Advances in Non-Hormonal Therapy for Advanced Prostate Cancer

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Depts. of Medicine and Urology
Medical Director, Tulane Cancer Center
Tulane Medical School
New Orleans, LA
Prostate Cancer Clinical States

**Hormone-Sensitive**

- Diagnoses: 240,000

  - Localized Disease
    - Local Therapy or no therapy
  - Rising PSA
    - Salvage Rx, ADT or no therapy
  - Rising PSA:
    - Castrate
    - No standard of care

**Castration resistant prostate cancer**

- Deaths: 29,000

  - Radiographic Metastases:
    - Castrate
    - Pre-chemo
    - Sipuleucel-T
    - Abiraterone
    - Enzalutamide
    - Radium-223
  - Radiographic Metastases:
    - Castrate
    - 1st-Line
    - Chemo
    - Docetaxel
  - Radiographic Metastases:
    - Castrate
    - Post-chemo
    - Cabazitaxel
    - Abiraterone
    - Enzalutamide
    - Radium-223

The first focus
Charles B. Huggins: Nobel Prize 1966

For discoveries related to the treatment of prostate cancer in 1941
Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.
CHAARTED Treatment for Metastatic Hormone Sensitive Prostate Cancer

STRATIFICATION

- Extent of Mets: High vs Low
- Other variables

Randomize

ADT +
Docetaxel at 75mg/m2 q 21 days for 6 cycles

Overall Survival

ADT (androgen deprivation therapy alone)

- ADT allowed up to 120 days prior to randomization
- Standard dexamethasone premed but no daily prednisone
E3805 Definition of High Volume

• High volume:
  – visceral metastases
  and/or
  – 4 or more bone metastases with at least 1 beyond pelvis and vertebral column

• At inception, only patients with high volume disease were to be accrued
CHAARTED Primary endpoint: Overall survival

HR=0.61 (0.47-0.80) p=0.0003
Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months

13.6 months at median
CHAARTED: Survival by extent of metastatic disease

B Patients with High-Volume Disease

Hazard ratio for death with ADT+docetaxel, 0.60 (95% CI, 0.45–0.81) P<0.001

ADT+docetaxel (median overall survival, 49.2 mo)

17 months better at median

C Patients with Low-Volume Disease

ADT alone (median overall survival, 32.2 mo)

Median OS not reached
## Hematologic Toxicity (%)

<table>
<thead>
<tr>
<th>Grade</th>
<th>ADT + Docetaxel (N=397)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4</td>
</tr>
<tr>
<td>Infection with neutropenia</td>
<td>1</td>
</tr>
<tr>
<td>Worst grade heme and non-heme toxicity per patient</td>
<td>16%</td>
</tr>
</tbody>
</table>

8% Grade 3-4 neutropenia with fever or infection
CHAARTED Conclusion

• High volume metastases, but not low volume, benefit from the addition of docetaxel to conventional ADT for metastatic disease

• Low volume patients may benefit but event rates are inconclusive at this time
Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

Nicholas James
University of Warwick and Queen Elizabeth Hospital Birmingham

on behalf of

Matthew Sydes, Malcolm Mason, Noel Clarke, David Dearnaley, Melissa Spears, Robin Millman, Chris Parker, Alastair Ritchie, J. Martin Russell, John Staffurth, Robert Jones, Shaun Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison Birtle, Joe O'Sullivan, Richard Cathomas, Mahesh Parmar and the STAMPEDE Investigators
The Amazing STAMPEDE Trial: How do they do that?
<table>
<thead>
<tr>
<th>%</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>WHO PS 2</td>
</tr>
<tr>
<td>21%</td>
<td>WHO PS 1</td>
</tr>
<tr>
<td>65yr</td>
<td>Median age</td>
</tr>
<tr>
<td></td>
<td>(min 40, max 84)</td>
</tr>
<tr>
<td>61%</td>
<td>Metastatic</td>
</tr>
<tr>
<td></td>
<td>(85% Bony mets)</td>
</tr>
<tr>
<td>15%</td>
<td>N+M0</td>
</tr>
<tr>
<td>24%</td>
<td>NOM0</td>
</tr>
</tbody>
</table>
Accrual

Comparison
Open:  Oct-2005
Closed:  Mar-2013
Accrual:  2962

Number of patients
1184  A  Standard-of-care (SOC)
593   B  SOC + zoledronic acid
592   C  SOC + docetaxel
593   E  SOC + zoledronic acid + docetaxel
### Treatment effect by metastatic status: FFS

#### Pre-planned analysis

<table>
<thead>
<tr>
<th>Mets status</th>
<th>FFS events</th>
<th>No. pts</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>255</td>
<td>686</td>
<td>0.98 (0.75, 1.28)</td>
</tr>
<tr>
<td>M1</td>
<td>866</td>
<td>1091</td>
<td>0.90 (0.78, 1.04)</td>
</tr>
<tr>
<td>Overall</td>
<td>1121</td>
<td>1777</td>
<td>0.93 (0.82, 1.05)</td>
</tr>
</tbody>
</table>

**Failure-free survival**

#### +ZA

<table>
<thead>
<tr>
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<th>No. pts</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>229</td>
<td>689</td>
<td>0.57 (0.42, 0.76)</td>
</tr>
<tr>
<td>M1</td>
<td>832</td>
<td>1087</td>
<td>0.62 (0.54, 0.73)</td>
</tr>
<tr>
<td>Overall</td>
<td>1061</td>
<td>1776</td>
<td>0.62 (0.54, 0.70)</td>
</tr>
</tbody>
</table>

**HR=0.57 for M0 and 0.62 for M1**

#### +Doc

<table>
<thead>
<tr>
<th>Mets status</th>
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<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>232</td>
<td>687</td>
<td>0.70 (0.52, 0.94)</td>
</tr>
<tr>
<td>M1</td>
<td>832</td>
<td>1090</td>
<td>0.60 (0.52, 0.70)</td>
</tr>
<tr>
<td>Overall</td>
<td>1064</td>
<td>1777</td>
<td>0.62 (0.54, 0.71)</td>
</tr>
</tbody>
</table>

#### +ZA+Doc

<table>
<thead>
<tr>
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<td>Overall</td>
<td>1064</td>
<td>1777</td>
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</tr>
</tbody>
</table>
Treatment effect by metastatic status: Overall survival

Pre-planned analysis

+ZA

<table>
<thead>
<tr>
<th>Metast</th>
<th>OS</th>
<th>No.</th>
<th>Haz. Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>M0</td>
<td>93</td>
<td>686</td>
<td>0.96 (0.62, 1.48)</td>
</tr>
<tr>
<td>M1</td>
<td>509</td>
<td>1091</td>
<td>0.92 (0.76, 1.11)</td>
</tr>
<tr>
<td>Overall</td>
<td>602</td>
<td>1777</td>
<td>0.93 (0.79, 1)</td>
</tr>
</tbody>
</table>

HR=1.01 for M0 disease but 0.73 for M1

+Doc

<table>
<thead>
<tr>
<th>Metast</th>
<th>OS</th>
<th>No.</th>
<th>Haz. Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>M0</td>
<td>93</td>
<td>689</td>
<td>1.01 (0.65, 1.56)</td>
</tr>
<tr>
<td>M1</td>
<td>477</td>
<td>1087</td>
<td>0.73 (0.59, 0.89)</td>
</tr>
<tr>
<td>Overall</td>
<td>570</td>
<td>1776</td>
<td>0.76 (0.63, 0.91)</td>
</tr>
</tbody>
</table>

+ZA+Doc

<table>
<thead>
<tr>
<th>Metast</th>
<th>OS</th>
<th>No.</th>
<th>Haz. Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>M0</td>
<td>91</td>
<td>687</td>
<td>1.03 (0.66, 1.61)</td>
</tr>
<tr>
<td>M1</td>
<td>495</td>
<td>1090</td>
<td>0.78 (0.65, 0.95)</td>
</tr>
<tr>
<td>Overall</td>
<td>586</td>
<td>1777</td>
<td>0.81 (0.68, 0.97)</td>
</tr>
</tbody>
</table>
Docetaxel: Survival – M1 Patients

- SOC: 343 deaths
- SOC+Doc: 134 deaths
- HR (95% CI): 0.73 (0.59, 0.89)
- P-value: 0.002
- Non-PH p-value: 0.23

- Median OS (95% CI):
  - SOC: 43m (24, 88m)
  - SOC+Doc: 65m (27, NR)

- 22 months!

- Restricted mean OS time:
  - SOC: 49.3m
  - SOC+Doc: 56.1m
  - Diff (95% CI): 6.8m (2.8, 11.0m)
## Grade 3+ adverse events ever reported

<table>
<thead>
<tr>
<th></th>
<th>A SOC</th>
<th>B SOC+ZA</th>
<th>C SOC+Doc</th>
<th>E SOC+ZA+Doc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomised</td>
<td>1184</td>
<td>593</td>
<td>592</td>
<td>593</td>
</tr>
<tr>
<td>Patients with adverse event data</td>
<td>1174</td>
<td>587</td>
<td>579</td>
<td>564</td>
</tr>
<tr>
<td>Grade 3-5 AE (G5)</td>
<td>N</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>363 (3)</td>
<td>185 (1)</td>
<td>291 (3)</td>
<td>294 (7)</td>
</tr>
<tr>
<td></td>
<td>31%</td>
<td>31%</td>
<td>51%</td>
<td>52%</td>
</tr>
<tr>
<td>Endocrine disorder</td>
<td>12%</td>
<td>12%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Blood and lymphatic (<em>febrile neutropenia</em>)</td>
<td>1%</td>
<td>2%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Blood/bone marrow (<em>neutrophils</em>)</td>
<td>1%</td>
<td>1%</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>General disorder</td>
<td>4%</td>
<td>5%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
<td>5%</td>
<td>5%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>3%</td>
<td>3%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>5%</td>
<td>4%</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Upfront Chemotherapy for Hormone-Sensitive Metastatic Prostate Cancer

- ADT + docetaxel is the new standard of care for men with hormone-sensitive metastatic prostate cancer
- The Brits did not address the high risk disease versus low risk disease issue
- Low risk disease in CHAARTED is too premature to comment
- Non-metastatic in STAMPEDE is too premature to comment but FFS clearly better
The evolutionary history of lethal metastatic prostate cancer


A - L. humerus BM
D - Sem. vesicle
C - Prostate
E - L. adrenal
F - R. adrenal
G - Bladder
H - Pelvic LN
I - L. pelvic LN
J - R. pelvic LN
K - L. pelvic LN
L - L. media. LN
M - L. rib
N - D. rib
O - R. rib
P - E. rib
Q - I. clavicle
R - I. liliac crest
S - H. Liver
T - N. GL5 EPE
U - Q. GL3/5
V - A. axillary LN
W - D. axillary LN
X - R. diaphragm
Y - R. rib
Z - E. Xiphoid
a - L. lobe liver
b - G. Falciform ligam.
If metastases are the source of additional metastases, then attempts to eradicate early metastatic disease makes sense.

If one eradicates visible metastases, should the primary be ignored?
Oligometastatic Disease

• How do we define?
  – Less than 3 mets? Less than 5 mets?
• Imaging is key
  – Old versus new imaging
  – What we see depends on how we look!
The Critical Role of Imaging

• How much you find depends on how you look
• If one contemplates eradication of the metastatic disease, one must image better
  – Micro-metastases will never be imaged
• Bone scan and CT scans are not up to the task
  – NaF PET
  – PSMA PET
  – Choline PET
  – MRI
    • DWI
    • Combidex
2nd Generation PSMA PET Imaging of Metastatic Prostate Cancer (^{18}\text{F}-\text{DCFPyL})

Improved Sensitivity for Detection of Nodal and Bone Metastatic PCa

Courtesy of Steve Y. Cho (UW) and Martin G. Pomper (JHU)
### High dose radiation (SBRT) to oligo-mets in prostate cancer: Is it worthwhile?

From Reyes and Pienta, Oncotarget 6:8491-8524, 2015

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stage</th>
<th>Grade</th>
<th>Dose</th>
<th>Metastasis</th>
<th>SBRT Details</th>
<th>PFS Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decaestecker, 2014 [144]</td>
<td>3iii/B</td>
<td>R</td>
<td>50</td>
<td>≤3 metastatic asymptomatic mets</td>
<td>SBRT (2 RT schedules used) +/- HT</td>
<td>Median PFS- 19mo; median ADT-FS- 25 month; 2-, 5yr PCSS-96%, 90%</td>
</tr>
<tr>
<td>Berkovic, 2013 [146]</td>
<td>3iii/Di</td>
<td>R</td>
<td>24</td>
<td>Biochemical recurrence after curative treatment to primary (RP, RT, or both), then ≤3 synchronous asymptomatic mets</td>
<td>SBRT</td>
<td>Androgen deprivation therapy-free survival (ADT-FS)- 1-, 2yr- 82%, 54%; clinical progression free survival- 1-, 2yr- 72% and 42%</td>
</tr>
<tr>
<td>Ahmed, 2013 [145]</td>
<td>3iii/B</td>
<td>R</td>
<td>17</td>
<td>≤5 metastatic lesions</td>
<td>SBRT</td>
<td>PEMB group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Local control-100% at 6mo; cancer specific survival (CSS)-6- and 12mo-100%; freedom from distant progression (FFDP)- 6- and 12mo- 74%, 40%</td>
<td></td>
</tr>
</tbody>
</table>
Approach to Oligo-Mets Today
Treatment of the Primary +/- with surgery or radiation

- ADT + docetaxel + radiation (SBRT) to mets
- ADT + radiation to mets
- ADT + docetaxel
- ADT
- Radiation to mets and avoidance of ADT
- Observation
- Something for everyone...a true “dealer’s choice”

But no data on what is best!
Prostate Cancer Clinical States

Hormone-Sensitive

- Diagnoses: 240,000
- Localized Disease
  - Local Therapy or no therapy
- Rising PSA
  - Salvage Rx, ADT or no therapy
- Rising PSA: Castrate
  - No standard of care

Castration resistant prostate cancer

- Deaths: 29,000
- Radiographic Metastases: Castrate
  - Pre-chemo
  - Sipuleucel-T
  - Abiraterone
  - Enzalutamide
  - Radium-223
- Radiographic Metastases: Castrate
  - 1st-Line Chemo
  - Docetaxel
  - Abiraterone
  - Enzalutamide
  - Radium-223

Overt Metastases

- ADT +/- docetaxel

Now CRPC focus
<table>
<thead>
<tr>
<th>TRIAL</th>
<th>PRE-DOCETAXEL</th>
<th>HR</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 327</td>
<td>Docetaxel/prednisone vs mitoxantrone/prednisone</td>
<td>0.79</td>
<td>19.3 vs 16.3*</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Sipuleucel-T vs Control</td>
<td>0.78</td>
<td>25.8 vs 21.7</td>
</tr>
<tr>
<td>COU-AA-302</td>
<td>Abiraterone/prednisone vs Placebo/prednisone</td>
<td>0.79</td>
<td>34.7 vs 30.3*</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>Enzalutamamide vs Placebo</td>
<td>0.71</td>
<td>35.3 vs 30.3*</td>
</tr>
<tr>
<td></td>
<td><strong>POST-DOCETAXEL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TROPIC</td>
<td>Cabazitaxel/prednisone vs mitoxantrone/prednisone</td>
<td>0.70</td>
<td>15.1 vs 12.7</td>
</tr>
<tr>
<td>COU-AA-301</td>
<td>Abiraterone/prednisone vs Placebo/prednisone</td>
<td>0.74</td>
<td>15.8 vs 11.2*</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>Enzalutamamide vs Placebo</td>
<td>0.63</td>
<td>18.4 vs 13.6</td>
</tr>
<tr>
<td></td>
<td><strong>PRE- and POST-DOCETAXEL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALSYMPCA</td>
<td>Radium-223/supportive care vs placebo/BSC</td>
<td>0.70</td>
<td>14.9 vs 11.3*</td>
</tr>
</tbody>
</table>

*updated analysis
How could we be smarter in choosing the right agent for the mCRPC patient?

• What discriminates patients from one another?
• Why do some people respond to agent X and others to agent Y?
• How can we better stratify people to increase their chances of responding?
• Biomarkers are the great hope
  – What do we test for that predicts therapeutic benefit????
# Two Types of Biomarkers: Tumor and Host

## Tumor Related
- Various proteins and isoforms: PSA, AR, and LDH
- DNA mutations, deletions, CNV, translocations, methylation, etc.
- RNA expression and/or alterations (big ones, little ones, coding, and non-coding)
- CTCs, oncosomes, exosomes, and all their contents
- Imaging galore

## Host related
- Pain
- Performance status
- Weight loss
- Alkaline phosphatase
- Albumin
- Tc-99 MDP bone scans
- Immune cell analysis
- Hematopoietic cell function: hemoglobin, NLR, platelets, etc.
Prognostic and Predictive Biomarkers

• Prognostic biomarkers
  – Associates with various endpoints including survival
  – i.e. LDH, Alk Phos, Hgb, PSA, NLT, extent of disease, site of metastases (liver), PS, pain, weight loss, etc.

• Predictive biomarkers
  – Predict response or resistance to therapy
  – AR Variant 7 in CTC RNA assays for abiraterone and enzalutamide but validation pending
  – AR copy number/mutations (L702H, T878A) for abiraterone
  – DNA repair defects and response to PARP inhibition or platinum are quite interesting!
Predictive Biomarkers: Focus on V7 and DNA Repair Defects
Ligand-Independent AR Variants Derived from Splicing of Cryptic Exons Are Clearly Described in Tumors and CTCs

PSA responses in Abi/Enza Treated Patients Stratified by AR-V7 Status in CTCs
Antonarakis et al, NEJM 371:1028, 2014
Experimental Concepts: Can we make AR-V7 irrelevant or simply go away?

- Hormonal agents that bind to ligand site in AR
  - Galeterone
  - High dose testosterone

- Non-hormonal agents
  - PSMA targeted concepts
  - N-Terminal AR targeted agents (Epi-506)
  - Niclosamide
  - Bromodomain inhibitors
  - Taxanes (new concepts)
  - Radiation (including Radium-223)
  - Immunotherapy
PSA Responses and Survival in Taxane Treated Patients Stratified by AR-V7 Status in CTCs

Antonarakis et al, JAMA Oncology, 1:582-591, 2015
Cabazitaxel activity is independent of AR-V7 expression
Onstenk et al. Eur Urol August, 2015 epub

Fig. 3 – (A) Progression-free survival and (B) overall survival as a function of AR-V7 in circulating tumor cells at baseline. The reported p value is from a log-rank test.
Converting AR-V7 CTCs from positive to negative with taxanes but not abiraterone/enzalutamide


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Remained AR-V7 positive</th>
<th>‘Reversions’ to AR-V7 negative</th>
<th>Unknown*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line ADT (n = 0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abiraterone (n = 5)</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Enzalutamide (n = 4)</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Docetaxel (n = 9)</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Cabazitaxel (n = 4)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total (n = 22)</td>
<td>13</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>
PSMA Targeted Therapy: i.e. Antibody Drug Conjugates (and others)

Note: PSMA upregulated in enzalutamide resistance
Study 2301

AR-V7 status does not confer resistance to PSMA ADC

- A total of 52 samples were analyzed for AR-V7
- 17/52 tested positive for N-term AR = AR+
- 35/52 were negative for N-term AR = AR-
- 17 proceeded to be tested for C-term AR
- All 17 had C-term loss to various degree, thus AR-V7+ (★)
- 11/17 responded to PSMA ADC (65%)

PSMA ADC can be effective in reducing PSA regardless of AR-V7 status
Immunotherapy is not V7 Dependent
Antigen Release from Dying Tumor Cells Activate Immune Responses:
Radiation Induces Death of Cancer Cells

Radium-223 + anti-PDL1 concept: Studies soon
A new predictive biomarker: DNA repair defects are more common than appreciated

Robinson et al. Cell 161:1215. 2015
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer


<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Response to Olaparib</th>
<th>No Response to Olaparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker Positive</td>
<td>Time on Treatment (wk)</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>24 12</td>
<td>24 11</td>
</tr>
<tr>
<td>ATM</td>
<td>36 14</td>
<td>36 11</td>
</tr>
<tr>
<td>FANCA</td>
<td>48 16</td>
<td>48 12</td>
</tr>
<tr>
<td>CHEK2</td>
<td>57 21</td>
<td>57 13</td>
</tr>
<tr>
<td>BRCA1</td>
<td>58 22</td>
<td>58 13</td>
</tr>
<tr>
<td>PALB2</td>
<td>73 23</td>
<td>73 13</td>
</tr>
<tr>
<td>HDAC2</td>
<td>57 24</td>
<td>57 13</td>
</tr>
<tr>
<td>RAD51</td>
<td>16 25</td>
<td>16 13</td>
</tr>
<tr>
<td>MLH3</td>
<td>19 26</td>
<td>19 13</td>
</tr>
<tr>
<td>ERCC3</td>
<td>26 27</td>
<td>26 13</td>
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<tr>
<td>MRE11</td>
<td>39 28</td>
<td>39 13</td>
</tr>
<tr>
<td>NBN</td>
<td>62 29</td>
<td>62 13</td>
</tr>
</tbody>
</table>

Legend:
- Orange: Frameshift mutation
- Green: Stop gain
- Teal: Single copy deletion
- Dark grey: Missense mutation
- Light grey: Homozygous deletion
- Purple: Copy-neutral loss of heterozygosity
- Star: Germline event
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer


A Radiologic Progression-free Survival

<table>
<thead>
<tr>
<th>Proportion of Patients vs. Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker-positive, median: 9.8 mo</td>
</tr>
<tr>
<td>Biomarker-negative, median: 2.7 mo</td>
</tr>
</tbody>
</table>

P<0.001 by log-rank test

B Overall Survival

<table>
<thead>
<tr>
<th>Proportion of Patients vs. Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker-positive, median: 13.8 mo</td>
</tr>
<tr>
<td>Biomarker-negative, median: 7.5 mo</td>
</tr>
</tbody>
</table>

P=0.05 by log-rank test
Multiple new concepts exploitable with DNA repair defects

- PARP inhibition has been shown in patients with no prior platinum exposure
- Various forms of radiation including radium-223
- Platinum and other DNA damaging patients
  - Extreme responder analysis by Beltran et al indicated that DNA repair defects may be involved
- Combinations of all the above
Summary

• The role of chemotherapy expands to the hormone-sensitive metastatic setting
• New concepts and new imaging provide new opportunities in oligo-metastatic disease
• Newer concepts in immunotherapy are worthy of exploration given success in other diseases
• New predictive biomarkers, especially DNA repair defects, are clinically exploitable in an important subset of patients