Updates on Systemic Therapy for Metastatic Prostate Cancer

Frontier in Urology 2016

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• Consulting fees: Bayer & Sanofi
Outline

• AR-V7, new agents targeting AR-V7

• Docetaxel vs Cabazitaxel for M1 castration resistant prostate cancer

• Emerging agent: PARP Inhibitor and targeting diminished DNA damage repair
Androgen Receptor (AR) Signaling and Aberrant Activation in Castration Resistant Prostate Cancer (CRPC)
AR-V7

- AR-V7 is a truncated form of AR that lacks the ligand binding domain and maintain the N terminal domain as well as the DNA binding domain through alternative splicing.

- This led to ligand independent, constitutively active AR, and resistance to Abiraterone and Enzalutamide.

- Other resistance mechanisms include AR amplification and AR mutation.
AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

ABSTRACT

BACKGROUND
The androgen-receptor isoform encoded by splice variant 7 lacks the ligand-binding domain, which is the target of enzalutamide and abiraterone, but remains constitutively active as a transcription factor. We hypothesized that detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells from men with advanced prostate cancer would be associated with resistance to enzalutamide and abiraterone.
Updated Hopkins Series on 202 subjects undergoing abiraterone and enzalutamide treatment for M1 CRPC

<table>
<thead>
<tr>
<th></th>
<th>PSA response rate</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC - AR-V7 -</td>
<td>73% (40/53)</td>
<td>best</td>
<td>best</td>
</tr>
<tr>
<td>CTC + AR-V7 -</td>
<td>52% (59/113)</td>
<td>intermediate</td>
<td>intermediate</td>
</tr>
<tr>
<td>CTC + AR-V7 +</td>
<td>14% (5/36)</td>
<td>worst</td>
<td>worst</td>
</tr>
</tbody>
</table>

External Validation (n=81) with *epic science* IF based AR-V7 CTC assay reported enrichment of AR-V7 + CTC with lines of Tx for M1 CRPC; +AR-V7 predicted worse OS in multivariable cox proportional hazard analysis with HR of 7.08, $P < 0.0001$

*Scher HI et al. Jama Oncol June 2016*
Targeting AR-V7

• **Docetaxel**, 7/12 AR-V7 + pts converted to AR-V7 – after 6 months of docetaxel  Nakazawa M et al. Annals Oncol 2015, 1859-65

• **Cabazitaxel**  Onstenk W et al. Eur Urol 2015, 939-945

• **Trials testing newer AR targeting agents**
  - ARMOR3 phase 3 Galeterone vs. Enzalutamide as front line therapy for AR-V7 + M1 CRPC  **CLOSED on 7/26/16**
  - EPI-506, AR N terminal domain inhibitor, phase ½ for M1 CRPC: post Abi, post Enza, or naïve
  - VT-464/Seviteronel, selectively inhibits CYP17 lyase & unique blocking effects on AR, phase 2 fro M1 CRPC post Abi, post Enza, or post both Abi & Enza
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 Shevlin, M.D.,
Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

ABSTRACT

BACKGROUND
Androgen-deprivation therapy (ADT) has been the backbone of treatment for metastatic prostate cancer since the 1940s. We assessed whether concomitant treatment with ADT plus docetaxel would result in longer overall survival than that with ADT alone.
Figure 1. Kaplan–Meier Estimates of Overall Survival. The median duration of follow-up was 28.9 months among all patients (Panel A), 29.2 months among patients with high-volume disease (Panel B), and 27.6 months among patients with low-volume disease (Panel C). ADT denotes androgen-deprivation therapy, and NR not reached.

Sweeney et al. NEJM 2015 373 (8)
Cabazitaxel vs Docetaxel in chemotherapy-naive patients with M1 CRPC: A three-arm phase III study (FIRSTANA)

<table>
<thead>
<tr>
<th>Day 1 Q3week</th>
<th>N</th>
<th>Median OS</th>
<th>HR C vs D75</th>
<th>PFS</th>
<th>G3-4 AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabazitaxel 20mg/m2</td>
<td>391</td>
<td>24.5 months</td>
<td>1.009 (0.85 to 1.197)</td>
<td>4.4 months</td>
<td>41.2%</td>
</tr>
<tr>
<td>Cabazitaxel 25mg/m2</td>
<td>389</td>
<td>25.2 months</td>
<td>0.97 (0.819 to 1.16)</td>
<td>5.1 months</td>
<td>60.1%</td>
</tr>
<tr>
<td>Doxetaxel 75mg/m2</td>
<td>388</td>
<td>24.3 months</td>
<td></td>
<td>5.3 months</td>
<td>46.0%</td>
</tr>
</tbody>
</table>

Among secondary endpoints only tumor responses were significantly superior for C25
Febrile neutropenia, diarrhea and hematuria were more frequent in C25; peripheral neuropathy, peripheral edema, alopecia and nail disorders were more frequent in D75  

Sartor et al. J Clin Oncol 34, 2016 (suppl; abstr 5006)
Phase III non-inferiority study of cabazitaxel (C) 20 mg/m² (C20) versus 25 mg/m² (C25) in pts with M1 CRPC previously treated with docetaxel (D). PROSELICA study

<table>
<thead>
<tr>
<th></th>
<th>Median OS months</th>
<th>Median PFS months</th>
<th>PSA response%</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>C20 (n=598)</td>
<td>13.4 (12.19 to 14.88)</td>
<td>2.9 (2.79 to 3.45)</td>
<td>29.5 (25.6 to 33.3)</td>
<td>18.5%</td>
</tr>
<tr>
<td>C25 (n=602)</td>
<td>14.5 (13.47 to 15.28)</td>
<td>3.5 (3.12 to 3.94)</td>
<td>42.9 (38.8 to 47.1)</td>
<td>23.4%</td>
</tr>
<tr>
<td>C20 vs C25</td>
<td>HR 1.099 (0.974 to 1.24)</td>
<td></td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

C20 demonstrates non-inferiority for OS compared with C25 and an improved overall safety profile.

*De Bono et al. J Clin Oncol 34, 2016 (suppl; abstr 5008)*
Mechanisms of DNA Repair

Environmental factors (UV, radiation, chemicals)
Normal physiology (DNA replication, ROS)
Chemotherapy (alkylating agents, antimetabolites)
Radiotherapy

Double Strand Breaks
- Non-homologous end-joining
- Homologous recombination
  - BRCA1/BRCA2
- Fanconi anemia pathway
- Endonuclease-mediated repair

Single Strand Breaks
- Nucleotide excision repair
- Base excision repair
  - PARP1

DNA Adducts/Base Damage
- Alkyltransferases
- Nucleotide excision repair
- Base excision repair
  - PARP1

Replication Lesions
- Base excision repair
  - PARP1

Homologous Recombination Repair: high fidelity repair of DNA double strand breaks
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

Prichard C et al., NEJM  June 2016

<table>
<thead>
<tr>
<th>Case Series</th>
<th>Description</th>
<th>Patients</th>
<th>Patients with Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stand Up To Cancer–Prostate Cancer Foundation discovery series</td>
<td>150</td>
<td>15 (10.0)</td>
</tr>
<tr>
<td>2</td>
<td>Stand Up To Cancer–Prostate Cancer Foundation validation series</td>
<td>84</td>
<td>9 (10.7)</td>
</tr>
<tr>
<td>3</td>
<td>Royal Marsden Hospital</td>
<td>131</td>
<td>16 (12.2)</td>
</tr>
<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>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>692</strong></td>
<td><strong>82 (11.8)</strong></td>
</tr>
</tbody>
</table>
Germline Mutations in DNA repair genes: 11.8% in metastatic vs. 4.6% in localized Prostate Cancer

- **BRCA2**: 37/692 = 5.3%
- **ATM**: 11/692 = 1.6%
- **CHEK2**: 10/534 = 1.9%
- **BRCA1**: 6/692 = 0.9%
Poly (ADP-ribose) polymerase 1 (PARP1)

Involved in DNA base-excision repair, B-NHEJ binds directly to ssDNA breaks, catalyzes the cleavage of NAD+ into nicotinamide and ADP-ribose, poly(ADP-ribosylation) then occurs through attaching several ADP-ribose to the target protein.

PARP family currently comprises 18 members. PARP1 & 2 are known to be involved in DNA damage repair.
PARP inhibition and tumor-selective synthetic lethality

DNA replication fork arrest and collapse

Normal BRCA1/BRCA2

HR-based repair

Chromosome Stability
Cell Survival

BRCA1/BRCA2 failure

Impaired HR repair

Alternative error prone repair

Chromosomal Instability
Cell Death

A BRCA2 mutation carrier with CRPC had >50% reduction in the PSA level & resolution of bone metastases after 58 wk of Tx with Olaparib.

T1-weighted MR images at the level of the right acetabulum in the pelvis obtained (a) prior to, and (c) three months after, initiating olaparib. The response at 3 months was documented by 30% inc in Apparent diffusion coefficient values (b,d). E) resolution of bone met after 1yr of tx

Fong PC, et al. NEJM 2009, 361 (2) 123-134
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Mateo J et al. NEJM 2015, 373(18):1697-708

- Phase 2 study 50 subjects with M1 CRPC (49 had received abiraterone or enzalutamide, and 29 had received cabazitaxel), Olaparib 400mg bid

- Targeted next-generation sequencing, exome and transcriptome analysis, and digital polymerase-chain-reaction testing were performed on samples from mandated tumor biopsies

- The primary end point was the response rate, defined either as an objective response according to RECIST 1.1, or as a reduction of at least 50% in the prostate-specific antigen level or a confirmed reduction in the circulating tumor-cell count from 5 or more cells per 7.5 ml of blood to less than 5 cells per 7.5 ml.
Genomic Aberrations in DNA Repair in Patients with M1 CRPC

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>17</th>
<th>15</th>
<th>14</th>
<th>20</th>
<th>30</th>
<th>39</th>
<th>55</th>
<th>16</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on Treatment (wk)</td>
<td>24</td>
<td>36</td>
<td>36</td>
<td>48</td>
<td>57</td>
<td>58</td>
<td>59</td>
<td>62</td>
<td>12</td>
</tr>
<tr>
<td>Biomarker Positive</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Response to Olaparib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No Response to Olaparib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

- **BRCA2**: Frameshift mutation, Single copy deletion, Missense mutation, Germine event, Stop gain, Homozygous deletion, Copy-neutral loss of heterozygosity
Antitumor Activity of Olaparib and Association with Defects in DNA-Repair Genes, According to Biomarker Status

HR 0.24  95% CI (0.11 to 0.50)  
HR 0.47 (95% CI, 0.22 to 1.02)
Antitumor Activity of Olaparib and Association with Defects in DNA-Repair Genes, According to Biomarker Status

C Changes in PSA during Treatment

D Changes in CTC Count during Treatment

No. of Patients

<table>
<thead>
<tr>
<th>Weeks since Treatment Initiation</th>
<th>Biomarker-negative</th>
<th>Biomarker-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>33 28 9 1 - -</td>
<td>16 16 14 11 5 4</td>
</tr>
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</table>

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<tr>
<td>No. of Patients</td>
<td>33 31 26 23 5 1 -</td>
<td>16 16 16 13 10 5 3</td>
</tr>
</tbody>
</table>
Lynparza™ (olaparib) granted Breakthrough Therapy designation by US FDA for treatment of BRCA1/2 or ATM gene mutated metastatic Castration Resistant Prostate Cancer

A Phase 3 trial on olaparib for M1 CRPC is planned
Co-targeting AR and DNA repair: A randomized ETS gene fusion-stratified trial of abiraterone + prednisone (Abi) +/- the PARP1 inhibitor veliparib for M1 CRPC patients

Hussain M et al. J Clin Oncol 34, 2016 (suppl; abstr 5010)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PSA RR</th>
<th>ORR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abi</td>
<td>74</td>
<td>63%</td>
<td>36%</td>
<td>8.5 months 95% CI (8.1-13.5)</td>
</tr>
<tr>
<td>Abi+Valiparib</td>
<td>79</td>
<td>67%</td>
<td>49%</td>
<td>11 months 95% CI (8.1-13.8)</td>
</tr>
</tbody>
</table>

No statistically significant difference in PSA RR, ORR, PFS between 2 arms or by ETS fusion status.
Exploratory analysis suggest that DRD is associated with better response to Abi + Valiparib
Future trial on Abi + Olaparib is planned in chemo naïve M1 CRPC setting