Joint ESUP-ESP Working Group Uropathology

Molecular alterations for a molecular tumor board for prostate cancer patients

European Congress of Pathology, Nice, Sept. 11, 2019

Sven Perner, MD, PhD, FRCPath

Professor and Chairman
Pathology of the
University Hospital Schleswig-Holstein, Campus Luebeck
and the
Research Center Borstel, Leibniz Lung Center

Wissen schafft Gesundheit
Molecular subtypes of prostate cancer

Alteration in clinically relevant pathways:

- 74% of cases harbored:
  - Gen fusion (**ERG, ETV1/4, FLI1**): not actionable
  - Mutation (**SPOP, FOXA1, IDH1**): only IDH1 inhibitor for cholangiocellular Ca but not approved for PCa
Molecular subtypes of prostate cancer
Alterations in clinically relevant pathways

Potentially actionable mutation in 25% of cases in PIK3CA/MAPK signaling pathway

Almost 20% mutation in DNA damage repair genes

Mutations in DNA damage repair genes

- Alteration in DDR genes highly common in advanced PCa
- **BRCA1**, **BRCA2** and **ATM** alterations in 11% of primary PCa (TCGA cohort)
- **BRCA2**, **BRCA1** and **ATM**, **CHEK2** alterations in 19% of metastatic PCa (SU2C cohort). Approximately half of these alterations are germline.

![Distribution of presumed pathogenic germline mutations in 692 men with metastatic PCa](image)
DNA damage repair deficiency in prostate cancer

**DNA DAMAGE**

**Double-strand break**
- Double-strand break repair
  - Homologous recombination
  - Non-homologous end joining

**Single-strand break**
- Base excision repair

**Base mismatch, insertions, deletions**
- Mismatch repair
  - MLH1, MSH2, MSH6, PMS2

**Bulky adducts**
- Nucleotide excision repair
  - ERCC1, ERCC2, ERCC4

**Base alkylation**
- Direct Reversal
  - MGMT

**DNA REPAIR PATHWAY**

**SELECTED KEY GENES**

- BRCA2, BRCA1, ATM, PALB2, CHEK2, RAD51
- PARP1, XRCC1, LIGASE3
- MLH1, MSH2, MSH6, PMS2
- ERCC1, ERCC2, ERCC4
- KU70/80, DNA-PK

**TREATMENT IMPLICATIONS**

- PARP inhibitors
  - Platinum chemotherapy

- Pembrolizumab, other checkpoint inhibitors

**BRCAness testing by NGS**
- (ATM, PALB2, CHEK2, RAD51 in validation)

20% of aggressive primary PCa and CRPC

Testing by IHC or molecular pathology

5-10% of aggressive primary tumors and CRPC

Cheng, Urol Oncol, 2018
# Potential role of PARP inhibitors in prostate cancer

## Examples of trials in prog with PARP inhibition in prostate cancer

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Drug</th>
<th>Phase</th>
<th>NCT #</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talazoparib + enzalutamide vs. enzalutamide</td>
<td>Talazoparib +/- Enzalutamide</td>
<td>3</td>
<td>NCT03395197</td>
<td>Metastatic Castrate Resistant</td>
</tr>
<tr>
<td>Monotherapy in mCRPC with deoxyribonucleic acid (DNA) damage repair deficiencies (DDR) (TALAPRO-2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Javelin PARP Medley: Avelumab Plus Talazoparib</td>
<td>Talazoparib + Avelumab</td>
<td>2</td>
<td>NCT03330405</td>
<td>Metastatic Castrate Resistant</td>
</tr>
<tr>
<td>In Locally Advanced Or Metastatic Solid Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I/II Study of the anti-programmed death ligand-1 antibody MEDI4736 in combination with olaparib and/or cediranib for advanced solid tumors and advanced or recurrent ovarian, triple negative breast, lung, prostate and colorectal cancers</td>
<td>Durvalumab + Olaparib and/or Cediranib</td>
<td>1/2</td>
<td>NCT02484404</td>
<td>Metastatic Castrate Resistant</td>
</tr>
<tr>
<td>trial of rucaparib in patients with metastatic hormone-sensitive prostate cancer harboring germline DNA repair gene mutations (TRIUMPH)</td>
<td>Rucaparib</td>
<td>2</td>
<td>NCT03413995</td>
<td>Metastatic Castrate Sensitive</td>
</tr>
<tr>
<td>Olaparib before surgery in treating participants with localized prostate cancer</td>
<td>Olaparib</td>
<td>2</td>
<td>NCT03570476</td>
<td>Localized Disease Pre-Surgery</td>
</tr>
<tr>
<td>Studying the effects of olaparib (± degarelix) given to men with intermediate/high risk prostate cancer before radical prostatectomy</td>
<td>Olaparib +/- Degarelix</td>
<td>1</td>
<td>NCT02324998</td>
<td>Localized Disease Pre-Surgery</td>
</tr>
<tr>
<td>Olaparib in men with high-risk biochemically-recurrent prostate cancer following radical prostatectomy, with integrated biomarker analysis</td>
<td>Olaparib</td>
<td>2</td>
<td>NCT03047135</td>
<td>Biochemically Recurrent</td>
</tr>
</tbody>
</table>

Yentz S.E. et al. Renal and Urology News 2018
### Potential role of PARP inhibitors in prostate cancer

Examples of trials in prog with PARP inhibition in metastatic prostate cancer

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Drug</th>
<th>Phase</th>
<th>NCT #</th>
<th>Primary endpoint</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR Deficient mCRPC (deleterious mt in BRCA1/2 or ATM or other HR genes)</td>
<td>Rucaprib</td>
<td>2</td>
<td>TRITON2 NCT02952534</td>
<td>Resistant objective response rate (ORR) and PSA response</td>
<td>Metastatic Castrate</td>
</tr>
<tr>
<td>mCRPC, HR deficient (BRCA1/2 or ATM) Rucaparib vs Investigator choice (Doc, Abi, Enz)</td>
<td>Rucaparib</td>
<td>3</td>
<td>TRITON3 NCT02975934</td>
<td>Resistant Radiographic progression-free survival (rPFS)</td>
<td>Metastatic Castrate</td>
</tr>
<tr>
<td>mCRPC (taxaned and AR pre-treated) (Biomarker positive for HR deficient)</td>
<td>Neraparib</td>
<td>2</td>
<td>NCT02854436</td>
<td>Resistant; response rate</td>
<td>Metastatic Castrate</td>
</tr>
</tbody>
</table>

PARP inhibitors in combination with standard of care treatment for CRPC
**BRCA diagnostic procedure**

1. Sample
2. DNA
3. NGS sequencing
4. Exon deletion / duplication
5. Bioinformatics
6. Result
7. Therapy plan

- No mutation
- Pathogenic mutation
- Unclassified variant
BRCA diagnostic procedure

Panel design

requirement:
• 48 coding exones BRCA1and 2 with 18078 base pairs
• 100% sequence coverage necessary

BRCA Oncomine
total bases attempted: 18514
Amplicon size: 170-190
Amplicon number: 203
Cumulative bp: 35708
Interpretation of sequence variants

BRCA diagnostic procedure

BRCA Mutation Database
Through collaborations with the University of Utah Huntsman Cancer Institute (HCl), and with the WHO International Agency for Research on Cancer (IARC), the University of Utah Department of Pathology and ARUP Laboratories is pleased to host the BRCA mutation database.

The purpose of this database is to provide information on BRCA1 and BRCA2 gene mutations and their impact on risk of developing breast cancer, ovarian cancer and certain other cancers.

Two types of databases are provided. One is a list of mutations curated from critical review of literature and family studies. The other provides in silico prediction of risk to help understand variants of unknown significance. Watch Dr. Towbog introductory talk. [15 min video]

BRCA1 and BRCA2 are curated separately. The two databases mentioned above are available for both genes. Go to the landing pages for each gene with the buttons below.

Breast Cancer Information Core
An Open Access On-Line Breast Cancer Mutation Data Base
An International Collaborative Effort hosted by NHGRI

LOVD - Leiden Open Variation Database
BReast CANcer 1 - literature unclassified variants (BRCA1)
Curators: Maaike Vreeswijk and Peter de Vries

LOVD Gene homepage
There is an increasing evidence that patients with MSI high/MMR deficient advanced prostate carcinoma could benefit from PD1/PDL therapy.
MSI high/MMR deficient

BRCAness testing by NGS (ATM, PALB2, CHEK2, RAD51 in validation)

Testing by IHC or molecular pathology

PARP inhibitors, Platinum chemotherapy
MSI high/MMR deficient PCa

• only 3% of prostate carcinoma cases show this phenotype
• of those patients a small part would respond to the therapy

However:

Opportunity for possible applications in predictive examination e.g. a large sequencing panel including TMB calculation and extrapolation of MSI status and molecular and immunohistochemical control of MMR status
Mutations in DNA damage repair mechanism: some treatment results

- Mateo et al. (TOPARP-B), 2019: response to the PARP inhibitor was greatest among people carrying \textit{BRCA1/2} or \textit{PALB2} mutations.
- Castro et al. JCO, 2017: DDR germline mutation is associated with poorer outcomes on treatment with abiraterone or enzulatamide.
- Antonarakis et al. EUR UROL, 2018: patients with DDR mutation are sensitive to prembulizomab.
- Hussain et al. JCO, 2018: patients with DDR mutation had a longer PFS after treatment with abiraterone+veliparib.
Status quo in therapy regimen

• All patients with metastatic prostate cancer should be offered somatic genomic testing of tumor tissue for HRD and MMR defects.
Testing of tumor tissue for:

- **BRCA1/2** somatic mutations ✓
- **BRCAness** Panel (in progress), containing **ATM, FANC, CDK12, RAD51B, RAD51C, PALB2, ATR, CHEK1, CHEK2,** and **ETS** gene fusions (**TMPRSS2:ERG**)
- Tumor mutation burden (in progress)
in mCRPC, biallelic loss of CDK12 that is mutually exclusive with tumors driven by DDR deficiency

CDK12 mutant cases are associated with elevated neoantigen

CDK12 inactivation mCRPC may benefit from immune checkpoint immunotherapy
**Gene expression of AURKA and N-Myc in benign prostate tissue, PCA, and NEPC**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Aurora A IHC</th>
<th>AURKA Amplification</th>
<th>MYCN Amplification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PCA</td>
<td>117</td>
<td>12%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>NEPC</td>
<td>29</td>
<td>76%</td>
<td>38%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Representative example of positive Aurora kinase A > Aurora kinase A inhibitor (Phase II clinical trial) overexpression by IHC, and MYCN and AURKA amplification by FISH in human NEPC.

*Beltran et al., Cancer Discov. 2011*
AR-variants

- Amplifications, mutation and splicing variants AR variants (AR-V7) are frequent and relevant in castration resistant PC
- AR amplifications are predictive for response to Abiraterone and Enzulatamide

Dan Robinson, Eli Van Allen, Bob Lonigro et al., Cell 2015
AR-variants

AR-V7 predicts therapy resistance against abiraterone and enzalutamide

Scher et al. *JAMA Oncol.* 2016
Status quo

- AR amplification and AR-V7 expression are prognostic in CRPC

- AR-V7 may be predictive, however no testing decision are being made based on AR-V7 expression

- Tissue based AR alteration assessment is not part of the clinical routine / has no clear utility
Thank you!

Questions?