Translational Laboratory Research: How it Advances Care

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Molecular and Medical Genetics
Co-Leader OHSU Prostate Cancer Program
Outline

• Translational research defined
• Refresher on genetics
• The problem of advanced prostate cancer
• How we move forward
Basic Research
- 1 set of words, tools, approaches
- Studying why cancer develops and how to target it in cell lines, animals in the laboratory

Clinical Research
- Another set of words, tools, approaches
- Studying whether treatments work in cancer patients in the clinic

Translational Research
- Speaking both of these languages to take the most critical insights from the lab and from the clinic in order to improve outcomes for patients
Genetic Code

- DNA
  - The blueprint of our cells
  - A library
- Genes are like individual books within that library that tell a specific story
  - Words in those books are spelled with an alphabet of 4 unique letters
    - C, A, T, and G
    - 3 billion letters in our DNA
Understanding the Normal Genetic Code

- Human Genome Project
  - Launched in 1990 by the National Institutes of Health
  - Determine the genetic code of DNA in a normal cell
    - Rosetta stone to compare against diseased cells
  - Completed in 2003
The Players in Our Cells

• DNA
  – The blueprint
  – Our genes

• RNA
  – The message made from this blueprint

• Protein
  – That message turned into an actual product that carries out a specific task in a cell
What is a DNA Mutation?

- Change in the DNA in a cell
  - CATCATCAT
    - Normal stretch of DNA
  - CAT-ATCAT
    - One of the Cs is missing, so the message changes
    - In many cases, the change in message means a protein stops working normally or is no longer made

E.G. CLOSETED -> CLOSED TD
The Problem of Advanced Prostate Cancer

<table>
<thead>
<tr>
<th>Estimated Deaths</th>
<th>Male</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>83,550</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>29,430</td>
<td>9%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>27,390</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>23,020</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>20,540</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,270</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,850</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,520</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,510</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>10,010</td>
<td>3%</td>
</tr>
<tr>
<td>All sites</td>
<td>323,630</td>
<td>100%</td>
</tr>
</tbody>
</table>

ACS Cancer Facts & Figures 2018
What are Obstacles to Progress

• Prostate cancer is not just one disease
  – Differences in the DNA of tumors
• What DNA changes matter?
  – Distinguishing between what is abnormal and what is important
• Why do drugs stop working?
  – Evolution
Biopsy
800 men with advanced metastatic prostate cancer

Goals:
- Classify advanced prostate cancer into subsets
- Find out what makes these subsets different
- Find out how cancers change after treatment

Prostate Cancer Foundation/Stand Up to Cancer Foundation Dream Team Efforts

- Tumor Histology (what the cancer looks like)
- Gene sequencing
- Blood Gene sequencing
Advanced Prostate Cancers Do Not All Appear the Same

Average survival:

- Adenocarcinoma: 42 months
- Small Cell/Neuroendocrine: 18 months

Aggarwal, et al Journal of Clinical Oncology 2018
Each Advanced Prostate Cancer Patient’s Blueprint is Different

Robinson, et al Cell 2015
Personalizing Therapy

• 70 year old university professor, husband, father
• Tumor resistant to nearly all approved therapies
• Hospice discussions
• Bone biopsy
  • Adenocarcinoma
  • BRCA2 gene mutation
Taking Advantage of BRCA2 Mutations in Cancer

Personalizing Therapy

• PARP inhibitor clinical trial
• Another year of life
• Insisted we re-biopsy his tumor at progression prior to passing away
What Happened in His Tumor To Allow It to Grow Again?

Normal DNA: “CLOSETED”

His tumor DNA before PARP inhibitor treatment: “CLOSETD”
  Gene not functioning properly

His tumor DNA after PARP inhibitor treatment: “CLOSET”
  Gene functioning properly again

The BRCA2 gene had returned to near normal so that the cancer cells had a way to resist the drug

Quigley and Alumkal, et al Cancer Discovery 2017
Cancer Progression is Like Evolutionary Natural Selection

• “That which does not kill me makes me stronger.”
  – Fredrick Nietzsche

• “That which is not killed is strong.”
How Do We Improve on Our Current Approach?
Discovery of HIV as the Cause of AIDS in 1983
Lessons from HIV

• 1983
  – HIV identified as the cause of AIDS
  – Patients and their families demanded federal investment and invested in research themselves

• Mid-1990s
  – Treatment with single HIV drugs began in mid-1990s
  – Death rate from AIDS was still nearly 100%

• Early 2000s
  – Patients and their families demanded federal investment and invested in research themselves
  – Scientists determined that the virus mutates and becomes resistant to single drug HIV treatment
  – Combination therapy with multiple HIV drugs at once

• 2018
  – AIDS does not occur in patients treated with these drugs
  – Patients with HIV are living normal lifespans
A Way Forward

• Understanding what is abnormal in a patient’s tumor
• Determining which abnormalities matter
OHSU Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) Trial

- Find gene mutations
- Determine genes that are on or off
- Histology
- Look at cells surrounding the tumor

Tailored combination drug therapy

- Grow tumors in the lab and test drugs against them
Summary

• Cracking the code of advanced prostate cancer is just the beginning

• Using the cancer’s own code against it is transforming prostate cancer treatment
  – The right combination of medicines in the right patient at the right time
Acknowledgements

• Patients and families
• Alumkal Lab
• Entire OHSU Prostate Cancer Research Program
• Our many collaborators throughout the Northwest and beyond
Current Management of Castration-resistant Prostate Cancer

Presented by Tomasz M. Beer, MD
Disclosures

• Consultant for AbbVie, AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, Clovis Oncology, Janssen Biotech, Janssen Japan, Merck, and Pfizer

• Grant/research support from Astellas, Boehringer Ingelheim, Bristol Myers Squibb, Janssen Research & Development, Medivation, OncoGeneX, and Sotio
Learning Objectives

• Review the spectrum of advanced prostate cancer, including castration-resistant prostate cancer (CRPC)
• Review the currently available treatment options for non-metastatic and metastatic CRPC
• Discuss recent advances in the understanding of molecular aberrations in advanced prostate cancer
• Review the most promising molecular targets that may impact on treatment choices in mCRPC
Disease States in Prostate Cancer

Localized disease

Biochemical Recurrence

mHSPC, metastatic hormone sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; L, line of treatment.
Disease States in Prostate Cancer

Focus of today’s talk: therapy selection here

Localized disease

Biochemical Recurrence

mHSPC

mCRPC L1

mCRPC L2

mCRPC L2+

mHSPC, metastatic hormone sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; L, line of treatment.
Metastatic Prostate Cancer

Courtesy of Tomasz M. Beer, MD
# CRPC Therapies with Survival Benefit

<table>
<thead>
<tr>
<th>Agent</th>
<th>Year approved</th>
<th>Indication</th>
<th>PFS benefit</th>
<th>OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>2004</td>
<td>mCRPC</td>
<td>?</td>
<td>√</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>2010</td>
<td>Asymptomatic or minimally symptomatic mCRPC</td>
<td>No</td>
<td>√</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>2010</td>
<td>Post-docetaxel mCRPC</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>2011 and 2012</td>
<td>mCRPC</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>2012 and 2014</td>
<td>mCRPC</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Radium-223</td>
<td>2013</td>
<td>Symptomatic bone predominant mCRPC</td>
<td>SSRE</td>
<td>√</td>
</tr>
</tbody>
</table>

PREVAIL: Enzalutamide vs Placebo Before Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>845</td>
<td>872</td>
</tr>
<tr>
<td>OS, median (months)</td>
<td>31.3</td>
<td>35.3</td>
</tr>
<tr>
<td>PFS, median (months)</td>
<td>5.4</td>
<td>20</td>
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</table>


Abiraterone Before Chemotherapy

**COU-AA-302 Phase 3 Trial: rPFS**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Abiraterone – prednisone</th>
<th>Prednisone alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>546</td>
<td>542</td>
</tr>
<tr>
<td>3</td>
<td>485</td>
<td>406</td>
</tr>
<tr>
<td>6</td>
<td>389</td>
<td>244</td>
</tr>
<tr>
<td>9</td>
<td>311</td>
<td>177</td>
</tr>
<tr>
<td>12</td>
<td>240</td>
<td>133</td>
</tr>
<tr>
<td>15</td>
<td>195</td>
<td>100</td>
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<tr>
<td>18</td>
<td>155</td>
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<td>21</td>
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<td>37</td>
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<td>24</td>
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<td>14</td>
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<tr>
<td>27</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Number at risk
- Abiraterone – prednisone: 546
- Prednisone alone: 542

**Progression-free Survival (%)**

- Abiraterone-prednisone: 16.5 mo
- Prednisone alone: 8.3 mo

**No. of Events**
- Abiraterone-prednisone: 271
- Prednisone alone: 336

**Hazard ratio, 0.53 (95% CI, 0.45-0.62) P<0.001**

Abiraterone Before Chemotherapy

**COU-AA-302 Phase 3 Trial: OS**

**Number at risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>36</th>
<th>18</th>
<th>12</th>
<th>9</th>
<th>6</th>
<th>4</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate plus prednisone</td>
<td>546</td>
<td>538</td>
<td>525</td>
<td>504</td>
<td>483</td>
<td>453</td>
<td>422</td>
<td>394</td>
<td>359</td>
<td>330</td>
</tr>
<tr>
<td>Placebo plus prednisone</td>
<td>542</td>
<td>534</td>
<td>509</td>
<td>493</td>
<td>466</td>
<td>438</td>
<td>401</td>
<td>363</td>
<td>322</td>
<td>292</td>
</tr>
</tbody>
</table>

**Median Overall Survival (OS)**

- Abiraterone acetate plus prednisone: 34.7 months (95% CI 32.7-36.8)
- Placebo plus prednisone: 30.3 months (95% CI 28.7-33.3)

**HR 0.81 (95% CI 0.70-0.93)**

**P = 0.0033**

Radium-223: Targets Bone Metastases

- Alpha-particles induce double stranded DNA breaks
- Short penetration of alpha emitters (2-10 cell diameters)

ALSYMPCA Phase 3 Study Design

• Symptomatic CRPC
• ≥2 bone metastases
• No known visceral metastases or >3-cm nodes
• Post-docetaxel or unfit for docetaxel or refusing docetaxel

Radium-223 (50 kBq/kg) + Best standard of care
6 injections at 4-week intervals

Placebo + Best standard of care

2:1

N = 922

• Stratifications: Total ALP: <220 U/L vs ≥220 U/L;
• Bisphosphonates: Yes vs No; Prior docetaxel: Yes vs No.

ALP: alkaline phosphatase.

Radium-223: Overall Survival


<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Radium-223</th>
<th>HR; P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>307</td>
<td>614</td>
<td></td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>11.3</td>
<td>14.9</td>
<td>0.70; &lt;.001</td>
</tr>
</tbody>
</table>
CHEMOTHERAPY IN MCRPC
Docetaxel: First to Improve Overall Survival

TAX 327

Median OS: 18.9 vs 16.5 mo; HR = 0.76 (CI: 0.62-0.94); P = .009

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>DOC Q3W, n = 296</th>
<th>DOC Q1W, n = 297</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain response</td>
<td>35 (P = .01)</td>
<td>31 (P = .07)</td>
<td>22</td>
</tr>
<tr>
<td>PSA response</td>
<td>45 (P = .005)</td>
<td>48 (P &lt; .001)</td>
<td>32%</td>
</tr>
<tr>
<td>QOL response (FACT-P)</td>
<td>22 (P = .009)</td>
<td>23 (P = .005)</td>
<td>13</td>
</tr>
<tr>
<td>Objective response</td>
<td>12</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>
Cabazitaxel vs Mitoxantrone for mCRPC Progressing After Docetaxel

**Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone Prednisone</th>
<th>Cabazitaxel Prednisone</th>
<th>HR; P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>377</td>
<td>378</td>
<td></td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>12.7</td>
<td>15.1</td>
<td>0.70; &lt;.0001</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>1.4</td>
<td>2.8</td>
<td>0.74; &lt;.0001</td>
</tr>
</tbody>
</table>

Sequencing Treatments in CRPC*

**ONE APPROACH**

- Sipuleucel-T in selected patients
- Enzalutamide or Abiraterone
- Docetaxel
- Abiraterone or Enzalutamide
- Cabazitaxel
- Radium-223

*There is a range of views on how to sequence these agents

Role of agents without a proven survival benefit
i.e. 1st generation AR antagonists, ketoconazole and mitoxantrone unclear. Rarely used today at our center.
Personalizing CRPC Therapy Today: Examples

- **Clinical features of disease presentation**
  - Sites of disease (bone predominant vs visceral)
  - Pace of disease
  - Presence or absence of significant symptoms

- **Patient health status**
  - Performance status
  - Co-morbidities relevant to tolerability of treatment

- **Therapy history**
  - Prior enzalutamide or abiraterone
  - Prior chemotherapy

- **Tumor histology**
  - Small cell carcinoma
  - Neuroendocrine/anaplastic

- **Molecular features?**
NONMETASTATIC CRPC: NEW RESULTS
Natural History of Non-Metastatic CRPC: Time to Bone Metastasis or Death

Eligibility
- nmCRPC
  - Pelvic nodes < 2 cm below iliac bifurcation (N1) allowed
  - PSADT ≤ 10 months

On-Study Requirement
- Continuous ADT

Stratifications
- PSADT > 6 mo or ≤ 6 mo
- Bone-sparing agents, y/n
- N0 or N1

Randomization
2:1 (N = 1207)

A palutamide (APA)
240 mg QD + ADT
(n = 806)

Placebo (PBO) + ADT
(n = 401)

Metastasis-free survival (primary end point)

Second Rx at MD's discretion including open-label ABI/PRED

2nd progression-free survival (PFS2)

NCT01946204

ABI/PRED, abiraterone acetate plus prednisone; nmCRPC, nonmetastatic castration-resistant prostate cancer; MFS, metastasis-free survival.

Presented by: Eric Small, MD, FASCO
Primary End Point: Metastasis-Free Survival
72% risk reduction of distant progression or death

HR, 0.28 (95% CI, 0.23-0.35)  
\( P < 0.0001 \)

Presented by: Eric Small, MD, FASCO
Secondary End Point: Overall Survival
30% risk reduction of death

[Graph showing overall survival data with Kaplan-Meier curves for APA and PBO.]

HR, 0.70 (95% CI, 0.47-1.04)
P = 0.07

104 events/427 target events = 24%

Presented by: Eric Small, MD, FASCO
## Results:
### Treatment Associated Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>APA (n = 803)</th>
<th>PBO (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Gr 3/4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Rash</td>
<td>23.8%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>16.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15.9%</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>15.6%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Fracture</td>
<td>11.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.1%</td>
<td>0</td>
</tr>
<tr>
<td>Seizure</td>
<td>0.2%</td>
<td>0</td>
</tr>
</tbody>
</table>

Presented by: Eric Small, MD, FASCO
PROSPER: Enzalutamide in Non-Metastatic CRPC

N = 1,560
- Non-metastatic CRPC
- Stratifications:
  - PSADT < or > 6 months
  - Baseline use of bone-targeting agent

- Primary endpoint: metastases-free survival
- Secondary endpoints:
  - OS
  - Time to pain progression, opiate use, chemo use, new antineoplastic use
  - PSA progression
  - PSA response rate
  - QoL

- Design: Multinational, phase 3, randomized, double-blind study

Primary Endpoint: MFS

- Median MFS was ≈ 22 months longer with enzalutamide than with placebo (71% reduction in relative risk of radiographic progression or death)

Abbreviations:
CI, confidence interval; ENZA, enzalutamide; NR, not reached; PBO, placebo.
Overall Survival: First Interim Analysis

- Median follow-up time was ≈ 22 months for each treatment arm
- There was a 20% reduction in the relative risk of death with enzalutamide vs placebo
Conclusions and questions

- M0 CRPC represents an asymptomatic disease entity with a variable prognosis
  - PSA kinetics predictive of the development of metastases
- Bone targeted approaches have disappointed
- Androgen receptor inhibitors now demonstrate benefit

- Difficult to distinguish between enzalutamide and apalutamide
  - Some toxicity differences perhaps
- Costs and toxicities of long term therapy a concern
- Can we treat intermittently or for a shorter period of time?
- Can we intensify therapy further and cure people?
Clinical Utility of Emerging Biomarkers

- DNA mismatch repair deficiency - “microsatellite instability”
  - Pembrolizumab clinically indicated regardless of tumor histology
- Allocation to investigational trials
  - DNA repair deficiency
    - Double stranded break repair defects
      - BRCA1, BRCA2, ATM, others
  - PI3K pathway
  - Raf kinases
  - AR defects
    - Amplification
    - Resistance mutations
    - Splice variants
      - AR-V7
Pembrolizumab in Enzalutamide-resistant Prostate Cancer

- Graff reported preliminary result of adding pembrolizumab while continuing enzalutamide in mCRPC patients (Oncotarget 2016 and ESMO 2016)

- Clinical activity was demonstrated by
  - 5 of 27 (19%) patients had a confirmed PSA response
    - 3 of 5 had measurable disease with at least a PR by radiographic assessment
  - 4 of 19 (21%) patients had stable disease > 6 months (range 34-64 weeks)

Not approved for prostate cancer in Japan or USA
Olaparib in DDR-Deficient CRPC
TOPARP-A Phase 2 Trial: OS

Overall Survival

P=0.05 by log-rank test

Biomarker-negative, median: 7.5 mo
Biomarker-positive, median: 13.8 mo

0.00 0.25 0.50 0.75 1.00
Proportion of Patients

Pritchard on germ line mutations: more common than previously thought, implications for care not yet worked out

Distribution of Germline Mutations

11.8% (82/692) with deleterious germline mutations in 16 DNA repair genes

59% (36/61) with avail. tumors had second allele affected by loss-of-function mutation or copy loss

Emerging biomarker driven therapy choices

• Double stranded DNA repair (homologous recombination) deficiency
  – PARP inhibitors and potentially platinum compounds
  – DNA mismatch repair deficiency (microsatellite instability)
    • PD-1 inhibitor immunotherapy

• Both strategies remain to be validated

• More to come as biomarkers are further studied
Advanced Prostate Cancer Clinical Trials

Hormone Naïve
- Non-Metastatic (BCR)
  - IRB 11268: Salvage RT +/- Enzalutamide
  - IRB 17717: Degarelix + abiraterone +/- apalutamide
- Metastatic (mHSPC)
  - IRB 16728: Docetaxel + apalutamide and abiraterone

Castrate Resistant
- Non-Metastatic (nmCRPC)
  - IRB 11227: CABENZ Enzalutamide + cabazitaxel
  - IRB 18231: CORT125281 (selective cortisol modulator) + enzalutamide
- Metastatic (mCRPC)
  - First Line
    - IRB 16093: KEYNOTE-199 Pembrolizumab added to enzalutamide
  - Second Line
    - IRB 17864: TRITON 3 DNA repair defect selected Rucaparib vs. docetaxel or abiraterone or enzalutamide
  - Chemotherapy
    - IRB 17864: Niraparib + Abiraterone
  - Post-Chemotherapy
    - IRB 18231: CORT125281 (selective cortisol modulator) + enzalutamide
  - Supportive Care
    - IRB 15944: Falls on enzalutamide
    - IRB 15921: Intense exercise for survival with mCRPC

Key
- Open for Enrollment
- In Development
New treatments on the horizon in 2018

Celestia (Tia) S. Higano, MD, FACP
Professor of Medicine
University of Washington and Fred Hutchinson Cancer Research Center
Overview

Selected new agents or combinations

“I-O”, Immuno-oncology

PSMA
- Imaging and therapy

Oligometastatic disease
- Systemic vs metastasis directed therapy
Selected new agents or combinations

PARP inhibitors

Combinations of FDA approved drugs
- Radium 223 + docetaxel (UW)
- Enzalutamide + cabazitaxel (OHSU, UW)
- Enzalutamide + pembrolizumab (OHSU, BC Ca)

Combinations of FDA approved and investigational drugs
- Enzalutamide + CC-115 (UW)
- Abiraterone + AZD-8186 (UW)
- Enzalutamide + BET inhibitor (OHSU)
- Abiraterone + niraparib (OHSU)
- Abiraterone + niraparib (BC Ca)
- Durvalumab +/- tremelimumab (BC Ca)
PARP inhibitors

Single strand DNA damage repair crew, BRCA1 and BRCA2

Double strand DNA damage repair crew, PARPs
  ◦ Good in healthy cells
  ◦ But, in cancer cells, PARPs can prevent death of cancer cells, especially if single strand DNA repair mechanism is deficient, e.g. loss of BRCA2

Inhibition of PARP can lead to cell death because of inability to repair DNA damage
## Selected PARP inhibitors

<table>
<thead>
<tr>
<th>PARPi</th>
<th>FDA approved</th>
<th>For tumor type</th>
<th>Prostate cancer trials</th>
</tr>
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<tbody>
<tr>
<td>olaparib</td>
<td>yes</td>
<td>ovarian, breast cancer with BRCA mutations</td>
<td>UW, OHSU, BC Ca</td>
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<tr>
<td>rucaparib</td>
<td>yes</td>
<td>ovarian</td>
<td>UW, OHSU,</td>
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<td>yes</td>
<td>ovarian</td>
<td>UW, OHSU, BC Ca</td>
</tr>
<tr>
<td>talazoparib</td>
<td>no</td>
<td></td>
<td>UW</td>
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</table>

Most of these clinical trials require that there be evidence of a DNA repair gene mutation such as BRCA1, BRCA2, ATM, etc.
Docetaxel and radium 223, DORA

Docetaxel was the first chemotherapy to improve survival in mCRPC, 2004

Radium 223 improves survival in mCRPC with bone metastases, 2013

Figure 3. Radiation travelling through human tissue
Immuno-oncology at UW

eFT508
VBIR
ES-414

OHSU and BC Cancer both have other ongoing immunotherapy trials
eFT508

- Potent, oral, highly selective, small molecule inhibitor of MNK1 and MNK2 activity
- MNK controls key regulators of the anti-tumor immune response
- eFT508 modulates anti-tumor immunity and effectively synergizes with immune checkpoint blockade in the laboratory
- Phase 2 study in prostate cancer
VBIR (Vaccine Based Immune Response)

Anti-tumor antigens in vaccine
- PSA (correlates with high Gleason score)
- PSCA (on >90% bone mets)
- PSMA (on > 80% lymph node mets)

Uses adenoviral vector to induce T cells

Tremilimumab is a subcutaneous anti-CTLA4 to expand T cells against the 3 antigens

Sunitinib maintains the T cell response
ES-414

- Bispecific antibody that binds PSMA and CD3
- Redirects T cells to kill PSMA-expressing tumor cells
Prostate Specific Membrane Antigen, PSMA

Present on the surface of 90-95% prostate cancer cells, but wide variation in how much is on the surface of each cell

Transports nutrients (or other agents that bind to it) into the cell

Promising target for imaging ($^{68}$Gallium) or for treatment ($^{177}$Lutetium or $^{225}$Actinium)

Also present in kidneys, salivary glands, tear glands, small intestines

$^{177}$Lu trials will be opening at BC Cancer, OHSU, UW
PSMA distribution in a volunteer

- Kidneys
- Salivary and tear glands
- Small intestine
Toxicities of PSMA targeted $^{177}$Lu therapy

Usually low grade
- 30% dry mouth
- Fatigue 25%
- Nausea 24-48 hr after dose 10%

Low blood counts are most common serious side effect
What is known so far in terms of outcomes?

No data from prospective trials

593 patients reported in 11 retrospective analyses, largest 145, median 31

- PSA decline of ≥50% in 30-70%
- CT scan shrinkage 11-40%

Up to 1/3 of patients do not respond, possibly due to different amounts of PSMA on tumor cells

- Low platelet count and pain are poor prognostic factors
- Bone metastases may not respond as well as soft tissue lesions in lymph nodes and liver or lung

Some responses can be impressive

Ferdinaandus et al, Urology 2018
PSMA targeted alpha emitters (\(^{225}\text{Actinium}\)) as 9\textsuperscript{th} line treatment
“Oligo” is from the Greek word meaning “few” or “little”

Clinical trials define it as 1, 3, or 5 metastatic lesions

Can occur in hormone sensitive or castration resistant disease

Can be defined by:
- routine imaging: bone scan and CT scan of CAP
- molecular imaging: \(^{11}\)C-choline or \(^{-}\)acetate PET scans, Ga-PSMA PET/CT or MRI, \(^{18}\)F-fluciclovine PET (Axumin®)
Approaches to oligometastatic disease

Systemic therapy
- Hormonal therapy (ADT), chemotherapy (docetaxel, cabazitaxel), abiraterone, enzalutamide

“Metastases directed therapy”, MDT
- Surgery
- Radiation therapy
- Stereotactic body radiation therapy
Goals of MTD

To delay use of ADT in hormone sensitive disease, usually biochemical relapse or BCR

To delay systemic treatments for:
- Non-metastatic CRPC (apalutamide, enzalutamide)
- Metastatic CRPC (docetaxel, cabazitaxel, abiraterone, enzalutamide, radium)

To prolong survival?

Most data reported for MDT is retrospective but proper prospective trials are planned or in progress at all 3 institutions
Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

Piet Ost, Dries Reynders, Karel Decaestecker, Valérie Fonteyne, Nicolaas Lumen, Aurélie De Bruycker, Bieke Lambert, Louke Delruel, Renée Bultijnck, Tom Claey, Els Goetzheber, Geert Villeirs, Kathia De Man, Filip Ameye, Ignace Billiet, Steven Jonniau, Friedi Vanhaverbeke, and Gert De Meerleer

![Graph showing survival rates and biochemical recurrence-free survival rates for ADT-free survival and MDT with corresponding time periods and hazard ratios.](image-url)
Complete PSA Response Following Stereotactic Ablative Radiotherapy for a Bony Metastasis in the Setting of Castrate-Resistant Prostate Cancer

ADT then dutasteride vs placebo

gefitinib
Take Home Messages

“There’s nothing new under the sun.”, Solomon, Book of Ecclesiastes 1:9

Interpretation: Innovations do not amount to a change in the world or human nature

Yes, but what about the many new treatments that impact the individual prostate cancer patient, his partner and family?

There will always be something new under the sun but to prove that a new innovation is truly beneficial, we must conduct prospective clinical trials. Please consider enrolling on a trial if available!!

Clinicaltrials.gov