Alpha Therapeutics from a Prostate Oncologic Standpoint

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Alphas in Prostate Cancer: Rich in Opportunities and Targets Given the Prostate Cancer Bone Ecology

PC₃ cells, 7 days after injection, at lateral endortical bone surface, rich in osteoblast lineages and growth factors

Mineral apposition rate and bone formation rate

Wang et al., JBMR, 2014
Logothetis, Morris, et al, Cancer and Met Rev, 2018
FDA approval of therapies that target bone and tumor and its growth pathways

- **1993**: Sr-89
- **1996**: Sm-153
- **1999**: Mitoxantrone
- **2002**: Docetaxel
- **2005**: Zoledronic Acid
- **2008**: Sipuleucel
- **2011**: Cabazitaxel
- **2014**: Denosumab
- **2017**: Apalutamide
- **2018**: Radium 223

**Therapy Approvals**

- **Palliation**
- **SRE Prevention**
- **Life Prolongation**
- **MFS**
Today’s landscape

Docetaxel (CHAARTED and STAMPEDE)
Abiraterone (LATITUDE and STAMPEDE) - 2018
Enzalutamide (ARCHES)
Apalutamide (TITAN)

Abiraterone (2011 and 2012)
Docetaxel (2004)
Radium 223 (2013)
Cabazitaxel (2010)
Pembro (MSIH 2017)

Enzalutamide (2012 and 2014)
Sip-T (2010)

Enzalutamide (2012 and 2014)
Apalutamide (SPARTAN) - 2018
Darolutamide (ARAMIS) - pending

Olaparib (2016)/Rucaparib (2018)
FDA Breakthrough status
The increasingly important roadmap for drug development and clinical decision-making is genetic.
Why we are in a golden age of drug development…

• Good biologic underpinning

• Outstanding collaborations between investigators, sponsors, and regulatory agencies in advancing regulatory science with treatment and basic science

• Validation of new endpoints for drugs beyond OS
  – rPFS per PCWG2 and PCWG3
  – Metastasis free survival

• Well-designed, standardized, thoughtfully conceived prospective clinical trials
Alpha Targeting of Bone Microenvironment

Suominen, et al. AACR 2015, Parker et al., NEJM 2013
Radium in the Future?

1. Chemotherapy

2. AR

3. DNA repair deficient population
   - Alone vs. with PARPi

4. IO/Checkpoint inhibitors
   - Can we turn an immunologically cold to a hot tumor?
A platform for Dual Targeting the Bone Microenvironment and Tumor

Morris, Taskar, Carrasquillo, JCO, 2009
Phase I/IIa Randomized Study: Integrated alpha bone and tumor targeting with docetaxel +/- radium 223 (2:1 randomization)

- **Objectives:**
  - To define the RP2D
  - To establish the biomarker changes to:
    - PSA (tumor directed)
    - Alk Phos (bone directed)
    - Imaging (bone directed)

- **Design:**
  - Dose escalation
  - 2:1 randomization to combination therapy vs. chemo monotherapy

- 6 centers
# Adverse Events

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Any Grade</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223 + Docetaxel N = 33</td>
<td>Docetaxel N = 13</td>
</tr>
<tr>
<td>Any</td>
<td>33 (100)</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Hematological*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (30)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (9)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2 (6)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Nonhematological†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (45)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Back pain</td>
<td>13 (39)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Gastrointestinal reflux disease</td>
<td>1 (3)</td>
<td>4 (31)</td>
</tr>
</tbody>
</table>
Biomarkers suggest more profound treatment effects on the tumor and bone microenvironment with dual targeting.

Submitted, Morris et al
Advancing to Phase III: DORA trial

- 25 centers US and Netherlands
- Primary Endpoint: OS
  - Projected HR of 0.75
  - 738 patients
- Secondary:
  - PSA, bone markers, imaging, QOL
- Correlative:
  - CTC enumeration, ARV7 characterization, cfDNA, aBSI
- Strat factors
  - Prior docetaxel for hormone sensitive disease
  - Visceral disease (presence or absence)
  - Prior treatments
  - Known neuroendocrine disease

**Diagram:**

- **Arm A**
  - Docetaxel 75 mg/m² q 3 weeks x 10 doses
  - 5 mg prednisone b.i.d.

- **Arm B**
  - Docetaxel 60 mg/m² q 3 weeks x 10 doses
  - 5 mg prednisone b.i.d.
  - Radium -223 at 55 kBq/kg bw, 6 injections at 6 weeks intervals
ERA 223: Abiraterone/Pred + Radium vs. Abiraterone/Pred

<table>
<thead>
<tr>
<th>Fractures</th>
<th>AAP plus radium-223 group (n=392)</th>
<th>AAP plus placebo group (n=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one fracture by investigator assessment</td>
<td>112 (29%)</td>
<td>45 (11%)</td>
</tr>
<tr>
<td>Time to first fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>45 (11%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>6 to &lt;12 months</td>
<td>46 (12%)</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>12 to &lt;24 months</td>
<td>19 (5%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>≥24 months</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Patients with independently reviewed fracture imaging scans</td>
<td>80 (20%)</td>
<td>27 (7%)</td>
</tr>
<tr>
<td>Patients with at least one fracture confirmed by independent assessment</td>
<td>76 (19%)</td>
<td>23 (6%)</td>
</tr>
<tr>
<td>Bone metastasis at site of fracture</td>
<td>20/76 (26%)</td>
<td>6/23 (26%)</td>
</tr>
<tr>
<td>New bone lesion</td>
<td>15/76 (20%)</td>
<td>5/23 (22%)</td>
</tr>
<tr>
<td>Old bone lesion</td>
<td>6/76 (8%)</td>
<td>1/23 (4%)</td>
</tr>
<tr>
<td>No bone metastasis at site of fracture</td>
<td>60/76 (79%)</td>
<td>17/23 (74%)</td>
</tr>
<tr>
<td>Type of fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological</td>
<td>19/76 (25%)</td>
<td>6/23 (26%)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>27/76 (36%)</td>
<td>13/23 (57%)</td>
</tr>
<tr>
<td>Osteoporotic</td>
<td>37/76 (49%)</td>
<td>4/23 (17%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>1/76 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Smith et al, Lancet Oncol 2019
Radium and DNA Repair Defects

Table 3 – PSA and ALP responses in HRD(+) and HRD(−) patients

<table>
<thead>
<tr>
<th></th>
<th>HRD(+)</th>
<th>HRD(−)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 10</td>
<td>N = 18</td>
<td></td>
</tr>
<tr>
<td>PSA (≥50%) response</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>ALP (≥30%) response</td>
<td>80% (8)</td>
<td>39% (7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with ALP normalization (if baseline ALP was elevated)</td>
<td>100% (5)</td>
<td>33% (3)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

ALP = alkaline phosphatase; HRD = homologous recombination deficiency; PSA = prostate-specific antigen.

*Response rate is defined as a decrease in PSA of ≥50% and in ALP of ≥30% from baseline within 12 wk.
## Trial Schema

### Overall Schema

<table>
<thead>
<tr>
<th>Niraparib(^1) + Radium-223 Dose Finding</th>
<th>Niraparib(^1) + Radium-223 Dosing at MTD/RP2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib 100 mg QD</td>
<td>Niraparib MTD/RP2D</td>
</tr>
<tr>
<td>Niraparib 200 mg QD</td>
<td></td>
</tr>
<tr>
<td>Niraparib 300 mg QD</td>
<td></td>
</tr>
<tr>
<td>Dose Escalation by TITE CRM(^*)</td>
<td></td>
</tr>
</tbody>
</table>

### Dose Schema

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Niraparib</th>
<th>Radium-223 (Xofigo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 mg p.o. daily</td>
<td>55 kBq (1.35 microcurie) per kg body weight, given at 4 week intervals for 6 injections.</td>
</tr>
<tr>
<td>2</td>
<td>200 mg p.o. daily</td>
<td>55 kBq (1.35 microcurie) per kg body weight, given at 4 week intervals for 6 injections.</td>
</tr>
<tr>
<td>3</td>
<td>300 mg p.o. daily</td>
<td>55 kBq (1.35 microcurie) per kg body weight, given at 4 week intervals for 6 injections.</td>
</tr>
</tbody>
</table>

Radium-223 (Xofigo) 55 kBq (1.49 microcurie) per kg body weight, given at 4 week intervals for 6 injections.

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https://clinicaltrials.gov/ct2/show/NCT03076203
Radiation and Immune Checkpoint Inhibition

Kim, Clin Genit Ca 2017
Radium + Atezolizumab

Study Schema

Initial Concurrent Dosing Evaluation

Cohort 1: Concurrent Dosing
Radium-223 on D1C1
Atezolizumab on D1C1
DLT observation for one 28-day cycle
3+3 design (n=3-6)

Not Tolerated

Staggered Dosing Evaluation

Cohort 2: Staggered Dosing,
28-Day Radium-223 Run-In
Radium-223 on D1C1
Atezolizumab on D1C2
DLT observation for one 28-day cycle
3+3 design (n=3-6)

Not Tolerated

Cohort 3: Staggered Dosing,
56-Day Radium-223 Run-In
Radium-223 on D1C1
Atezolizumab on D1C3
DLT observation for one 28-day cycle
3+3 design (n=3-6)

Not Tolerated

Discontinue Enrollment

Tolerated

Randomized Treatment Evaluation

Arm A: Concurrent Dosing
Radium-223 on D1C1
Atezolizumab on D1C1
(n=10)

Arm B: Staggered Dosing,
28-Day Radium-223 Run-In
Radium-223 on D1C1
Atezolizumab on D1C2
(n=10)

Arm C: Staggered Dosing,
28-Day Atezolizumab Run-In
Atezolizumab on D1C1
Radium-223 on D1C2
(n=10)

Expansion

(n=9-12 across selected arms)

Radium-223 on D1C1
Atezolizumab on D1C1

Radium-223 on D1C1
Atezolizumab on D1C2

Atezolizumab on D1C1
Radium-223 on D1C2

Patients

- Progressive CRPC during or following treatment with an androgen pathway inhibitor
- At least two bone metastases
- Measurable non-liver visceral metastasis or lymphadenopathy
- Disease amenable to serial biopsy
Bone vs. Tumor Targeting – The Essential Dilemma

Hydroxyapatite Targeting

Bone only
Tumor may largely be intact w/ treatment
Nominal side effects

Tumor Targeting

Tumor directly impacted
May have off-target effects

12/2014
PSA = 2923 ng/ml

7/2015
PSA = 0.26 ng/ml

9/2015
PSA < 0.1 ng/ml

12/2014
PSA = 2923 ng/ml

7/2015
PSA = 0.26 ng/ml

9/2015
PSA < 0.1 ng/ml
Moving Beyond Chemotherapy for Tumor Targeting: Optimizing *Tumor* Targeting by Selecting a *Tumor* Specific Target

- Cloned at MSK by Dr. Heston
- An ideal target for both therapy and imaging
- High tumor specificity
- Regulated by AR (decreased signaling results in increased expression)
- We had been refining dosing and dosimetry since early 2000’s
PSMA tumor targeting and toxicity: size matters

Viola-Villegas, Mol Pharm 2014
Tumor and normal organ biodistribution can vary by the targeting agent.

Pandit-Taskar, JNM, 2016
Ac225 PSMA, 14 pts, retrospective

Kratochwil, JNM 2017
Ac225 PSMA 617 in mCSPC Pilot Trial, with intrapatient dose de-escalation

- 17 pts
- Descriptive tox section
  - Grd 1/2 xerostomia 100%
  - No grd 3-4
- Appears to be good response
- Still needs a formal phase I study to understand dose, interval, and relationship to tox

Sathekge, Eur JNMMI, 2019
PSMA-TTC: Alpha PSMA-Directed Alpha Therapy

An open-label, first-in-human, multicenter, Phase I study to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of PSMA-TTC in patients with mCRPC (recruiting)

**Patient population**
- N=108 (planned)
- Documented progression of mCRPC
- At least 1, but no more than 2, prior taxane regimens
- Previous treatment with at least one novel androgen axis drug (NAAD)
- ECOG PS: 0 or 1

**Dose escalation**
Th-227 dose escalated to the MTD
Starting antibody dose: 50 mg
(Dose range: 20–100 mg)

**Primary objective:** To determine the safety and tolerability and MTD of PSMA-TTC

**Dose expansion**
Selection of dose/regimen based on data from dose escalation
- Expansion Cohort 1
  - Dose/Regimen 1
- Expansion Cohort 2
  - Dose/Regimen 2


PSMA: Heterogeneity in advanced disease

2. DISCORDANT FDG+ PSMA-

Hofman et al, ESMO 2017

Morris et al, ESMO 2017
Dose Density and Cell Growth Kinetics Matter if You Want to Cure Cancer

Norton/Simon: the rate of destruction by chemotherapy is proportional to the rate of growth of the unperturbed tumor (Simon, Norton, Nat Rev Clin Oncol 2006)

Lopez, et al. 2019 Communications in Nonlinear Science and Numerical Simulation
Where we’d like to go…

63 y.o.
PSA 7
Gleason 4+5
13/16 positive cores

Much disease on his MRI of his prostate….

Bone scan looks good

PSMA scan with metastatic disease

Michael J. Morris, MD
What is Clinical Benefit?

- Drugs must show clinical benefit
  - Feel, function, or survive
  - Some other endpoint, associated with OS
    - PSA consistently fails this test
    - No radiographic “response” by any imaging modality has been validated to correlate with OS or a clinical benefit to date
    - rPFS per PCWG2 and 3 has received regulatory recognition
      - MFS has received regulatory recognition for non-metastatic disease
      - Alterations in PSMA imaging is a PD indicator, not a demonstration of benefit
Enthusiasm cannot replace equipoise

During clinical trials, actinium-225 wiped out late-stage prostate cancer in three treatments. Now, #NationalLab scientists are working to expand this treatment. Find out how ➡️ [go.usa.gov/xQhnM](go.usa.gov/xQhnM) @DOEScience
Phase II studies with promising results based on response or even OS do not necessarily predict for OS, even in advanced patients.

ProstVac  
Gulley, JCO, 2019

Cabozantonib  
Smith, JCO, 2016

Tasqiunimod  
Median OS  
Tasqiunimod: 21.3 months (95% CI, 18.6 to 23.0 months)  
Placebo: 24.0 months (95% CI, 21.4 to 25.9 months)  
HR: 1.037 (95% CI, 0.638 to 1.642 months; P = .247

Sternberg, Eurol Oncol, 2016
Future Directions

• We need alternatives to PSMA as tumor directed therapy
  – HK2

• We will need formal trials that address the toxicity and risks of prostate cancer
  – Alternative targets
  – Reconsiderations of the optimal molecule size
  – Other salivary gland agents

• Need to have some prospective data supporting *actual* clinical benefit