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)**

Michael Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony Joshua, Jeffrey Goh, David Pattison, Hsiang Tan, Ian Kirkwood, Siobhan Ng, Roslyn Francis, Craig Gedye, Natalie Rutherford, Alison Zhang, Margaret McJannett, Martin Stockler, John Violet, Scott Williams, Andrew Martin, Ian Davis

TheraP is a partnership between ANZUP Cancer Trials Group and the Prostate Cancer Foundation of Australia (PCFA) in collaboration with the NHMRC CTC and the Australasian Radiopharmaceutical Trials Network (ARTnet) with support from the Australian Nuclear Science and Technology Organisation (ANSTO) and Endocyte Inc., a Novartis company

Clinicaltrials.gov NCT03392428
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
  - Life prolonging therapies include docetaxel, abiraterone, enzalutamide, sipuleucel-T and 223Ra
  - Docetaxel-resistant mCRPC: cabazitaxel ↑OS compared to mitoxantrone and 2nd line novel anti-androgen

- 177Lu-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
  - Phase II study: PSA ≥ 50% in 64% of men with low toxicity

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)
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, hematologic and liver function
- ECOG performance status 0-2

68Ga-PSMA + 18F-FDG PET/CT
- PSMA SUVmax > 20 at any site
- Measurable sites SUVmax > 10
- No FDG positive/PSMA negative sites of disease
- Centrally reviewed

177Lu-PSMA-617
- 8.5 GBq IV q6 weekly
- 0.5 GBq each cycle
- Up to 6 cycles

CABAZITAXEL
- 20mg/m² IV q3 weekly, Up to 10 cycles

200 men 1:1 randomisation
11 sites in Australia
Stratified by:
- Disease burden (>20 sites vs ≤ 20 sites)
- Prior enzalutamide or abiraterone
- Study site

SPECT/CT @ 24 hours
suspend Rx if exceptional response; recommence upon progression

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.
CONSORT Diagram for Key Details in TheraP

N=291 Registered

N=91 Ineligible
  Low PSMA expression (n=29)
  FDG discordant disease (n=51)
  Other (n=11)

N=200 Randomised

N=99 Lu-PSMA
  N=98 Treated

N=101 cabazitaxel
  N=85 Treated
  N=16 Not Treated
    Met exclusion criterion (n=1)
    Withdrawal of consent (n=15)

N=1 Not Treated
  Died prior to treatment (n=1)

Intention-to-treat (ITT) analysis + sensitivity analysis for per-protocol analysis
Patient selection: PSMA and FDG PET/CT

<table>
<thead>
<tr>
<th>PSMA-</th>
<th>FDG+</th>
<th>PSMA+</th>
<th>FDG+ PSMA-</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>

- Ineligible (n=80, 28%)
- Eligible (n=200)

- n=29 (10%)
- n=51 (18%)
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
## Results: patient characteristics

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

- 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 $\geq 50\%$ response \((\text{PSA50-RR})\)

Lu-PSMA: \textbf{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)

Based on 157 of the required 170 events*

HR = 0.69 (95% CI: 0.50 to 0.95; p=0.02#)

There have been 71 deaths in total.

* 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

<table>
<thead>
<tr>
<th>Term</th>
<th>Cabazitaxel (N=85)</th>
<th>Lu-PSMA (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G1-2</td>
<td>G3-4</td>
</tr>
<tr>
<td>Neutropenia (+/- fever)</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Thrombocytopaenia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Dry eye</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy (motor or sensory)</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>72</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL (all AEs)</strong></td>
<td><strong>40</strong></td>
<td><strong>54</strong></td>
</tr>
</tbody>
</table>

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 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
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
Acknowledgements

We thank:
• Patients and support network
• Principal and co-investigators
• Study coordinators
• Nurses
• Radiopharmacists/chemists
• Nuclear medicine technologists
• Clinical research associates
• Data managers

Industry support:
• PSMA-617 supply and financial support: Endocyte Inc., a Novartis company
• Lutetium-177 no carrier added supplied from Australian Nuclear Science and Technology Organisation (ANSTO)

Funding:
• Prostate Cancer Foundation of Australia with thanks to community generosity of
  • Movember
  • It’s a Bloke Thing Foundation
  • Can4Cancer
• Cancer Australia (ANZUP infrastructure support)
• M Hofman: Peter MacCallum Foundation
• I Davis: NHMRC Practitioner Fellowship

Study designed and conducted by the ANZUP in collaboration with:
• NHMRC Clinical Trials Centre at the University of Sydney
• Australasian Radiopharmaceutical Trials Network (ARTnet)

All slides can be downloaded at:
www.anzup.org.au/therap

@ANZUP #TheraP