Precision Oncology for Veterans with Prostate Cancer: Who, What, How, and Why

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Univ Washington
Conflicts and Off Label Uses

Research support in the last 2 years from; Janssen Oncology, AstraZeneca, Clovis, Beigene, Essa, Astellas

Off label uses: Off label use of PARP inhibitors and platinum agents to treat prostate cancer will be discussed
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<th>The scope of prostate cancer in the VA</th>
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<td>Precision Oncology.</td>
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<td>What is it and how is it relevant to prostate cancer?</td>
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<td>What are the targets in prostate cancer?</td>
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<td>“How”</td>
<td>How do you approach instituting a system that could be implemented across the VA?</td>
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“Who” – A Veteran With Prostate Cancer

Prostate Specific Ag (PSA)

Docetaxel x 3
Doc/Carbo
Doc/Carbo
Mito x 5
DC x 6
“Who” – Cancer In Veterans

- 50,000 Veterans diagnosed with and treated for cancer annually
- Veterans account for 3.5% of all cancer cases in the U.S
- Prostate cancer is the most common cancer in veterans

Zullig and Kelley, Military Medicine, 2017.
“Who” – Prostate Cancer In Veterans

“Who” – Prostate Cancer In Veterans

“What” Is Precision Oncology?

“Identifying treatment based on a biomarker which reflects biology and targeting that biology to optimize efficacy and minimize toxicity”

The most effective therapy with the fewest side effects

Success;

- CD20 (Rituxan), HER2 (Herceptin), BCR-ABL (imatinib), mismatch repair deficiency (pembrolizumab)...
- 150 indications for targeted therapy in 28 different tumors

The therapeutic landscape of targeted therapy for adenocarcinoma of the lung, circa 2006
Success In Precision Oncology
Carcinoma of Lung

**Key**
1 - Phase I
2 - Phase II
3 - Phase III
4 - Approved

**EGFR Sensitizing**
- Gefitinib 4
- Erlotinib 4
- Afatinib 4
- Osimertinib 4
- Necitumumab 4
- Rociletinib 3

**ALK**
- Crizotinib 4
- Alectinib 4
- Ceritinib 4
- Lorlatinib 2
- Brigatinib 2

**MET**
- Crizotinib 2
- Cabozantinib 2

**HER2**
- Trastuzumab emtansine 2
- Afatinib 2
- Dacomitinib 2

**ROS1**
- Crizotinib 4
- Cabozantinib 2
- Ceritinib 2
- Lorlatinib 2
- DS-6051b 1

**BRAF**
- Vemurafenib 2
- Dabrafenib 2

**RET**
- Cabozantinib 2
- Alectinib 2
- Apatinib 2
- Vandetanib 2
- Ponatinib 2
- Lenvatinib 2

**PIK3CA**
- LY3023414 2
- PQR 309 1

**MEK1**
- Trametinib 2
- Selumetinib 3
- Cobimetinib 1

**Unknown Oncogenic Driver Detected**
- 31%

**Other 4%**
- EGFR

**Detected**
- 7%

**Unknown**
- 25%

**Detected**
- 31%

**> 1 Mutation 3%**

**HER2 2%**

**ROS1 2%**

**BRAF 2%**

**RET 2%**

**NTRK1 1%**

**PIK3CA 1%**

**MEK1 <1%**

Frances Shepherd - 2019 ASCO Annual Meeting
Why Do Patients Have Such Diverse Outcomes?

Docetaxel chemotherapy

Survival after therapy
Resource

Integrative Clinical Genomics of Advanced Prostate Cancer

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and Arul M. Chinnaiyan 1,2,17,18,42,44,*
Precision Oncology: Prostate Cancer

VERY COMMON

COMMON

RARER
• DNA repair deficiency is present in > 20% of metastatic, resistant prostate cancer
• In the first cohort, half of the patients had inherited the DNA repair deficiency
• DNA repair deficiency is immediately targetable
Frequency of an Inherited Reason for Metastatic Prostate Cancer

Figure 2. Distribution of Presumed Pathogenic Germline Mutations.
Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.
Precision Oncology In Prostate Cancer

Prostate cancer 2014

- BRCA1/BRCA2 5%
- Untargetable 95%

Prostate cancer 2020

- PTEN, 40%
- RB1, 10%
- PI3K pathway, 14%
- BRCA2, 13%
- ATM, 6%
- CDK12, 7%
- MMR, 4%
- RAF fusions, 5%
- Brca1, 1%
- Untargetable 50%

- Platinum
- Olaparib
- Niraparib
- Rucaparib
- Pembrolizumab
- Nivolumab
- Trametinib
- Dabrafenib
“Who” – A Veteran with Prostate Cancer

Prostate Specific Ag (PSA)

Docetaxel x 3
Doc/Carbo

Primary biopsy = BRCA2 biallelic copy loss
**Gene Mutation(s)**

**PALB2**
- c.1032 1033 dup FS
- COPY LOSS

**Prior therapy (outside)**
- Docetaxel
- Cabazitaxel
- Thalidomide
- abiraterone
everalutamide

**Clinical Bx**
- Provenge
- mitoxantrone
- docetaxel + carboplatin

**Graphical Representation**

- Precision oncology – BRCA+ Prostate Cancer

- Gene: **PALB2**
  - Mutation(s): c.1032 1033 dup FS, COPY LOSS
  - Status: Germline
The Impact of DNA Sequencing

Androgen Deprivation
Bicalutamide
Sequencing - loss of BRCA2

Carbo/Doc x 9
Carbo/Doc x 8

PCF.org/vets
Sequencing – mismatch repair deficiency

The benefits of immunotherapy in the right veteran
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

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Docetaxel chemotherapy

Survival after therapy
Precision Oncology
Personalized Medicine

DNA sequencing

Mismatch repair deficiency
BRCA2, PALB2
CDK12
How Do We Implement Precision – Culture

• “If you don’t look, you won’t find”
• How you look matters
• System wide access, standardized approaches
• Education
• Access to drugs
• Access to studies
• Leveraging VA data
“How” – A Nationwide Precision Oncology Program

DNA sequencing of tumor tissue for any veteran with incurable malignancy
Available to any VA clinical site which is interested in subscribing
The largest system-wide sequencing effort in any health care system in the U.S.
“How” – VA/PCF Network of Precision Oncology Centers

- **Manhattan, NY** – The John and Daria Barry Foundation Precision Oncology Center of Excellence at the VA Manhattan
- **Bronx, NY** – The Blavatnik Family Foundation Precision Oncology Center of Excellence at the VA Bronx
- **Durham, NC** – PCF Durham VA Center of Excellence
- **Ann Arbor, MI** – The Stewart J. Rahr Foundation Precision Oncology Center of Excellence at the VA Ann Arbor
- **Chicago, IL** – The Robert Frederick Smith Precision Oncology Center of Excellence at the VA Chicago
- **Minneapolis, MN** – Minneapolis VA Health Care System
- **Seattle, WA** – The Stephen J. Cloobeck Precision Oncology Center of Excellence at the VA Puget Sound
- **Portland, OR** – VA Portland Health Care System
- **San Francisco, CA** – San Francisco VA Health Care System
- **Los Angeles, CA** – The Michael and Lori Milken Family Foundation Precision Oncology Center of Excellence at the West Los Angeles VA
- **Dallas, TX** – Dallas VA Medical Center
- **Houston, TX** – The Michael E. DeBakey Houston VA Medical Center
- **Philadelphia, PA** – PCF Philadelphia VA Center of Excellence
- **Washington, DC** – The Evans Foundation Precision Oncology Center of Excellence at the VA Washington, DC
- **Tampa, FL** – The John and Daria Barry Foundation Precision Oncology Center of Excellence at the VA Tampa
- **Orlando, FL** – Orlando VA Medical Center

ChooseVA

VA

U.S. Department of Veterans Affairs
“How” Do We Look

- Germline testing – DNA sequencing of normal DNA to look for inherited defective genes predispose to cancer (e.g. BRCA, Lynch)

- Genetic/genomic/somatic testing – DNA sequencing of tumor DNA to look for tumor specific alterations. Tumor biopsies or circulating tumor DNA (e.g. BRCA, tumor only mismatch repair deficiency)

- Others – analysis of RNA or protein expression is not as consistent or as targetable as DNA alterations at the moment
How Do We Give Access to Research Prostate cancer Analysis for Therapy Choice “PATCH”

Julie Graff, M.D. Portland VAMC & POPCAP investigators
Phase II study to compare the efficacy of carboplatin followed by docetaxel versus docetaxel followed carboplatin: BRACeD: BRcA deficient prostate cancer treated with Carboplatin or Docetaxel

- University of Washington/FHCRC
- VA Puget Sound
- VA Greater LA
- VA Ann Arbor
- VA Bronx
- VA Manhattan
- Jesse Brown VA Chicago

VA CSR&D
A single-arm, open-label, phase II study of CHeckpoint inhibitors in men with progressive Metastatic castrate resistant Prostate cancer characterized by a mismatch repair deficiency or biallelic CDK12 inactivation. (CHOMP)

### Inclusion Criteria
- Progressive mCRPC with at least prior abiraterone and/or enzalutamide
- Metastatic lesion suitable for biopsy
- dMMR or CDK12-/- status via OncoPlex seq of biopsy or ct DNA
- ECOG 0-2
- Adequate organ function

### Protocol Outline

<table>
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<tr>
<th>Determination of dMMR and CKD12 status</th>
<th>Biopsies Blood (ct DNA)</th>
<th>At progression</th>
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<tr>
<td>GNRH</td>
<td>Pembrolizumab q3 weeks</td>
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### Treatments During Study Period
- anti PD-1 Pembrolizumab 200 mg IV every 3 weeks until disease progression or unacceptable toxicity
- GnRH analog to maintain T < 50 ng/dL

### Endpoints
- **Primary:** Composite of objective response rate (iRECIST), or radiographic progression free survival at 6 months, or PSA50 ≥ 12 weeks after treatment initiation
- **Secondary:** time to PSA progression, maximal PSA response, time to initiation of alternative anti-neoplastic therapy, time to radiographic progression, overall survival, safety/tolerability

### Statistics
N = 26 evaluable patients for 0.90 power and alpha of 0.05 to detect a 50% response rate. Total study N = 30.

Matt Rettig, VA CSR&D
How Do We Test for Inherited Prostate Cancer

Establishing Infrastructure for Pilot Project

- Identification of 20 sites for germline testing of 600 men with metastatic prostate cancer (complete)
- Generation of MOU for 20 sites (VAPSHCS and Salt Lake City (GMS))
- Placement of IFC at sites and intake as VAPSHCS (IT)
- Purchase 500 saliva kits VAPSHCS
- Establish tracking system for kit distribution and result receipt
- Distribute standard germline testing consent for use as templated note at all sites

Pilot initiation: Expect duration of pilot 2 years

- Entry of order for "Germline testing of veteran with metastatic prostate cancer"
- VAPSHCS review of EMR to establish presence of documented discussion and diagnosis of metastatic prostate cancer

Mailout saliva test kit to patient and initiation of tracking

- Kit received at vendor. Result communicated to VAPSHCS and ordering provider
- If kit not received at vendor at six weeks, provider notified – provider or VAPSHCS contacts patient
- Positive test – post test counseling VAPSHCS or GMS or referral for local genetic counseling (Provider preference). Provider and patient notified of clinical studies available in VA or academic medical center

Negatives test – provider provides result to patient, counsels that no testing of FDR next

- Nationwide germline testing of men with metastatic prostate cancer with referral to VA centers participating in Precision Oncology Clinical studies
- Implement IFC entry to all VA Medical Centers with testing center either at VA Puget Sound or GMS. Post-test counseling virtually distributed (Seattle and Salt Lake)

Study completion Metric – Comparison of number of veterans tested per unit time

Montgomery, Ball, Lynch
Returning clinically actionable results to MVP participants with metastatic prostate cancer: a pilot study

Montgomery, Lynch, Pritchard, Cheng, Meeks
Why Do We Test

<table>
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<tr>
<th>Risk group</th>
<th>Clinical/pathologic features</th>
<th>Germline testing</th>
<th>Molecular and biomarker analysis of tumor</th>
<th>Initial therapy</th>
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<tr>
<td>Regional</td>
<td>Any T, N1, M0</td>
<td>Recommended&lt;sup&gt;c,k&lt;/sup&gt;</td>
<td>Consider tumor testing for homologous recombination gene mutations and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR)&lt;sup&gt;dd,ee&lt;/sup&gt;</td>
<td>See PROS-10</td>
</tr>
<tr>
<td>Metastatic&lt;sup&gt;ff&lt;/sup&gt;</td>
<td>Any T, Any N, M1</td>
<td>Recommended&lt;sup&gt;c,k&lt;/sup&gt;</td>
<td>Consider tumor testing for homologous recombination gene mutations and for MSI or dMMR&lt;sup&gt;dd,ee&lt;/sup&gt;</td>
<td>See PROS-14</td>
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Why We Test

PROfound STUDY DESIGN

Key eligibility criteria
- mCRPC with disease progression on prior NHA, eg abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR*

Stratification factors
- Previous taxane
- Measurable disease

Cohort A:
- BRCA1, BRCA2 or ATM
- N=245

Cohort B:
- Other alterations
- N=142

2:1 randomization
- Open-label

Olaparib 300 mg bid
- n=162

Physician's choice‡
- n=83

Upon BICR progression, physician’s choice patients were allowed to cross over to olaparib

Primary Endpoint
- Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key Secondary Endpoints
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A
Primary endpoint

rPFS by BICR in patients with alterations in BRCA1, BRCA2, or ATM (COHORT A)

- **6-mo rate**: 59.76%
- **12-mo rate**: 28.11%

**Olaparib (N=162)**
- Events (%): 106 (65.4)
- Median rPFS (months): 7.39
- Hazard ratio (95% CI): 0.34 (0.25, 0.47)
- \( P < 0.0001 \)

**Physician's choice (N=83)**
- Events (%): 68 (81.9)
- Median rPFS (months): 3.55

**Hussain et al 2019**

Hussain et al 2019
Why We Test – Cascading Impact

~2 in 10 men with metastatic prostate cancer have mutation in "BRCA"

~1:10 men inherited the mutation

Siblings and children 50% chance inheriting same mutation

Precision therapy opportunities:
PARP inhibitors and platinum

SISTERS:
Tailored screening and risk-reduction

BROTHERS
↑risk of prostate cancer

DAUGHTERS
Tailored screening and risk-reduction

SONS
↑risk of prostate cancer

Heather H. Cheng
Why Do We Test

![Graph showing PSA levels and treatment options with labels for Doc/Carbo and Mito x 5 with DC x 6.]

![Table showing event rates and median rPFS with hazard ratio and p-value.]

- 6-mo rate: 59.76% vs 22.63%
- 12-mo rate: 28.11% vs 9.40%
- Median rPFS (months): 7.39 vs 3.55
- Hazard ratio (95% CI): 0.34 (0.25, 0.47)
- p-value: <0.0001

Go to PCF.org/vets for more information.
DNA Repair (BRCA1/2, ATM, etc.) \( 20\% \)
MMR / MSI \( 5\% \)
CDK12 \( 7\% \)

The challenge \( 70\% \)
Conclusions

• Improving precision oncology in lung and prostate cancer is the vision for the future in VA

• VA is the right health care system for precision oncology (EMR, largest care system in the US, standardized practice)

• VA data can inform care for veterans and their families

• VA can lead the way in research for men with prostate cancer

• All veterans with metastatic prostate cancer should undergo germline and somatic testing (mismatch repair, BRCA, PALB2)
Conclusions (for veterans)

- If you haven’t been screened for prostate cancer, discuss with your provider
- If you have prostate cancer, discuss this information with your doctor and if appropriate reach out to a VA/PCF network site
- If you know a veteran with prostate cancer, tell them about this initiative in VA
Conclusions (for all of us)

- Together we can make this effort successful and lead the nation in oncology care
Thank you