Integrating Current & Novel Treatment Strategies for the Management of CRPC

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Progress in Metastatic Prostate Cancer

FDA Approvals in Castration-Resistant Prostate Cancer


- Strontium-89
- Samarium-153
- Zoledronic acid
- Denosumab
- Radium-223
- Cabazitaxel
- Abiraterone
- Sipuleucel-T
Available Treatment Agents for Advanced Prostate Cancer

Androgen deprivation therapy (ADT)

Local therapy

Therapies after ADT

Hormone sensitive

mCRPC asympotomatic (failed ADT)

mCRPC mildly symptomatic

mCRPC symptomatic

mCRPC post-docetaxel

Death

ADT

Abiraterone

Enzalutamide

Docetaxel

Cabazitaxel

Radium 223

supportive care (eg denosumab/bisphosphonates)

1. How do we define Castration Resistant Prostate Cancer?

Progression of Disease despite a suppressed (castrate) testosterone level (<50ng/dL)

2. What makes prostate cancer lethal and how do we assess prognosis in patients?

Lethal Prostate cancer
What's the Prognosis?

CRPC Chemo-naïve Prognostic Nomogram

Wide Range....

Halabi et al JCO 2014

Persistant AR Signaling Pathway is the Pivotal Target of CRPC treatment

Depiction of mechanisms of resistance to androgen deprivation therapy:

- AR amplification
- increased intratumoral androgen synthesis
- hypersensitivity of AR
- mutations of AR
- alternative splicing of AR to constitutively active splice variants.

Mechanism #1

**Immunotherapy**

**Provenge: Background**

- **Results: Time to Objective Progression (ITT population)**
  - APCX-015 (n=82)
  - Placebo (n=45)

- **Results: Overall Survival (ITT population)**
  - APCX-015 (n=82)
  - Placebo (n=45)

Provenge: (second) Pivotal Trial Results

Phase 3 design allowed for crossover from placebo to vaccine

Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>PROVENGE (n=241)</th>
<th>Control (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–5 (%)</td>
</tr>
<tr>
<td>Chills</td>
<td>54.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Fever</td>
<td>29.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Headache</td>
<td>16.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>9.8</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>5.3</td>
<td>0</td>
</tr>
<tr>
<td>Groin pain</td>
<td>5.0</td>
<td>0</td>
</tr>
</tbody>
</table>

Control was nonactivated, autologous, peripheral blood mononuclear cells.
Mechanism #2

Targeting Persistent AR signaling

The Human Endocrine System Drives Prostate Cancer Growth

Hypothalamus (Brain) → LHRH → Pituitary Gland → FSH, LH → Testicles → Testosterone → DHT → PROSTATE CANCER CELLS

- LHRH agonists (Lupron, Zoladex)
- Estrogen
- orchiectomy

Antiandrogens: Casodex Flutamide, Nilutamide, Enzalutamide, Apalutamide

Abiraterone
Model of AR Amplification as Mechanism of Resistance to Androgen Deprivation Therapy

Supplementary Figure 3

**Supplementary Fig. 3** - Model of prostate cancer progression. Hormone therapy, consisting of androgen-lowering drugs and competitive androgen receptor antagonists, decreases the number of active receptors leading to a clinical response (hormone sensitive disease). Failure of therapy (hormone refractory disease) results from increased receptor level which inverts the response to antagonists and amplifies the response to all ligands - residual androgens, antagonists and other steroids (not depicted).

Chen et al., 2004 Nature Medicine

AR targeting:
Abiraterone – Intracrine Androgens
Enzalutamide – AR amplification

CRPC samples have robust AR expression
Mohler et al

Montgomery RB et al Cancer Res. 2008 Jun 1;68(11):4447-54

1. Transcripts encoding steroidogenic enzymes are detected within tumor
2. Tumor androgens in CRPC metastases from androblast patients exceed levels in prostate cancer tissues from eugonadal subjects
3. These may be particularly relevant for tumors with overexpressed AR
Prostate Cancer can make its own androgens

Montgomery RB et al Cancer Res. 2008 Jun 1;68(11):4447-54

Mostaghel et al. Urol Oncol 2009; 27(3): 251-257

Testosterone Levels Within Metastases From the Castrate Men Exceeded Serum Levels

The level of androgen in the tumor tissue

- Serum testosterone castration stage cannot completely eradicate androgens in PC environment
- There are enough androgens within the tumor tissue to activate AR

DHT, dihydrotestosterone; T, testosterone
Enzalutamide (Xtandi)

- Oral drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway.
- No demonstrated agonist effects in pre-clinical models.

**Hormonally Driven Resistance**

**Pre-Receptor (Ligand) and Receptor Events**

**Receptor events:**
- AR Amplification and Mutation
- AR Splice Variants

Ryan, Tindall Journal of Clinical Oncology 2011

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**Two very active agents**

**Abiraterone/Pred vs Prednisone**

**Enzalutamide Vs Placebo**

- Hazard Ratio: 0.186 (95% CI: 0.15, 0.23) $P < 0.0001$
- Hazard Ratio: 0.706 (95% CI: 0.60, 0.84) $P < 0.0001$

Progress for Most (69% of patients respond to abiraterone)

- 29% of patients on the prednisone control arm had a decline in PSA by ≥ 50%
- 69% of patients on the abiraterone arm had a decline in PSA by ≥ 50%

IA3 data. A negative percent indicates a decline in PSA. A positive percent indicates that the subject never has a decline in PSA.

Time to All Landmarks Favored Abiraterone ...for the population as a whole

Secondary Endpoints
- PSA Progression
- Tumor/Bone Progression
- Chemotherapy
- ECOG PS Decline
- Pain
- Death

Primary Endpoints: rPFS and OS

ECOG PS = Eastern Cooperative Oncology Group Performance Status.
Ryan et al Proc ASCO 2012
...But not a home run for all

A patient who does not respond to abiraterone has rPFS and OS no different from Tax 327 data of a decade ago.

Who “Does Best” with Abiraterone/Enzalutamide?

<table>
<thead>
<tr>
<th>Baseline risk factor</th>
<th>p Value</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPI (2-3 vs 0-1)</td>
<td>&lt; 0.0001</td>
<td>1.71 (1.34-2.17)</td>
</tr>
<tr>
<td>LDH ( &gt; ULN [234 IU/L] vs ≤ ULN)</td>
<td>&lt; 0.0001</td>
<td>2.03 (1.51-2.74)</td>
</tr>
<tr>
<td>ALP ( &gt; ULN [131 IU/L] vs ≤ ULN)</td>
<td>0.0004</td>
<td>1.60 (1.23-2.08)</td>
</tr>
<tr>
<td>Bone metastases (≥ 10 vs &lt; 10)</td>
<td>&lt; 0.0001</td>
<td>1.92 (1.49-2.47)</td>
</tr>
</tbody>
</table>

B

Number of risk factors
- 1 (intermediate)
- 2-4 (poor)

Favors patient group with good prognosis

2.48 (1.93-3.19)

5.11 (3.72-7.02)

Relative Hazard Ratio* (95% CI)
Sequencing: Retrospective Experience
Abiraterone after enzalutamide
Very Modest response

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sequence (order drugs administered)</th>
<th>PSA Response Enzalutamide Therapy (≥50%)</th>
<th>PSA Response (≥50%)</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileana 2012</td>
<td>24</td>
<td>Docetaxel Enzalutamide Abiraterone</td>
<td>-</td>
<td>13%</td>
<td>2.4 months</td>
<td>-</td>
</tr>
<tr>
<td>Noonan 2013</td>
<td>30</td>
<td>Docetaxel Enzalutamide Abiraterone</td>
<td>60%</td>
<td>3%</td>
<td>15.4 weeks</td>
<td>50.1 weeks</td>
</tr>
<tr>
<td>Loriot 2013</td>
<td>38</td>
<td>Docetaxel Enzalutamide Abiraterone</td>
<td>-</td>
<td>8%</td>
<td>2.7 months</td>
<td>7.2 months</td>
</tr>
</tbody>
</table>

Earlier Intervention for More Survival Benefits with 11.8 mo of OS Extended

2016 EAU COU-AA-302 stratified analysis
Earlier Stage of Chemotherapy-naive mCRPC subjects:
[BPI] Short Form score 0-1
[PSA] < 80 ng/ml
[GS] Gleason score < 8

Treatment with AA + P significantly prolonged OS to 53.6 months

COU-AA-302 randomized, double-blind, placebo-controlled phase II clinical study. The median treatment period abiraterone + prednisone 20.4m, placebo + prednisone 11.2m (HR 0.61; 95% CI 0.43-0.87, p = 0.0055).

Miller K, et al. Poster (#775) presented at the 31st Annual EAU Congress, 11-15 March 2016, Munch, Germany
Primary Resistance

30% = Primary Resistance

(?)% Resistance with Phenotypic Change: e.g. Neuro-endocrine

60+% = Acquired Resistance:

Death Non-PC Cause

Enzalutamide Or Abiraterone

CRPC

ASI = Androgen Synthesis Inhibitor
ART = AR Targeted Therapy

AR-V7: AR SPLICe VARIANT

“half AR” – Activated without Binding Androgen

CRPC contains variants which lack LBD

No current therapies can inhibit because they work through LBD

NTD DBD Hinge LBD

AR Splice Variants (AR-Vs)

**ARV7**
- More abundant than others:
  - Compatible with detection in clinical samples
- Constitutively active:
  - Cannot be inhibited by LBD-targeting drugs
- Produces translated protein product:
  - Not affected by nonsense-mediated mRNA decay
- Expression increased (~20 fold) in CRPC

Prevalence of AR-V7 in CRPC (n=62)

- Pre-Enza, Pre-Abi: **11.6%**
- Post-Enza only: **25.0%**
- Post-Abi only: **51.2%**
- Post-Enza and Post-Abi: **66.7%**
AR-V7 and Resistance to Enzalutamide and Abiraterone in CRPC

PSA Responses According to AR-V7 Status

Enzalutamide-Treated Patients

Abiraterone-Treated Patients

The dotted line shows the threshold for defining a PSA response (≥50% reduction in PSA level from baseline).

*Increase seen of >100% in best PSA response.

†Patients in the enzalutamide cohort who previously received abiraterone and patients in the abiraterone cohort who previously received enzalutamide.

Conversions of ARV-7

Table 5: Conversions and prevelance in AR-V7 status during treatment with AR-directed therapies and immune checkpoint therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Retained AR-V7 negative</th>
<th>Converted to AR-V7 positive</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR-V7 negative at baseline (N = 15)</td>
<td>Retained AR-V7 negative</td>
<td>Converted to AR-V7 positive</td>
<td>Unknown</td>
</tr>
<tr>
<td>First line ADT (n = 2)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abiraterone (n = 1)</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Enzalutamide (n = 1)</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Docetaxel (n = 2)</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Cabazitaxel (n = 2)</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total (N = 15)</td>
<td>7</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>AR-V7 positive at baseline (N = 52)</td>
<td>Retained AR-V7 positive</td>
<td>Converted to AR-V7 negative</td>
<td>Unknown</td>
</tr>
<tr>
<td>First line ADT (n = 8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abiraterone (n = 1)</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>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total (N = 52)</td>
<td>13</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

(a) Number of baseline AR-V7-negative individuals that either remained AR-V7 negative or converted to AR-V7 positive during treatment.

(b) Number of baseline AR-V7-positive individuals that either remained AR-V7 positive or reverted back to AR-V7 negative during treatment.

*Status had no sample collected at progression, so progression has not yet occurred.
ARV7 ratio to flAR: ARV7 is a function of AR amplification

Antonarakis NEJM 2014

Combination Phase III: Alliance: A031201 - PI Michael Morris (accrued)

Metastatic progressive CRPC:
• No prior chemo for mets
• ≤1 wk prior keto
• No significant pain

Stratification factor: prior chemo

Randomize

Arm A: Enzalutamide

Arm B: Enzalutamide Abiraterone Prednisone

Total of 616 deaths, log-rank statistic 90% power (one sided type I error rate of 0.025) to detect HR of 0.77 in favor of arm B
Radium-223 Targets Bone Metastases

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer)
Phase III Study Design

PATIENTS
• Confirmed symptomatic CRPC
• ≥ 2 bone metastases
• No known visceral metastases
• Post-docetaxel or unfit for docetaxel

STRATIFICATION
• Total ALP: < 220 U/L vs ≥ 220 U/L
• Bisphosphonate use: Yes vs No
• Prior docetaxel: Yes vs No

TREATMENT
6 injections at 4-week intervals

Radium-223 (50 kBq/kg)
+ Best standard of care
Placebo (saline)
+ Best standard of care

RANDOMISED
N = 922

Planned follow-up is 3 years

Clinicaltrials.gov identifier: NCT00699751.

ALSYMPCA Overall Survival

HR 0.695; 95% CI, 0.552-0.875
P = 0.00185

Radium-223, n = 541
Median OS: 14.0 months

Placebo, n = 268
Median OS: 11.2 months
How to use radium?

• Chemo refusers?
• Frailer patients?
• Post chemo
• In combination

Mechanism #4

Targeting Variant Histologies
Treatment Mediated Selection Pressure: Neuro-En

AR directed therapy “eliminates” Adenocarcinoma

AR Driven Adenocarcinoma

Neuro-endocrine/small cell predominant

mCRPC Tissue Collection: West Coast Dream Team Approach

Discriminative network: Abiraterone Naive vs Resistant
Histology of 124 Evaluable Biopsies
74% were “pure” with a single histologic subtype (**isolated by LCM)**
Remainder (26%) were comprised of mixed populations

<table>
<thead>
<tr>
<th>Histological Features</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdenoCA + IAC separate clusters</td>
<td>11</td>
</tr>
<tr>
<td>IAC + SCNC separate clusters</td>
<td>4</td>
</tr>
<tr>
<td>AdenoCA + SCNC separate clusters</td>
<td>1</td>
</tr>
<tr>
<td>Non-adenoCA cytology with adenoCA architecture</td>
<td>11</td>
</tr>
</tbody>
</table>

Overall survival as function of biopsy pathology
Grouping IAC and SCNC

Presented By Eric Small at 2015 ASCO Annual Meeting
Need to Reconcile clinical vs histological vs genomic

Clinically “Anaplastic”

Histologically “Small Cell”

Genomic Target Present?

But the holy grail is the liquid biopsy

Scher et al Proc ASCO GU 2016
Harnessing Multi-platform informatics to discover

NEXT Ideal: A marker that melds Predictive and prognostic

- Prognostic “how sick is patient?”
  - LDH
  - AlkPhos
  - Opiates y/n?
  - Visceral Disease

- Predictive “Will drug work?”

– Does Prognostic trump Predictive?
- If a predictive pattern is identified in a patient will they still be able to receive the intervention?
Mechanism #5

Targeting DNA repair

BRCA and prostate cancer

• Germline BRCA 1,2 are rare in prostate cancer
  — present in 0.33-5%
• HOWEVER
  — Homologous DNA repair defects (HR) are common in prostate cancer
• Germline and somatic inactivating mutations in HR DNA repair genes collectively occur in up to 20%-25% of prostate cancers
  — CHEK2, BRIP1/FANCI, SBS1, BRCA1 and ATM
Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer.

Antitumor Activity of Olaparib and Association with Defects in DNA-Repair Genes, According to Biomarker Status.
PARP inhibitors in development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tumor types</th>
<th>Company</th>
<th>Most advanced development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>Breast, endometrial, gastric, glioblastoma, head and neck, lung, ovarian, pancreatic, prostate, sarcomas</td>
<td>AstraZeneca</td>
<td>• FDA-approved in ovarian cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Phase III in breast cancer, pancreatic, ovarian, gastric</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>Breast, ovarian, pancreatic</td>
<td>Clovis Oncology</td>
<td>Phase III in endometrial epithelial ovarian, primary peritoneal or fallopian tube cancer</td>
</tr>
<tr>
<td>Niraparib (MK.44E27)</td>
<td>Breast, Ewing sarcoma, ovarian</td>
<td>Tesaro</td>
<td>Phase III in ovarian, breast cancer</td>
</tr>
<tr>
<td>Velparib (ABT-888)</td>
<td>Breast, cervical, colorectal, glioblastoma, head and neck, lung, leukemias, multiple myelomas, non-Hodgkin lymphoma, ovarian, pancreatic, prostate</td>
<td>AbbVie</td>
<td>Phase III in breast cancer, non-small cell lung cancer, glioblastoma</td>
</tr>
<tr>
<td>Talazoparib (BMN-673)</td>
<td>Breast, endometrial, leukemias, ovarian, solid tumors</td>
<td>BioMarin Pharmaceutical</td>
<td>Phase III in breast cancer</td>
</tr>
<tr>
<td>BGB-290</td>
<td>Solid tumors</td>
<td>BeiGene</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

Carboplatin also targets defective DNA repair

- Platinum based chemotherapy active
- Underutilized.
- May ‘double cover’ neuroendocrine and HRD tumors
- Generic, well tolerated
- Need trials!
Prior studies of platinum-based therapy

<table>
<thead>
<tr>
<th>Gene Expression Profile of BRCAness That Correlates With Responsiveness to Chemotherapy and With Outcome in Patients With Epithelial Ovarian Cancer</th>
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</table>

Do we know how to select patients??

<table>
<thead>
<tr>
<th>Table 1: Summary of identified platinum trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
</tr>
<tr>
<td>Mirboxytrex</td>
</tr>
<tr>
<td>Carboplatin</td>
</tr>
<tr>
<td>Carboplatin combination</td>
</tr>
<tr>
<td>Carboxplatin combination with other chemotherapeutic agents</td>
</tr>
<tr>
<td>Carboxplatin in small cell lung carcinoma</td>
</tr>
<tr>
<td>Carboxplatin in small cell breast cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Summary of identified platinum trials</th>
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<tbody>
<tr>
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<tr>
<td>Carboxplatin in small cell breast cancer</td>
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</table>

The slides mention various studies on platinum-based therapy and the selection of patients for treatment. The table summarizes studies on platinum trials, indicating that prior studies have shown varying best responses to chemotherapy.
Integrating Biology into CRPC Management

• AR signaling is the key to most CRPC

• Variant histologies also may be implicated.

• DNA Repair defects are a ‘new’

• Tumor interrogation imperative to future therapy development