PSMA Targeted Therapies

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## Disclosures

<table>
<thead>
<tr>
<th>Disclosure Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support</td>
<td>Endocyte (a Novartis company)</td>
</tr>
<tr>
<td>Consulting</td>
<td>none</td>
</tr>
<tr>
<td>Honoraria/travel support</td>
<td>Janssen, Sanofi Genzyme, Ipsen</td>
</tr>
<tr>
<td>Stock ownership</td>
<td>None</td>
</tr>
<tr>
<td>Study Chair</td>
<td>TheraP</td>
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Prostate Specific Membrane Antigen (PSMA)
THERANOSTICS
TARGETED THERAPEUTIC + DIAGNOSTIC COMPANION

radioactive small molecule targeting prostate specific membrane antigen (PSMA) highly over-expressed in prostate cancer

177Lu-PSMA-617 SPECT

Post-therapy SPECT/CT

68Ga-PSMA-11 PET

Pre-therapy PET/CT
Lutetium-177 (\(^{177}\text{Lu}\)): short path-length beta emitter
mean path length 1mm, average penetration 0.3mm, 6.7 day half-life

targeted drug: “too smart”

nearby cells not expressing target
develop resistance

1mm path-length: cross-fire effect

all cells in 1mm radius targeted
2014: high activity of **small molecule** (not Ab) targeting PSMA


Serial $^{124}$I-MIP-1095 PET

Best PSA response in 25 pt PSA $\geq$ 50% in 61%

$^{131}$I-MIP-1095
2015: retrospective data suggests high activity of $^{177}$Lu

**Best PSA Response in 37 patients**

Baum R et al, 3rd World Congress in Theranostics, John Hopkins Medical Centre, USA, March 2015
2015: 1st published report of $^{177}$Lu-PSMA617

DOI 10.1007/s00259-014-2978-1
Theranostics @ Peter Mac

No of therapies per year

177Lu-PSMA
1st PSMA therapy in Australia

177Lu-DOTATATE

Gastro-entero-pancreatic Neuroendocrine Tumours
Prostate
2015-8: 1st prospective phase II study @ Peter Mac

[177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

Michael S Hofman*, John Violet*, Rodney J Hicks, Justin Ferdinandus, Sue Ping Thang, Tim Akhurst, Amir Iravani, Grace Kong, Aravind Ravi Kumar, Declan G Murphy, Peter Eu, Price Jackson, Mark Scalzo, Scott G Williams, Shahneen Sandhu

Remarkable responses in patients who progressed after conventional therapies
Peter Mac Phase II Baseline characteristics & schema

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median or N (%)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>71</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>131</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>189.8</td>
</tr>
<tr>
<td>PSA doubling time (ng/mL/month)</td>
<td>2.6</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>1</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>2</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Prior treatments</td>
<td></td>
</tr>
<tr>
<td>Abiraterone or enzalutamide or both</td>
<td>45 (90%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>42 (84%)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Docetaxel + abi / enza ± Cabazitaxel</td>
<td>39 (78%)</td>
</tr>
</tbody>
</table>

median follow-up: 31.4 months

75 pt screened for eligibility

50 enrolled

Up to 4 cycles $^{177}$Lu-PSMA

50 included in analysis

median follow-up: 31.4 months
Best PSA Response \( (N=50) \)

<table>
<thead>
<tr>
<th>PSA Response</th>
<th>N (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30%</td>
<td>37 (74%)</td>
<td>60 - 84</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>32 (64%)</td>
<td>50 - 77</td>
</tr>
<tr>
<td>≥ 80%</td>
<td>22 (44%)</td>
<td>30 - 59</td>
</tr>
</tbody>
</table>

Hofman MS et al, ASCO GU 2019.
## Treatment-emergent adverse events attributable to Lu-PSMA

<table>
<thead>
<tr>
<th>Condition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>29 (58%)</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>7 (14%)</td>
<td>13 (26%)</td>
<td>16 (32%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (22%)</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (30%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (40%)</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3 (6%)</td>
<td>6 (12%)</td>
<td>5 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (12%)</td>
<td>6 (12%)</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>5 (10%)</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (22%)</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>8 (16%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Renal injury*</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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</tbody>
</table>

*51Cr-EDTA GFR measured 3 months after completion of $^{177}$Lu-PSMA-617 in 28 pt demonstrated mean decline of -11.7 mL/min (95% CI -19 to -4)
Lu-PSMA re-treatment

75 pt screened for eligibility

Up to 4 cycles $^{177}$Lu-PSMA

50 included in analysis

15 (30%) received further LuPSMA

PSA ≥50% response: 73%

Hofman MS et al (unpublished)
69yo progressed after docetaxel, enzalutamide, abiraterone & cabazitaxel

Baseline

175 Gy after LuPSMA #1
* LuPSMA

PSA (μg/L)

months from Lu-PSMA
↑ QoL

![Diagram showing changes in Brief pain inventory and Pain Interference across cycles and 3 month FU, with mean difference from cycle 1 on the x-axis.](image-url)
How do our results compare to others?

**PSA ≥50% in 64%**
Hofman MS et al

**PSA ≥50% in 45%**
Rahbar K et al
46 pt had PSA follow-up less than 8 wk
PSA ≥50% in 64%
Hofman MS et al

PSA ≥50% in 45%
Rahbar K et al

PSA ≥50% in 32%
Heck et al
Is this patient suitable?

SUVmax 70

PSMA
FDG PET: see something different

PSMA 20 SUV

(B)

FDG 10 SUV
FDG+ PSMA- disease in liver (& bone)

Thang SP et al Eur Urology Oncology 2018
Disease heterogeneity: what does it mean?

Thang SP et al *Eur Urology Oncology* 2018
## PSMA/FDG phenotypes

<table>
<thead>
<tr>
<th>PSMA- FDG+</th>
<th>PSMA+ FDG+ discordant</th>
<th>PSMA+ FDG+ concordant</th>
<th>PSMA+ FDG-</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUVmax 7</td>
<td>15</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72</td>
<td>n/a</td>
</tr>
</tbody>
</table>

### Unsuitable

### Suitable

#APCCC2019
What happened to the patients we didn’t treat?

16 patients excluded
- low PSMA-expression (50%)
- discordant FDG+ disease (50%)

Median OS 2.5 months
(95% CI 1.7 – 5.0 months)

Thang SP et al Eur Urology Oncology 2018
Overall survival (n=50)

OS=13.3 months (95% CI 10.5 - 18.7)

Best PSA response

PSA≥50%: 18.4 months (95% CI 13.8 – 23.8)
PSA<50%: 8.7 months (95% CI 6.5 to 13.4)

Hofman MS et al ASCO GU 2019 (updated May 2019)
PSA $\geq 50\%$: significantly longer overall survival

PSA $\geq 50\%$: 18.4 months (95% CI 13.8 – 23.8)
PSA $< 50\%$: 8.7 months (95% CI 6.5 to 13.4)

Hofman MS et al ASCO GU 2019 (updated May 2019)
Prognostic markers with Lu-PSMA

FerdinandusJ, Hofman MS et al, (unpublished)
Theranostics: we can quantify radiation dose ("dosimetry")

Violet J … Hofman MS, JNM 2019
3 x qSPECT/CT

4hrs  24hrs  96hrs

CT-CT deformable image registration

voxelised kinetics

\[ C = A_1 \cdot e^{-k_1 \cdot t} + A_2 \cdot e^{-k_2 \cdot t} + A_3 \cdot e^{-k_3 \cdot t} \]
“Whole body” tumour dose correlates with PSA response @ 12 weeks

<10 Gy:
10 non-responders
1 responder
TheraP Trial: $^{177}$Lu-PSMA-617 vs. cabazitaxel

Metastatic castration-resistant prostate cancer post docetaxel suitable for cabazitaxel

**PSMA + FDG PET/CT**
- SUVmax > 20 at a site of disease
- Measurable sites SUVmax > 10
- No discordant FDG+ PSMA-disease
- Centrally reviewed

**$^{177}$Lu-PSMA-617**
- 8.5GBq ↓ 0.5GBq/cycle
- Up to 6 cycles

**cabazitaxel**
- 20mg/m2 IV q3 weekly
- Up to 10 cycles

**SPECT/CT @ 24 hours**
- Suspend Rx if exceptional response
- Recomence upon progression

**N = 200; 11 sites (Australia)**
1:1 randomisation stratified by:
- disease burden (>20 sites vs ≤ 20 sites)
- prior enzalutamide or abiraterone
- site

**Endpoints**
1. PSA response
2. OS
3. rPFS / PSA PFS
4. QoL
5. AEs
TheraP Trial: $^{177}$Lu-PSMA-617 vs. cabazitaxel

Metastatic castration-resistant prostate cancer post docetaxel suitable for cabazitaxel

- PSMA + FDG PET/CT
  - SUVmax > 20 at a site of disease
  - Measurable sites SUVmax > 10
  - No discordant FDG+PSMA-disease
  - Centrally reviewed

- $^{177}$Lu-PSMA-617
  - 8.5GBq ↓ 0.5GBq/cycle
  - Up to 6 cycles

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

Patients randomised

https://clinicaltrials.gov/ct2/show/NCT03392428
Australian Sponsor: ANZUP
Study Chair: Prof Michael Hofman
Co-ordinating Centre: NHMRC Clinical Trials Centre
Collaborative Group Chair: Prof Ian Davis
Funding: Prostate Cancer Foundation of Australia (PCFA), Endocyte, ANSTO, Movember
Senior Statistician: Dr Andrew Martin | CTC Clinical Lead: Prof Martin Stockler

1 more patient to recruit!
VISION Trial: $^{177}$Lu-PSMA versus best supportive care

**Progressive mCRPC**
- PSMA+
- Previous taxane therapy and previous novel androgen axis therapy

**Best supportive/best standard of care**

**Randomization**
- 2:1 randomization

**Primary Endpoint**
- Overall survival

**Key Secondary Endpoints**
- Radiographic progression-free survival (rPFS)
- RECIST response
- Time to first symptomatic skeletal event (SSE)

- 9 Countries (NA and EU)
- >750 patients recruited
- 12-14 months FU min 15 month

$^{177}$Lu-PSMA-617 (7.4GBq, 6 wkly X6) + Best supportive/best standard of care
PRINCE Trial

PSMA-lutetium Radionuclide therapy and ImmunoNotherapy in prostate Cancer

@UCSFImaging
NCT03805594
Dr Rahul Aggarwal
Dr Tom Hope

Metastatic CRPC
Progressed after enzalutamide, abiraterone or apalutamide

PSMA + FDG PET/CT

Pembroluzimab 200mg
3 weekly

177Lu-PSMA-617
6 weekly, 4 cycles
Day 4 ± 2 days
8.5 GBq, ▼0.5 GBq/cycle

clinicaltrials.gov: NCT03658447
PI: A/Prof Shahneen Sandhu
LuPARP Trial

Phase 1 trial of $^{177}$Lu-PSMA-617 therapy and Olaparib (PARPi)

- Metastatic CRPC
- Progressed after 2nd generation AR-targeted agent
- Post taxane chemotherapy

PSMA + FDG PET/CT

- $^{177}$Lu-PSMA-617
  - 6 weekly, 4 cycles
  - 7.4 GBq

- Olaparib
  - day 2-15
  - 3+3 dose escalation design
  - 50mg to 300mg bd
  - (6 levels of increment)

clinicaltrials.gov: NCT03874884
PI: A/Prof Shahneen Sandhu
#UpFrontPSMA: high-volume metastatic hormone naïve PC

**ARM A (n = 70)**
Upfront Lu-PSMA x 2-3 + ADT followed by Docetaxel x 6

**ARM B (n = 70)**
ADT + Docetaxel x 6

**De novo High-Volume mHNPC**
- ≥ 4 bone mets with ≥ 1 extra-axial AND/OR
- Visceral mets

**Primary endpoint: undetectable PSA at 12 months**

**Statistical assumptions**
- P1 0.5, P2 0.25
- 2-sided alpha=0.05, beta=0.8

PI: A/Prof Arun Azad
#LuTectomy: $^{177}$Lu-PSMA prior to surgery

High-risk localised prostate cancer ± N1

High PSMA Expression

$^{177}$Lu-PSMA x 1-2 cycles

At 6-8 weeks:
- Prostatectomy + pelvic LN dissection

Primary endpoints:
- Dosimetry

Key Secondary endpoints
- Safety
- PSMA PET Response

Correlative samples
- Tumour tissue
- PBMCs
- ctDNA, serum

GG9 post docet, abiraterone & cabazitaxel

45 Gy mean, 78 Gy max

Hofman et al [unpublished]
\[^{177}\text{Lu-PSMA}\] shows promise: can it be used earlier?
\(^{177}\)Lu-PSMA shows promise: can it be used earlier? +/- combined with other therapies?
Thank-you #GoNuclear

Molecular Imaging | Nuclear Medicine
- Rod Hicks (Director)
- Amir Iravani, Aravind Ravi Kumar, Grace Kong, Tim Akhurst, Ramin Alipour (Nuc Med “Dream Team”)
- A/Prof Louise Emmett (St Vs, Sydney)
- Peter Eu (Radiopharmacist)
- Mark Scalzo (Lead Technologist)
- Price Jackson (Medical Physicist)

Uro-oncology Multi-Disciplinary Team
- Scott Williams, John Violet, Shankar Siva (Rad Onc)
- Shahneen Sandhu, Arun Azad, Ben Tran (Med Onc)
- Declan Murphy, Nathan Lawrentschuk (Urology)
- Gail Risbringer (Laboratory Research)

Funding partners (alphabetical order)
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- Cancer Australia
- Endocyte / AAA (Novartis)
- Movember
- Peter MacCallum Foundation
- Prostate Cancer Foundation (PCF)
- Prostate Cancer Foundation of Australia (PCFA)
- Victorian Cancer Agency (VCA)

Collaborative partners
- ANZUP Prof Ian Davis | Margaret McJannett
- ARTnet A/Prof Ros Francis
- BaCT
- NHMRC CTC
- PropPSMA & TheraP investigators