Germline mutations: The evolving role of cancer genetics in advanced prostate cancer

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## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tr>
<td>Research Support/P.I.</td>
<td>Astellas</td>
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<td>Employee</td>
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<td>Consultant</td>
<td>Astellas, Janssen, Novartis</td>
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<td>Major Stockholder</td>
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<td>Speakers Bureau</td>
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<td>Scientific Advisory Board</td>
<td>Astellas, Novartis, Sanofi, Astra-Zeneca,</td>
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<td>Tolmar, Pfizer, Janssen</td>
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Overview
Germline mutations in advanced prostate cancer

- Genes involved
- Frequency of mutations
- Testing for mutations
- Therapeutic implications
Heritability of prostate cancer (PCa)

Family history is strong risk factor

- Nordic twin study\(^1\)
  - 57% heritability for PCa
  - Only melanoma had higher heritability (58%)

- BUT…..identifying specific genes that contribute to this risk has proven challenging
  - Genetic linkage studies in multi-case PCa families over 2 decades revealed few candidates e.g. \textit{HOXB13} G84E mutation present in 3.1% of familial PCa\(^2\)

\(^1\)Mucci et al. JAMA. 2016 Jan 5;315(1):68-76
\(^2\)Ewing et al. JAMA. 2016 Jan 5;315(1):68-76
Heritability of prostate cancer (PCa)
DNA repair gene mutations

- Evolution of next-generation sequencing has allowed germline DNA repair gene mutations to be linked to PCa

<table>
<thead>
<tr>
<th>Single strand DNA repair pathways</th>
<th>Double strand DNA repair pathways</th>
</tr>
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<tbody>
<tr>
<td>Mismatch repair (MMR)</td>
<td>Homologous recombination (HR)</td>
</tr>
<tr>
<td>Base excision repair</td>
<td>Non-homologous end joining (NHEJ)</td>
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<tr>
<td>Nucleotide excision repair</td>
<td></td>
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DNA damage response (DDR)

Common to malignant and non-malignant cells

- Genome under constant stress
  - Endogenous e.g. replication stress
  - Exogenous e.g. toxins, radiation

- DDR enables cells – that would otherwise succumb to genotoxic stress – to repair damage and survive

- DDR can become aberrant and act as a key pro-survival mechanism for malignant cells
  - Accumulation of aggressive, genomically damaged tumour cells (“The angry tumour”)
Germline DNA repair gene mutations
Higher risk of developing PCa

<table>
<thead>
<tr>
<th>Mutated gene</th>
<th>Increased risk of PCa</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>Up to 8.6 fold</td>
<td>Br J Cancer. 2011;105(8):1230-4</td>
</tr>
<tr>
<td>BRCA1</td>
<td>3.75 fold</td>
<td>Br J Cancer. 2012;106(10):1697</td>
</tr>
<tr>
<td>ATM</td>
<td>2.2 fold</td>
<td>Nat Genet. 2015;47(8):906</td>
</tr>
<tr>
<td>CHEK2</td>
<td>1.6 fold</td>
<td>J Clin Oncol. 2016;34(11):1208</td>
</tr>
<tr>
<td>NBN</td>
<td>3.9 fold</td>
<td>Cancer Res. 2004;64(4):1215</td>
</tr>
<tr>
<td></td>
<td>0.4% of metastatic PCa</td>
<td></td>
</tr>
<tr>
<td>MMR/Lynch</td>
<td>4.9 fold</td>
<td>Genet Med. 2014;16(7):553</td>
</tr>
</tbody>
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Germline DNA repair gene mutations

More aggressive PCa (vs. non-carriers)

- **BRCA2**
  - Younger onset, higher T stage, higher Gleason, more LN involvement, shorter PCa-specific survival and OS$^{1,2}$

- **BRCA2** or **BRCA1** or **ATM**:  
  - 4-fold higher risk lethal PCa, shorter OS$^3$

- **BRCA1**:  
  - Higher recurrence rates, shorter PCa-specific survival$^4$

$^1$J Natl Cancer Inst. 2007;99(12):929  
$^2$J Clin Oncol. 2013;31(14):1748  
$^3$Eur Urol. 2017;71(5):740  
$^4$Clin Cancer Res. 2010;16(7):2115
Germline DNA repair gene mutations

Frequency: Localised PCa

- *BRCA2* or *BRCA1* or *ATM* (n = 799)
  - 6% in lethal PCa vs. 1.4% in indolent PCa\(^1\)

- “Non-indolent” PCa (n = 477)
  - 9.9%\(^2\)

- TCGA cohort (n=499)
  - 4.6%

- Exome Aggregation Cohort (n=53000)
  - 2.7%

\(^1\)Eur Urol. 2017;71(5):740
\(^2\)Nature. 2017;541(7637):359-364
Germline DNA repair gene mutations

Frequency: Advanced PCa

• Pritchard et al (n = 692)\textsuperscript{1}
  • \textbf{11.8\%: BRCA2 (5.3\%), ATM (1.6\%), CHEK2 (1.9\%), BRCA1 (0.9\%), RAD51D (0.4\%), PALB2 (0.4\%)}

• Robinson et al (n = 150)\textsuperscript{2}
  • \textbf{8\%: BRCA2 (5.3\%)}

\textsuperscript{1}N Engl J Med. 2016;375(5):443-53
\textsuperscript{2}Cell. 2015;161(5):1215-1228
Germline DNA repair gene mutations

Testing recommendations

- Known familial cancer mutation predisposing to PCa
- Family history suggestive of hereditary PCa syndrome, hereditary breast and ovarian cancer syndrome, or Lynch syndrome
- Identification of somatic mutation in hereditary cancer risk genes
- High-risk sub-groups e.g. African-Americans
Germline DNA repair gene mutations

Testing recommendations: broadening the target population?

• Do we test high-risk localised + metastatic patients?
  • “Germline genetic testing and genetic counseling should be considered in all men with high risk, very high risk, regional, or metastatic prostate cancer.” (NCCN guidelines)

• Do we test all metastatic patients?
  • 20% always, 62% sometimes, 18% never (St Gallen meeting)

• Do we test all metastatic CRPC patients?
  • “Agreement was moderate to test all men with metastatic castration-resistant PCa, regardless of family history” (Philadelphia meeting)

Therapeutic implications
Germline DNA repair gene mutations & SOC agents

• Poor responses to Abiraterone or Enzalutamide\(^1\)
  • N = 319 mCRPC, 22 germline DNA repair genes sequenced
  • Median time to PSA progression 3.3 months

• Shorter cancer-specific survival (CSS) for 1\(^{st}\) line taxanes in mCRPC patients with germline BRCA2 mutations\(^2\)
  • N = 419, 3 DNA repair genes sequenced
  • Median CSS 24.5 vs. 12.8 months for no germline mutation vs. gBRCA2

\(^1\)Eur Urol. 2017;72(1):34-42
\(^2\)Annals of Oncology (2017) 28 (suppl_5): v605-v64
Therapeutic implications
Germline DNA repair gene mutations & SOC agents

• **No difference in PFS and RR to Abiraterone or Enzalutamide**\(^1\)
  - N = 390 mCRPC, 20 germline DNA repair genes sequenced
  - Median PFS 8.3 vs. 8.3 months & 46% vs. 56% for mutation+ vs. mutation-

• **Improved outcomes with Abiraterone or Enzalutamide in BRCA/ATM but not non-BRCA/ATM germline mutations**\(^2\)
  - N = 172, 50 germline DNA repair genes sequenced

• **Improved PFS with Abiraterone if germline DNA repair gene mutation**\(^3\)
  - Median PFS 16.6 vs. 8.2 months (germline vs. wild type) in Phase II trial of Abiraterone +/- Veliparib

\(^1\)Eur Urol. 2018;73(5):687-693
\(^2\)Eur Urol. 2018;74(2):218-225
\(^3\)J Clin Oncol. 2018;36(10):991-999
Therapeutic implications
Synthetic lethality: exploiting germline mutations
Therapeutic implications

Synthetic lethality: exploiting germline mutations

22.7% DNA repair defects (34/150)

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

Robinson et al, Cell 2015
Therapeutic implications

Synthetic lethality: exploiting germline mutations

Mateo et al, NEJM 2015

49 evaluable pts
-RR 33%

16/49 pts had DNA repair defect
-RR 88%
# Single Agent Trials In Progress

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinicaltrials.gov ID: Trial name</th>
<th>Phase; Study size</th>
<th>Setting; Comparator (if applicable)</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>NCT01682772 II N=89 (adaptive design)</td>
<td>mCRPC, post 1-2 taxane chemotherapy(ies)</td>
<td>RR</td>
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<tr>
<td>Niraparib</td>
<td>NCT028054436 Galahad II N=160</td>
<td>mCRPC, post 1+ chemotherapy and 1+ AR-targeting agent(s)</td>
<td>ORR</td>
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<tr>
<td>Rucaparib</td>
<td>NCT02952534 TRITON2 II N=160</td>
<td>mCRPC, post 1+ chemotherapy and 1-2 AR-targeting agent(s)</td>
<td>ORR + PSA response</td>
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<tr>
<td>Talazoparib</td>
<td>NCT03148795 II N=100</td>
<td>mCRPC, post 1-2 chemotherapy and 1+ AR-targeting agent(s)</td>
<td>ORR</td>
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<tr>
<td>Olaparib</td>
<td>NCT03263650 II Randomized N=96</td>
<td>mCRPC with aggressive features; maintenance after 6 cycles cabazitaxel + carboplatin Olaparib vs. observation</td>
<td>PFS</td>
<td></td>
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<tr>
<td>Olaparib</td>
<td>NCT03047135 II N=50</td>
<td>Biochemical recurrence post-RP; PSA doubling ≤6 months</td>
<td>PSA response</td>
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<tr>
<td>Rucaparib</td>
<td>NCT03413795 TRIUMPH II N=30</td>
<td>mFSPC, not on ADT</td>
<td>PSA response</td>
<td></td>
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<tr>
<td>Olaparib</td>
<td>NCT02987543 PROfound III N=340</td>
<td>mCRPC, post 1+ AR-targeting agent(s) vs. Investigator choice (abiraterone / enzalutamide)</td>
<td>rPFS</td>
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<tr>
<td>Rucaparib</td>
<td>NCT02975934 TRITON3 III N=400</td>
<td>mCRPC, chemotherapy-naïve vs. Investigator choice (abiraterone / enzalutamide / docetaxel)</td>
<td>rPFS</td>
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Presented By Carmel Pezaro at 2018 ASCO Annual Meeting
Combination Abiraterone +/- Veliparib (NCI 9012)

Randomised Phase II trial; biomarker stratified
Preclinical data supports synergy for AR targeting + PARP inhibition, especially in presence of an ETS fusion-positive tumor

No difference in response rate or PFS, irrespective of ETS status or treatment arm (despite DDR mutation):

Presented By Carmel Pezaro at 2018 ASCO Annual Meeting
### Combination Trials In Progress

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<tr>
<th>Drug</th>
<th>Clinicaltrials.gov ID; Trial name</th>
<th>Phase; Study size</th>
<th>Setting; Comparator (if applicable)</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib</td>
<td>NCT01376172</td>
<td>II Randomized N=114</td>
<td>mCRPC, prior chemotherapy allowed Randomized, abiraterone +/- veliparib</td>
<td>PSA response</td>
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<tr>
<td>Olaparib</td>
<td>NCT01972217</td>
<td>II Randomized N=159</td>
<td>mCRPC, post docetaxel Randomized, abiraterone +/- olaparib</td>
<td>rPFS</td>
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<tr>
<td>Olaparib</td>
<td>NCT02893917</td>
<td>II Randomized N=90</td>
<td>mCRPC, post 1+ therapy for CRPC Randomized, olaparib +/- cediranib</td>
<td>rPFS</td>
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<tr>
<td>Olaparib</td>
<td>NCT03317392</td>
<td>II Randomized N=112</td>
<td>mCRPC with bone metastases Randomized: Ra-223 +/- olaparib</td>
<td>(Phase II) rPFS</td>
</tr>
<tr>
<td>Olaparib</td>
<td>NCT03012321</td>
<td>II Randomized N=70</td>
<td>mCRPC, post docetaxel Randomized to abiraterone / olaparib / combination</td>
<td>PFS</td>
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<tr>
<td>Rucaparib</td>
<td>NCT03338790 CheckMate 9K</td>
<td>II Randomized N=300</td>
<td>mCRPC, prior chemotherapy allowed Randomized to nivolumab + one of: rucaparib / docetaxel / enzalutamide</td>
<td>ORR + PSA response</td>
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<tr>
<td>Talazoparib</td>
<td>NCT0395197 TALAPRO-3</td>
<td>III N=444</td>
<td>mCRPC, chemotherapy-naïve Randomized to AR-targeting agent +/- talazoparib</td>
<td>rPFS</td>
</tr>
</tbody>
</table>

**PLUS:**

Other DDR targets being tested in Phase I-II trials:
Chk1/2 (Prexasertib), DNA-PK (LY-3023414), WEE1, ATR, ATM, MTH1...
Germline DNA repair gene mutations

Take home messages in prostate cancer

- Not uncommon
  - Approx. 5% localised vs. 10% metastatic PCa

- Testing strategies unclear
  - All patients: not feasible, resource-hungry
  - Sub-groups: Family Hx, African-American, high-risk localised?, metastatic CRPC?

- Associated with more aggressive cancer
  - Worse outcomes in localised disease
Germline DNA repair gene mutations

Take home messages in prostate cancer

• **Not necessarily associated with worse outcomes on standard-of-care agents for mCRPC**
  • Mixed results from studies
  • Assay/context dependent?

• **Therapeutically exploitable**
  • Some dramatic responses seen with single-agent PARP inhibitors
  • Immune checkpoint blockade for MMR/Lynch

• **But….PARP inhibitors may have activity in combination with AR-targeted therapy in unselected patients**
  • PARP has broader biological functions than just DNA repair
THANK YOU