NEW DRUG TARGETS

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### Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Companies</th>
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<tbody>
<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>Astellas, Janssen, Novartis, Amgen</td>
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<td>Honoraria</td>
<td>Astellas, Janssen, Novartis, Tolmar, Amgen, Pfizer</td>
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<td>Scientific Advisory Board</td>
<td>Astellas, Novartis, Sanofi, Astra-Zeneca, Tolmar, Pfizer</td>
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Shifting Treatment Landscape for CRPC: Positive Phase 3 Trials


- Mitoxantrone
- Zoledronic Acid
- Docetaxel
- Enzalutamide
- Abiraterone acetate
- Cabazitaxel
- 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
- 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

49 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
  - Phase III olaparib

- Multiple single-agent Ph II studies open
  - Pfizer, Janssen, Clovus

- Combination studies with PARPi +
  - AR-targeted agents
  - I/O (PD-1 or PD-L1)
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%)

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

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

NCT01485861.

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 PO QD\(^a\)

\(+\) Ipatasertib

400 mg QD

Abiraterone PO QD\(^a\)

\(+\) Ipatasertib

200 mg QD

Abiraterone PO QD\(^a\)

\(+\) Placebo

QD\(^b\)

R 1:1:1

Double blind

N = 253

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PRESENTED AT: ASCO ANNUAL MEETING '16

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Results

Radiographic progression-free survival\(^a\)

- 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

Abi, abiraterone; Ipat, ipatasertib; HR, hazard ratio.

\(^a\) rPFS event is determined by RECIST PD of soft tissue, or bone scan PD, or death within 30 days of last dose.

\(^b\) 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>
<thead>
<tr>
<th>Treatment</th>
<th>PTEN loss HR (95% CI)</th>
<th>PTEN non-loss HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipat 400 mg + Abi</td>
<td>0.39 (0.22-0.70)</td>
<td>0.84 (0.51-1.37)</td>
</tr>
<tr>
<td>Pbo + Abi</td>
<td>Median 11.5 mo</td>
<td>Median 7.5 mo</td>
</tr>
<tr>
<td>Ipat 200 mg + Abi</td>
<td>0.46 (0.25-0.83)</td>
<td>1.13 (0.69-1.85)</td>
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<tr>
<td>Pbo + Abi</td>
<td>Median 11.1 mo</td>
<td>Median 4.6 mo</td>
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</table>

* Unstratified HR; 99% CI.

d e Bono et al, Ipatasertib, ESMO 2016
Targeting PI3K/Akt in mCRPC: ongoing/upcoming trials

- Ph III study Abiraterone +/- Ipatasertib (IPATential)
- Ph II study Enzalutamide +/- AZD5363 (AKTi)
- Ph I study Enzalutamide + GSK2636771 (PI3Kβi)
Prostate-specific membrane antigen
- 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?

Lu-PSMA theranostics phase II trial

- Single-centre, phase II study of 30 patients with PSMA-avid mCRPC
- 4 cycles of Lu-PSMA
- Heavily pre-treated: 83% prior abi and/or enza, 87% prior chemo
- Primary endpoint: PSA response rate (PSA RR)
- PSA RR 57%
- Improvements in pain, QoL
- Gr3 haem AEs 17% (reversible)

Hofman et al, ESMO 2017 (Abstract 785O)
Targeting PSMA in mCRPC: ongoing/upcoming trials

- TheraP trial
  - Ph II Lu-PSMA vs. Cabazitaxel in post-docetaxel mCRPC
  - Opening late 2017 at 6 centres in Australia
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

Overall survival

Progression-free survival

Kwon et al, Lancet Oncol 2014
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

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)

<table>
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<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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<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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<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>
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<td>82.43 → 17.34 → 0.3 → 0.01</td>
<td>n/a</td>
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<td>5</td>
<td>June 2016</td>
<td>250 → 88.69 → 5.1 → 0.43 → 0.18*</td>
<td>PR</td>
<td>pending</td>
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I/O in mCRPC: Ongoing/upcoming trials

- Keynote-199: Pembro
- Keynote-265: Pembro + multiple combination arms
- CA209-9KD: Nivo + multiple combination arms

Abi or Enza resistant mCRPC (n=25)

Avelumab (PD-L1) + SABR (up to 3 mets)

Primary endpoint: rPFS at 6 months

Phase II IIS opened Nov 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
  - PSMA (theranostic)
  - I/O
THANK YOU