IMMUNOTHERAPY AND OTHER NEW DRUG TARGETS

A/Prof. Arun Azad MBBS PhD FRACP
Medical Oncologist – Monash Health, Melbourne, Australia
Translational Researcher - Monash University, Melbourne, Australia
Chair - Translational Research Committee, ANZUP Clinical Trials Group
## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Company/Company Names</th>
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<tr>
<td>Research Support/P.I.</td>
<td>Astellas</td>
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<tr>
<td>Employee</td>
<td>N/A</td>
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<td>Consultant</td>
<td>Astellas, Janssen, Novartis</td>
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<td>Major Stockholder</td>
<td>N/A</td>
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<td>Speakers Bureau</td>
<td>Janssen</td>
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<td>Honoraria</td>
<td>Astellas, Janssen, Novartis, Tolmar, Amgen</td>
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<td>Scientific Advisory Board</td>
<td>Astellas, Novartis, Sanofi, Astra-Zeneca, Tolmar</td>
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Shifting Treatment Landscape for CRPC: Positive Phase 3 Trials

- Mitoxantrone
- Zoledronic Acid
- Docetaxel
- Abiraterone acetate
- Cabazitaxel
- Enzalutamide
- Sipuleucel-T
- Denosumab
- Radium-223

Symptom benefit
Skeletal Related Event (SRE) benefit
Overall survival benefit ± symptom/SRE benefit
1999
Median survival from time of first mitoxantrone chemotherapy = 12.3 months

2012
Median survival from time of first docetaxel chemotherapy = 32.6 months

Kantoff, JCO, 1999; Chi, J Clin Oncol 30, 2012 (suppl 5; abstr 15)
But……

- Metastatic CRPC remains incurable

- Most men with metastatic CRPC will die from their disease

- Existing drugs work well in many cases but adaptive resistance is essentially inevitable

- So, we urgently need new drugs to emerge into the clinic
Emerging drug targets in CRPC

- PARP
- PI3K/Akt
- AR (non-ligand binding domain)
- Prostate-specific membrane antigen (PSMA)
- Immune checkpoints
PARP inhibitors
Synthetic lethality

- Single Strand Break → PARP
- Single Strand Break → PARP → Double Strand Break → HR
- Single Strand Break → PARP → Double Strand Break
  - HR → Death
  - BRCA Deficiency
BRCA -/- cells are exquisitely sensitive to PARP inhibition

Farmer et al, Nature 2005

Bryant et al, Nature 2005
DNA repair defects in metastatic CRPC

22.7% DNA repair defects (34/150)

12.7% BRCA2 altered (19/150) including 5.3% germline (8/150)

Robinson et al, Cell 2015
TOPARP trial

Mateo et al, NEJM 2015

11 evaluable pts
-RR 33%
16/49 pts had DNA repair defect
-RR 88%
TOPARP trial

Mateo et al, NEJM 2015
Targeting PARP in mCRPC: ongoing/upcoming trials

- PROfound trial opening Q12017
  - Phase III olaparib

- Multiple single-agent Ph II studies open/near opening
  - Medivation, Janssen, Clovus

- Combination studies with PARPi + AR-targeted agents
PI3K/Akt
PI3K-AKT signalling cascade

Controls key cellular processes including growth, survival, proliferation & angiogenesis
PI3K-AKT signalling cascade

PI3K pathway alterations in 73/150 (49%)

Reciprocal regulation between AR & PI3K
Strong pre-clinical rationale for co-targeting

Robinson et al, Cell 2015
Toren et al, Eur Urol 2015
Background

A.MARTIN Phase II trial design

- This Phase II study evaluated the Akt inhibitor ipatasertib in combination with the anti-androgen abiraterone in patients with mCRPC.

- Patients were stratified accordingly:
  - Enzalutamide (yes or no)
  - Number of chemotherapy regimens (1 vs > 1)
  - Progression (PSA only vs other)

- Co-primary efficacy endpoints were rPFS in the all-comer population and in patients whose tumors had PTEN loss.

- Secondary endpoints included safety, OS, time to PSA progression and PSA response rate.

R 1:1:1
Double blind

- Metastatic or advanced prostate adenocarcinoma
- Previous docetaxel-based therapy
- Progressed during ≥1 hormonal therapy
- ECOG PS 0-1
  N = 253

Abiraterone
PO QD
+ Ipatasertib
400 mg QD

Abiraterone
PO QD
+ Ipatasertib
200 mg QD

Abiraterone
PO QD
+ Placebo
QD

NCT01485961.
ECOG PS, Eastern Cooperative Oncology Group performance score; mCRPC, metastatic castration-resistant prostate carcinoma; OS, overall survival; PO, by mouth; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog; QD, daily; rPFS, radiographic progression-free survival.

* Abiraterone 1000 mg with prednisone/prednisolone 5 mg twice daily.

* Further randomized 1:1 ratio to ipatasertib 400 mg QD/placebo and 200 mg QD/placebo arms.
Results

Radiographic progression-free survival\textsuperscript{a}

- A total of 173 rPFS events (68\% event rate) had occurred at the time of data cutoff for the primary analysis
- rPFS was prolonged in the ipatasertib 400 mg + abiraterone arm compared with the placebo + abiraterone arm relative to the ipatasertib 200 mg + abiraterone arm

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Abi, abiraterone; Ipat, ipatasertib; HR, hazard ratio.
\textsuperscript{a}rPFS event is determined by RECIST PD of soft tissue, or bone scan PD, or death within 30 days of last dose.
\textsuperscript{b}Stratified HR.

Data cutoff date, September 1, 2015.
PTEN loss: a key predictive biomarker

COPRIMARY ENDPOINT: RPFS WITH IPATASERTIB OR PLACEBO + ABIRATERONE BY ICR IHC

<table>
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<tr>
<th>Treatment</th>
<th>PTEN loss</th>
<th>PTEN non-loss</th>
</tr>
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<tbody>
<tr>
<td>Ipat 400 mg + Abi</td>
<td>HR, p 0.39 (0.22-0.70)</td>
<td>HR, p 0.84 (0.51-1.37)</td>
</tr>
<tr>
<td>Median 11.5 mo</td>
<td>Pbo + Abi Median 4.8 mo</td>
<td></td>
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<tr>
<td>Ipat 200 mg + Abi</td>
<td>HR, p 0.46 (0.25-0.83)</td>
<td>HR, p 1.13 (0.69-1.85)</td>
</tr>
<tr>
<td>Median 11.1 mo</td>
<td>Pbo + Abi Median 4.6 mo</td>
<td></td>
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* Unstratified HR, 95% CI

ce Bonet et al, Ipatasertib, ESMO 2016
Targeting PI3K/Akt in mCRPC: ongoing/upcoming trials

- Ph III study Abiraterone +/- Ipatasertib in PTEN loss mCRPC
- Ph II study Enzalutamide +/- AZD5363
- Ph I study Enzalutamide + GSK2636771
AR (non-ligand binding domain)
EPI-001: N-terminal domain inhibitor

EPI-001: N-terminal domain inhibitor

EPI-001 identified by screening a library of marine sponge extracts

RJ Andersen...M Sadar, Cancer Cell 17:535, 2010
EPI-001: Targeting ARV+ PCa

A phase 1/2, open-label study of safety and antitumor activity of EPI-506, a novel androgen receptor (AR) N-terminal domain (NTD) inhibitor, in men with metastatic castration-resistant prostate cancer (mCRPC) with progression after enzalutamide and/or abiraterone

Robert R. Montgomery, Emmanuel S. Antonarakis, Maha Husein, Karim Fizazi, Anthony M. Joshua, Gerhardt Altieri, Marianne Sarder, Frank Pecorin, Kim N. Chi

University of Washington Oncology, Seattle, WA, USA; b The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; c University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; d Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Sud, Villejuif, France; e Princess Margaret Cancer Centre, Toronto, Ontario, Canada; f The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; g Genome Sciences Centre, British Columbia Cancer Agency, Vancouver, British Columbia, Canada; h ISCGA Pharmaceuticals, Houston, TX, USA; i British Columbia Cancer Agency, Vancouver, British Columbia, Canada.

EPI-001 efficacious against CRPC with FL-AR and ARVs

Myung et al, JCI 2013
Prostate-specific membrane antigen
PSMA

- Type 2 transmembrane protein over-expressed on prostate adenocarcinoma cells
  - PSMA PET widely adopted in Australia as superior sensitivity to CT + WBBS

- Also can be expressed on:
  - Tumour neovasculature (including colon, breast and renal cancer and subtypes of bladder cancer)
  - Any new blood vessels
  - Astrocytes

Maurer et al, Nat Rev Urol 2016
Lu-PSMA: A new theranostic?

Lu-PSMA: A new theranostic?

Immune checkpoints
Immunotherapy: The new frontier?
Targeting CTLA-4 in CRPC

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

Kwon et al, Lancet Oncol 2014

Overall survival
Progression-free survival
Targeting PD-1 in CRPC

0/17 (0%) RR in mCRPC patients
PDL1 expression increases on resistance to enzalutamide

Pembrolizumab = PD1-i

200mg iv q3wk x4 doses

Hansen et al
- Ph 1b pembro
- CRPC cohort (n=23)
- RR 13%, SD 39%

No prior chemotherapy

Med time on Enza 52wk

Prior response on Enza: 23 pts

<table>
<thead>
<tr>
<th>Responder</th>
<th>Cycle 1</th>
<th>PSA (ng/ml) every 3-weeks and nadir</th>
<th>Best Radiologic Response</th>
<th>MSI</th>
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<tbody>
<tr>
<td>1</td>
<td>April 2015</td>
<td>70.65 → 11.11 → 1.18 → 0.11 → 0.08</td>
<td>PR</td>
<td>present</td>
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<tr>
<td>2</td>
<td>October 2015</td>
<td>46.09 → 41.22 → 12.99 → 9.89 → 0.02</td>
<td>n/a</td>
<td>n/a</td>
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<td>3</td>
<td>January 2016</td>
<td>2502.75 → 1.26 → 0.07 → 0.01 → &lt;0.01</td>
<td>PR</td>
<td>absent</td>
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<tr>
<td>4</td>
<td>March 2016</td>
<td>82.43 → 17.34 → 0.3 → 0.01</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>5</td>
<td>June 2016</td>
<td>250 → 88.89 → 5.1 → 0.43 → 0.18*</td>
<td>PR</td>
<td>pending</td>
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PSA response:
- 5 of 27 (19%) patients had a confirmed PSA response
- 4 of 19 (21%) patients had stable disease > 6 months (range 34-64 weeks)
I/O in mCRPC: Ongoing/upcoming trials

- Keynote-199: Pembro
- Keynote-265: Pembro + multiple combination arms
- Multiple Ph I/II I/O studies with a mCRPC cohort

Abi or Enza resistant mCRPC (n=25)
Avelumab (PD-L1) + SABR (up to 3 mets)
Primary endpoint: rPFS at 6 months

Phase II IIS opening early 2017 (Arun Azad, study chair)
Summary

- Rapid explosion in systemic therapies for prostate cancer
- Most men with advanced disease still die from their cancer
- Improving outcomes requires new drugs/targets
  - PARP
  - PI3K/Akt
  - AR non-LBD
  - PSMA (theranostic)
  - I/O
THANK YOU