4	0	**30**	0
Dysgeusia	**27**	0	12	0
Neuropathy (motor or sensory)	**26**	1	10	0
Fatigue	72	4	70	5
Nausea	34	0	39	1
Anaemia	12	8	18	8
Vomiting	12	2	12	1
TOTAL (all AEs)	**40**	**54**	**53**	**35**

Discontinuations for toxicity occurred in 1/98 (1%) Lu-PSMA vs. 3/85 (4%) Cabazitaxel-treated.
There were no Lu-PSMA related deaths; 5 G5 AEs for cabazitaxel and 11 G5 AEs for Lu-PSMA.

Strengths and Limitations

Strengths

- First randomised trial of Lu-PSMA
- Active and clinically relevant control arm
- Use of ^{18}F-FDG and ^{68}Ga-PSMA PET/CT to select patients
- Large difference in primary endpoint

Limitations

- Await further follow-up for results of other key secondary endpoints including:
  - Radiologic PFS (next planned analysis after 170 events)
  - Quality of Life
  - PFS / OS
- Not blinded
- Withdrawal before treatment
  - PSA50-RR intention to treat analysis
  - PSA50-RR per protocol analysis

	Lu-PSMA		Cabazitaxel
Withdrawal before treatment	1/99 (1%)	vs	16/101 (16%)
PSA50-RR intention to treat analysis	65/99 (66%)	vs	37/101 (37%), difference 29%, p < 0.0001
PSA50-RR per protocol analysis	65/98 (66%)	vs	37/ 85 (44%), difference 23%, p = 0.0016

Clinical interpretation

- Novel class of radiopharmaceutical with high activity and relatively low toxicity, consistent with results of prior single-center phase II data[1]
- May represent favourable treatment option compared to Cabazitaxel in a selected population with high PSMA-expression (72%)
- Improvement in overall survival not yet defined
  - Results of upcoming phase 3 VISION trial (NCT03511664) pending
- Warrants study in earlier phases of prostate cancer and/or in combination with other therapies

[1]Violet *J Nucl Med* 2019 ;Nov 15 epub

Conclusion

In men with progressive disease following docetaxel, Lu-PSMA was more active (higher PSA50-RR) than Cabazitaxel, with relatively fewer G3-4 AEs, and PSA-PFS favouring Lu-PSMA

Lu-PSMA represents a potential new class of effective therapy for men with metastatic castration-resistant prostate cancer

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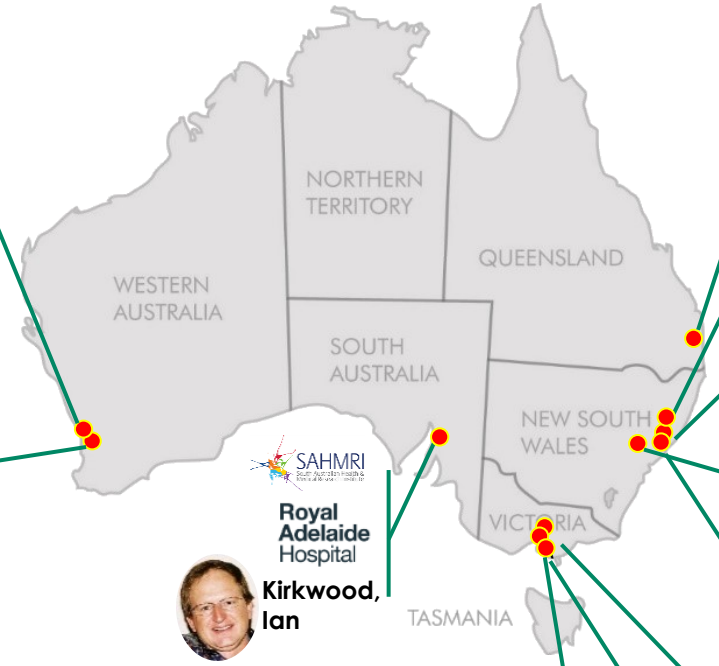
- Australasian Radiopharmaceutical Trials Network (ARTnet)

#TheraP Study Team



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