Educational 6: Translational Oncology

“DNA repair in Prostate Cancer: from genetics to targeted therapies”

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CNIO-IBIMA Genito-Urinary Cancer Unit
Disclosures

- **Participation in advisory boards:** Janssen, Astellas, Bayer, Sanofi, Astra-Zeneca, Genetech, Veridex

- **Research Funding:** Janssen, Bayer and Astra-Zeneca
Summary

• DNA repair and genomic instability as a Hallmark of Cancer

• Germline mutations in Prostate Cancer

• Somatic mutations

• Molecular characteristics

• Standard treatment implications

• Novel treatment approaches
Summary

- DNA repair and genomic instability as a Hallmark of Cancer
  *Our approach to study DNA repair impact in Prostate Cancer*

- Germline mutations in Prostate Cancer:

- Somatic mutations

- Molecular characteristics

- Standard treatment implications

- Novel treatment approaches
DNA repair pathways

Hallmarks of cancer
“The emerging role of DNA repair deficiency”
DNA repair deleterious mutations
Prevalence in Prostate Cancer

• Excluding age, family history is considered the strongest risk factor to develop prostate cancer¹

• Until recently:
  • GWAS have identified multiple low-modest RR loci of PCa, which, taken together, explain approximately 30% of the familial PCa risk¹
  • Rarer genetic variants conferring higher PCa was associated to a small percentage of PCa:
    • Germline BRCA2 mutations were associated with higher risk of PCa (RR 8.6 in men ≤65 years)² - 1.5% all PCa
    • BRCA1 also increases the risk of PCa, but its effect was more modest (RR 4.5 in men ≤65 years)³ - 0.44% all PCa
    • CHEK2, NBN, Lynch Syndrome MMR genes, HOXB13

• NGS studies (since 2013) suggest that up to 23% of mCRPC harbour germline and/or somatic DNA repair genes aberrations

Clinical studies

2008-2012 – over 2000 patients
Restrospectively collected outcomes
All commers (mostly localised)
All Europe (Mostly UK based)
Published 2013
Clinical studies

PROREPAIR-A since 2013
N=32
Known mutation carriers
Retrospective
Tumour characterization

PROREPAIR-B

PROREPAIR-C

The UK Genetic Prostate Cancer Study
EMBRACE Study

kConFab

Prostate Cancer Group. CNIO & IBIMA
Clinical studies

PROREPAIR-A
N=32
Known mutation carriers
Retrospective
Tumour characterization

PROREPAIR-B

PROREPAIR-C

Australian series
Collaboration since 2014
N=45
Clinical studies

PROREPAIR-A

PROREPAIR-B SINCE 2013
Not Known carriers, Sporadic mCRPC
Prospective: germline and somatic
CSS & Response to treatments

PROREPAIR-C
Clinical studies

PROREPAIR-A

PROREPAIR-B

PROREPAIR-C SINCE 2013

Sporadic localized PrCa: RT or RP
Retrospective, bPFS, CSS
Germline and somatic, N=700
Summary

- DNA repair and genomic instability as a Hallmark of Cancer

- **Germline mutations in Prostate Cancer:**
  - Somatic mutations
  - Molecular characteristics
  - Standard treatment implications
  - Novel treatment approaches
**Prevalence of germline DNA repair mutations in the NGS era**

**mCRPC**
Anglo-American SU2C-PCF consortium
NEJM 2016
692 mCRPC
12%

**Early PrCa**
TCGA Prostate Cell 2015
333 primary PCa
5%

**General Population**
EXAC database
53000 unselected individual genomes
3%

*TCGA. Cell 2015; Pritchard et al. NEJM 2016*
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.

<table>
<thead>
<tr>
<th>Case Series</th>
<th>Description</th>
<th>Patients</th>
<th>Patients with Mutations</th>
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<tbody>
<tr>
<td>1</td>
<td>Stand Up To Cancer–Prostate Cancer Foundation discovery series</td>
<td>150</td>
<td>15 (10.0)</td>
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<td>2</td>
<td>Stand Up To Cancer–Prostate Cancer Foundation validation series</td>
<td>84</td>
<td>9 (10.7)</td>
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<tr>
<td>3</td>
<td>Royal Marsden Hospital</td>
<td>131</td>
<td>16 (12.2)</td>
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<tr>
<td>4</td>
<td>University of Washington</td>
<td>91</td>
<td>8 (8.8)</td>
</tr>
<tr>
<td>5</td>
<td>Weill Cornell Medical College</td>
<td>69</td>
<td>7 (10.1)</td>
</tr>
<tr>
<td>6</td>
<td>University of Michigan</td>
<td>43</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>7</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>124</td>
<td>23 (18.5)</td>
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<tr>
<td>Total</td>
<td></td>
<td>692</td>
<td>82 (11.8)</td>
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mCRPC germline DNA repair mutations

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</tr>
<tr>
<td>ATR</td>
</tr>
<tr>
<td>BAP1</td>
</tr>
<tr>
<td>BARD1</td>
</tr>
<tr>
<td>BRCA1</td>
</tr>
<tr>
<td>BRCA2</td>
</tr>
<tr>
<td>BRIP1</td>
</tr>
<tr>
<td>CHEK2</td>
</tr>
<tr>
<td>FAM175A</td>
</tr>
<tr>
<td>GEN1</td>
</tr>
<tr>
<td>MLH1</td>
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<tr>
<td>MRE11A</td>
</tr>
<tr>
<td>MSH2</td>
</tr>
<tr>
<td>MSH6</td>
</tr>
<tr>
<td>NBN</td>
</tr>
<tr>
<td>PALB2</td>
</tr>
<tr>
<td>PMS2</td>
</tr>
<tr>
<td>RAD51C</td>
</tr>
<tr>
<td>RAD51D</td>
</tr>
<tr>
<td>XRCC2</td>
</tr>
</tbody>
</table>

Pritchard et al. NEJM 2016
mCRPC & prevalence of germline DNA repair mutations

Spanish Prospective study in mCRPC

492 a priori eligible pts

1 sample belonged to an XX individual
1 poor QC after repeat seq
6 poor QC DNA
4 Hormonosensitive Pca after CRF review
3 Never treated pts after CRF review
8 duplicates (same pt in diferent PROCURE studies)
48 ineligible (no 1st line and >6 months since CRPC)

419 confirmed eligible patients

<table>
<thead>
<tr>
<th>Gene</th>
<th>N=692</th>
<th>%</th>
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<td>ATM</td>
<td>11</td>
<td>1.59</td>
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<tr>
<td>ATR</td>
<td>2</td>
<td>0.29</td>
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<tr>
<td>BAP1</td>
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<td>0</td>
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<tr>
<td>BARD1</td>
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<td>0</td>
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<td>BRCA1</td>
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<tr>
<td>FAM175A</td>
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<tr>
<td>GEN1</td>
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<tr>
<td>MLH1</td>
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<td>0</td>
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<td>MRE11A</td>
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<td>MSH6</td>
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<tr>
<td>NBN</td>
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<td>PALB2</td>
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<tr>
<td>PMS2</td>
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<td>0.29</td>
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<tr>
<td>RAD51C</td>
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<td>RAD51D</td>
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<tr>
<td>XRCC2</td>
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</table>

Pritchard et al. NEJM 2016; Castro & Olmos (PROCURE studies network) Unpublished
**mCRPC & prevalence of germline DNA repair mutations**

**Spanish Prospective study in mCRPC**

- 12% vs x
- Different population may have different backgrounds:

**Anglo-American study:**
- 50% and 24% of the **BRCA1** and **BRCA2** mutations were founder Ashkenazi mutations
- 55% of **CHEK2** were the Eastern European founder mutation c.1100delC
Prevalence of BRCA mutations in different ovarian cancer populations

- **Australia**: 14% overall, 17% serous
- **Florida (USA)**: 14-16% overall
- **Canada**: 12-13% overall, 33-36% serous
- **Sweden**: 8% overall, 8% serous
- **Norway**: 23% overall
- **Denmark**: 6% overall, 5% serous
- **Greece**: 10% overall, 60% serous (BRCA1)
- **Nederlands**: 6% overall, 11% serous
- **Israel**: 26% overall, 32% serous
- **Sweden**: 8% overall, 8% serous
- **Brazil**: 12-13% overall, 33-36% serous
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Summary

• DNA repair and genomic instability as a Hallmark of Cancer

• Germline mutations in Prostate Cancer:
  • Somatic mutations
  • Molecular characteristics
  • Standard treatment implications
  • Novel treatment approaches
Somatic aberrations in DNA repair genes

150 mCRPC
23% mutations in DNA repair genes
8% germline mutations

• 228/936 (24%) unique samples had at least one mutation in a DNA repair gene

• The highest rates of DNA repair mutations were found in visceral metastases including brain, pelvis and liver, which were significantly higher that either prostate tissue (20%) and bone sites (19%) (p<0.01)

• The most commonly mutated genes in the DNA repair pathways were: BRCA2 (11.4%), ATM (5.8%), MSH6 (2.5%), MSH2 (2.1%), ATR (1.6%), MLH1 (1.3%) and BRCA1 (1.2%)

Figure 1: Frequencies of DNA repair mutations by tissue type
Summary

- DNA repair and genomic instability as a Hallmark of Cancer

- Germline mutations in Prostate Cancer:
  - Somatic mutations

- Molecular characteristics

- Standard treatment implications

- Novel treatment approaches
gBRCA2 mutant PCa molecular studies

High CNV burden  Structural rearrangements  c-Myc Amplification

High methylation

BRCA2 LOH
Rb1

74% Primary Prostate Cancer had at least one identifiable driving event

26% miscellaneous:
- High-burden CNV
- DNA hypermethylation
- *TP53* mutant
- *Myc* Amplification
**Somatic BRCA2 aberrations in PCa**

- Localised prostate cancer → Bone-, CT- and Choline-PET-scans M0
- Radical Prostatectomy plus PLND (pT2N0) Gleason 4+4
- M1 progression within 12 m, CRPC within 18 m since Dx

- NGS and FISH mapping of the whole tumour → early somatic bi-allelic loss
Summary

• DNA repair and genomic instability as a Hallmark of Cancer

• Germline mutations in Prostate Cancer:
  • Clinical impact
  • Somatic mutations
  • Molecular characteristics
  • Standard treatment implications
  • Novel treatment approaches
Different genes may have different impact

Mixing tigers and cats?
Germline BRCA1 and BRCA2 mutations are associated with aggressive presentation

- $gBRCA$ mutations are associated with:
  - Gleason $\geq 8$
  - Nodal involvement
  - Metastasis

- No association with:
  - PSA levels
  - Age at diagnosis

### BRCA Mutation Carriers

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Total (n = 79)</th>
<th>BRCA1 (n = 18)</th>
<th>BRCA2 (n = 61)</th>
<th>Noncarriers (n = 1,940)</th>
<th>P (carriers vs noncarriers)</th>
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<tr>
<td>Age, years</td>
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<td>60.8</td>
<td>57.5</td>
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<tr>
<td>Range</td>
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<td>48.3-72.5</td>
<td>41.7-88</td>
<td>32.3-88.9</td>
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<td>Histologic grade/Gleason score</td>
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<td>Gleason 6/grade 1</td>
<td>20</td>
<td>6</td>
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<td>Tumor stage, T</td>
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<tr>
<td>T1, not clinically apparent</td>
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<td>1</td>
<td>7</td>
<td>439</td>
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<td>T2, confined to prostate</td>
<td>25</td>
<td>6</td>
<td>19</td>
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<td>T3, palpable, beyond capsule</td>
<td>22</td>
<td>4</td>
<td>18</td>
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<td>T4, fixed or invading locally</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>71</td>
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<tr>
<td>Tx, cannot be assessed</td>
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<td>Nodal stage, N</td>
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<td></td>
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<tr>
<td>N0, no nodal metastasis</td>
<td>42</td>
<td>8</td>
<td>34</td>
<td>366</td>
<td>&lt;.001</td>
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<td>MO, no distant metastasis</td>
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<td>Median</td>
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<td>Range</td>
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<td>0.7-3,000</td>
<td>0.5-761</td>
<td>0.2-7,800</td>
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**IMPACT**

Targeted Prostate Cancer Screening

**EMBRACE Study**

Castro et al. J Clin Oncol 2013
Other germline mutations associated to N1-M1

Frequent germline deleterious mutations in DNA repair genes in familial prostate cancer cases are associated with advanced disease.

- PALB2 1 7.14%
- ATM 2 14.29%
- BRCA1 1 7.14%
- CHEK2 2 14.29%
- BRCA2 4 28.57%
- PMS2 1 7.14%
- MUTYH 1 7.14%
- BRIP1 2 14.29%

<table>
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<tr>
<th>Gleason score</th>
<th>Carriers n=14</th>
<th>Non-carriers n=140</th>
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<tr>
<td>Gleason ≤ 6</td>
<td>5</td>
<td>35.71 62</td>
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<td>21.43 15</td>
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<td>28.57 36</td>
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<td>21.43 38</td>
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<td>4</td>
<td>28.57 45</td>
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<td>T3</td>
<td>2</td>
<td>14.29 24</td>
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<td>T4</td>
<td>1</td>
<td>7.14 2</td>
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<td>TX</td>
<td>4</td>
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<td>NX</td>
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<td>21.43 5</td>
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<td>MX</td>
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<td>28.57 61</td>
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<th>AJCC prognostic groups</th>
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<td>21.43 68</td>
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<td>IV</td>
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<td>35.71 7</td>
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<tr>
<td>Unknown</td>
<td>6</td>
<td>42.86 75</td>
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Leongarmonlert et al, BJC, 2012
*gBRCA2* mutations are an independent prognostic factor for MFS and CSS.
Effect of other germline DNA repair mutations in outcomes

An inherited NBN mutation is associated with poor prognosis prostate cancer

NBS1 (NBN) 657del5

CHEK2 1100delC, IVS2+1G, del5395, I157T

5y-CSS 49% vs 72% p=0.008

5y-CSS 71% vs 72% p=0.95
Summary

• DNA repair and genomic instability as a Hallmark of Cancer

• Germline mutations in Prostate Cancer:
  • Somatic mutations
  • Molecular characteristics

• **Standard treatment implications**

• Novel treatment approaches
Outcomes in localised Pca treated with EBRT or Surgery

Metastasis Free Survival

Cause-Specific Survival

Castro et al. Eur Urol 2015
Restrospective: 2 cohorts of sporadic PrCa patients
- Contemporary simultaneous (2005-2012)
- Intermediate- and high-risk localised prostate cancer

**BRCARAD** (CNIO-HURYC-IBIMA): RT cohort
- **N=360** (2x2 design, alpha of 0.05 and a power of 90%, OR 2.5)
- **Primary aim:** 5-years bPFS of homo-/heterozygous BRCA2 loss
- Other germline and somatic DNA repair genes aberrations
- CSS, MFS, response to systemic treatments

**BRCAPROS** (CNIO-FIVO-IBIMA): RP cohort
- **N=340** (2x2 design, alpha of 0.05 and a power of 90%, OR 1.8)
- **Primary aim:** 5-years bPFS of homo-/heterozygous BRCA2 loss
- Other germline and somatic DNA repair genes aberrations
- CSS, MFS, response to systemic treatments

Prostate Cancer Group. CNIO & IBIMA
319 mCRPC screened for germline mutations
7.5% mutation carriers in BRCA2, BRCA1, ATM, PALB2
(8.2% Pritchard et al, NEJM, 2016)

Retrospective clinical data from 22 carriers and 112 non-carriers

Shorter response to AR therapies, U. Michigan suggests the opposite
Same response to docetaxel
Primary aim: impact of BRCA1, BRCA2, ATM, PALB2 germline mutations on CSS from mCRPC

Sample size: 408 Pts (171 deaths)
- Mutations prevalence of 5%
- Estimated median CSS 30 months
- HR Carriers/Non-carriers 3.33
- alpha of 0.05 and a power of 0.80

Enrollment
- January 2013 to April 2016
  431 pts (40 months) but only 419 eligible

Follow-up
- 176 deaths by May 1st, 2017
Summary

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• Germline mutations in Prostate Cancer:
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  • Molecular characteristics
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• Novel treatment approaches
DNA repair defects in PCa
Treatment opportunities

Platinum-based chemotherapy

Deficient HR-FA pathway:
- PARPi
- DNA-Pki

Deficient DNA damage response
- ATRi
- CHEK1/2i

Deficient MMR
- Hypermutator phenotype
- Novel neoantigens
- Inmune-Chekpoints inhibitors
DNA repair defects and platine-based chemotherapy

21 Germline and/or somatic BRCA2, PALB2, ATM

Kumar, Nat Medicine, 2016

Cheng, Eur Urol, 2016
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

DNA repair defects

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<thead>
<tr>
<th>DNA repair defects</th>
<th>Responder</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (N=33)</td>
<td>Yes (N=16)</td>
<td>Total (N=49)</td>
</tr>
<tr>
<td>Biomarker Negative</td>
<td>31</td>
<td>33 (67.3%)</td>
</tr>
<tr>
<td>Biomarker Positive</td>
<td>2</td>
<td>16 (32.7%)</td>
</tr>
</tbody>
</table>

Fishers' exact p-value: p<0.001

Sensitivity: 87.5%
Specificity: 93.9%

OR (95% CI), p value*: 108.5 (13.84, 850.5), p<0.001

Legend:
- Frameshift mutation
- Single copy deletion
- Missense mutation
- Germline event
- Stop gain
- Homozygous deletion
- Copy-neutral loss of heterozygosity
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

**Figure:**

**A. Radiologic Progression-free Survival**
- Biomarker-positive, median: 9.8 mo
- Biomarker-negative, median: 2.7 mo

**B. Overall Survival**
- Biomarker-positive, median: 13.8 mo
- Biomarker-negative, median: 7.5 mo

*P < 0.001 by log-rank test* and *P = 0.05 by log-rank test*.

*Mateo et al, NEJM, 2015*
Responses to PARPi

- Somatic bi-allelic BRCA2 loss and response to Veliparib

PARPi trials in patients with HR defects

- **Olaparib**
  - Phase III post-abi and/or post-enza

- **Nediraparib**
  - Phase II single-arm post-abi/-enza & post-docetaxel

- **Talazoparib**
  - Phase II single-arm post-abi/post-enza

- **Rucaparib**
  - Phase II single-arm post-abi/-enza & post-docetaxel
  - Phase III post-abi or post-enza

Source: ClinicalTrials.gov
Take home messages

• DNA repair defects are a common event in prostate cancer

• BRCA2, BRCA1 and possible ATM germline mutations are associated to shorter survival

• The impact of somatic mutations in outcomes remains unknown

• Retrospective evidence suggest that Germline mutation carriers have poor responses to AR targeting agents, with responses to taxanes similar to that of non-carriers

• Somatic and germline mutations are associated with response to PARP inhibitors and platinum-based chemotherapy

• The role of inmunotherapy is being analyzed in clinical trials
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