Translational Laboratory Research: How it Advances Care

Ryan Kopp, MD
Assistant Professor, Urology
Urologic Oncology, Portland VA Healthcare System

Biography:
Dr. Kopp is an Assistant Professor of urologic oncology at OHSU and Portland VA Medical Center. He specializes in treatment of urologic cancers, including kidney, testis, prostate, and bladder cancers. He has extensive training in laparoscopic, robotic and open surgery, including complex surgery for advanced cancers. Dr. Kopp has a focused interest in the early detection of prostate cancer, including integration of advanced imaging and molecular biomarkers to identify aggressive tumors.
Disclosures

• Investigator: Hoffman La Roche (Genentech), Merck Sharp & Dohme
• Discounted services: Seer Bio
• Special thanks Dr. Beer and Dr. Alumkal for slides
Outline

• Translational research defined
• Refresher on genetics
• The problem of advanced prostate cancer
• How we move forward
Types of research

**Basic research**
- **Goal**: provide fundamental knowledge
- Studying a disease process:
  - Why cancer develops
  - When does it become aggressive
  - How to target it in cell lines, animals in the laboratory
  - Example: How is the function and structure of DNA altered in prostate cancer?

**Clinical Research**
- **Goal**: evaluate patient outcomes
- Prevention, diagnosis, or treatment of disease
- Study safety and effectiveness:
  - Drug interventions
  - Devices: diagnostic, prognostic
  - Example: Is docetaxel chemotherapy safe and effective in metastatic prostate cancer
Types of research

**Translational research**

- **Goal:** To improve health outcomes
- **Studying observations from the lab and from the clinic or trials. Integrates information.**
  - Translate findings from “bench to bedside”
  - Create new therapies, procedures, or diagnostics
  - Discovery and clinical validation (early phase trials)
- **Translate findings from clinical trials to broader community**
  - Clinical implementation (late phase trials, clinical guidelines)
Translational Research Continuum

Basic Research

Early Phase Clinical Trials

Late Phase Clinical Trials

Clinical Implementation

Re-evaluation

Re-evaluation to investigate differences in health outcome
Translational research tools

• Clinical data
  – Patient Outcomes
  – Images (CT, MRI, PET scans)
  – Tissue histology/pathology
  – Clinical bloodwork (hemoglobin, calcium)

• Biospecimen (tissue, fluids) and molecular
  – DNA, RNA, protein
  – Cell lines and mouse models
  – Microscopy, tissue and molecular imaging
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
  – 1990-2003 by the National Institutes of Health
  – Determine the genetic code of DNA in a normal cell
    • “Rosetta stone” to decode DNA of diseases
  – Germline: DNA you are born with (may be altered)
  – Tumor: DNA acquires alterations or mutations

Rosetta stone connected Ancient Greek and Egyptian Languages
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
  - CATCATCH
    - 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-> CLOSETD
The Problem of Prostate Cancer

- 2nd most common cause of cancer death in men
- Many living with active prostate cancer who die of other causes
  - Symptoms from disease and treatments

ACS Cancer Facts & Figures 2018
What are Obstacles to Progress

• Prostate cancer is not just one disease
  – Identify lethal vs non-lethal tumors
• What DNA changes matter?
  – Distinguishing between what is abnormal and what is important
  – DNA only, or also RNA and protein?
• Why do drugs stop working?
  – Evolution
Primary prostate cancers are not all the same

- The Cancer Genome Atlas developed a map of prostate cancer
  - Significant variation within groups

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Germline DNA mutations among men with metastatic prostate cancer

- 84 of 692 men (11.8%) with germline mutations
- BRCA2 in 5.3% of men – also relatively more common mutation in tumors

Pritchard et al, NEJM 2016
Basic to translational research

• These studies provide fundamental knowledge

• How do we “translate” to improved patient outcomes?
  – Increase screening for germline mutations in men with metastatic prostate cancer
    • Impacts screening in family members
  – Search for “targetable” mutations in men with advanced disease
Personalizing Therapy

• 70 year old man with progressive prostate cancer
• Tumor resistant to nearly all approved therapies
• Hospice discussions
• Bone biopsy
  • Adenocarcinoma
  • BRCA2 gene mutation
Taking Advantage of *BRCA2* Mutations in Cancer
Personalizing Therapy

- Olaparib in metastatic castrate resistant prostate cancer (BRCA1/2 or ATM mutation)
  - FDA approved May 2020

De Bono, et al. NEJM 2020

Olaparib vs Control

36% reduced risk of death

Hazard ratio for death, 0.64 (95% CI, 0.43–0.97)
P=0.02
Significant reduction in bone disease on MRI, reduction in PSA level
Cancer Progression is Like Evolutionary Natural Selection

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
- Researchers at OHSU, collaborators throughout the Northwest and beyond
- Funding agencies
Current Management of Castration-Resistant Prostate Cancer

Tomasz M. Beer, MD
Professor of Medicine, Hematology & Medical Oncology
Deputy Director, OHSU Knight Cancer Institute

Biography:
Dr. Tomasz (Tom) Beer is a Professor of Medicine and Grover C. Bagby Endowed Chair for Prostate Cancer Research in the Division of Hematology & Medical Oncology, where he leads the Prostate Cancer Research Group, encompassing basic research, translational research, clinical trials of novel therapeutic strategies in prostate cancer, and studies aimed at enhancing cancer survivorship. He has authored or co-authored more than 200 peer reviewed articles on prostate cancer. Dr. Beer is particularly known for investigations of targeted therapies and immunotherapies in prostate cancer, including vitamin D receptor, the androgen receptor, and clustering targeting agents as well as cancer vaccines, CTLA-4 and PD-1 inhibitors, and others. He recently led the global randomized trial of enzalutamide vs placebo which demonstrated substantial improvements in overall and progression-free survival as well as quality of life and served as the basis for a global change in the standard of care for advanced prostate cancer. Dr. Beer serves as Deputy Director of the OHSU Knight Cancer institute, and NCI designated Comprehensive Cancer Center. He also serves as Chief Medical Officer for the Center for Early Detection Advanced Research within the Knight where he works closely with a diverse leadership team to speed advances in the early detection of lethal cancers. Dr. Beer cares for men with prostate cancer at OHSU and at the Portland VA Medical Center.
Disclosures

- Consultant for Arvinas, Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squib, Clovis Oncology, Novartis, Pfizer and Sanofi
- Stock holder for Arvinas and Salarius Pharmaceuticals
- Grant/research support from Alliance Foundation Trials, Astellas Pharma, Boehringer Ingelheim, Corcept Therapeutics, Endocyte Inc., Harpoon Therapeutics, Janssen Research & Development, Medivation, Sotio, Theraclone Sciences/OncoResponse and Zenith Epigenetics
Castration Resistant Prostate Cancer
What is New and what is important

• Non-metastatic CRPC
  – New data confirm survival advantage of early intervention
  – Multiple intervention options available
  – New imaging may upend the diagnosis

• Metastatic CRPC
  – Important:
    • Potent hormonal agents
    • Chemotherapy
    • Radium
  – New:
    • PARP Inhibitors
  – On the horizon
    • Lu-177-PSMA 617
Disease States in Prostate Cancer

Localized disease

Biochemical Recurrence

mHSPC

mCRPC L1

mCRPC L2

mCRPC L2+

Focus of today’s talk: therapy selection here

mHSPC, metastatic hormone sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; L, line of treatment.
NONMETASTATIC CRPC: NEW RESULTS
Natural History of Non-Metastatic CRPC: Time to Bone Metastasis or Death

**PSA**
- PSA <7.7 ng/mL
- PSA 7.7-24.0 ng/mL
- PSA >24.0 ng/mL

**PSADT**
- PSADT <6.3 months
- PSADT 6.3-8.8 months
- PSADT >18.8 months

Three similar drugs tested:

- Enzalutamide, Apalutamide, Darolutamide
- Metastases-free Survival and Overall Survival
Enzalutamide: 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 Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Median follow-up (months)</th>
<th>% died at time of OS analysis</th>
<th>Median OS (months)</th>
<th>OS HR (95% CI)</th>
<th>% Patients on Placebo who got active therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPER</td>
<td>47</td>
<td>31% / 38%</td>
<td>Not reached</td>
<td>0.73 (0.61-0.89)</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Estimated 67 / 56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAMIS</td>
<td>29</td>
<td>19% / 16%</td>
<td>Not estimated</td>
<td>0.69 (0.53-0.88)</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Estimated 74 / 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPARTAN</td>
<td>52</td>
<td>34% / 38%</td>
<td>Not reached</td>
<td>0.78 (0.64-0.96)</td>
<td>84%</td>
</tr>
</tbody>
</table>

**PROSPER**
- Median OS: Not reached
- OS HR: 0.73 (0.61-0.89)
- % Patients on Placebo who got active therapy: 84%

**ARAMIS**
- Median OS: Not estimated
- OS HR: 0.69 (0.53-0.88)
- % Patients on Placebo who got active therapy: 56%

**SPARTAN**
- Median OS: Not reached
- OS HR: 0.78 (0.64-0.96)
- % Patients on Placebo who got active therapy: 84%
# Selected Adverse Events in nmCRPC Studies of Enzalutamide and Darolutamide

Results from ARAMIS and PROSPER

<table>
<thead>
<tr>
<th></th>
<th>PROSPER</th>
<th>ARAMIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enzalutamide</td>
<td>Placebo</td>
</tr>
<tr>
<td>Any grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>33%</td>
<td>14%</td>
</tr>
<tr>
<td>Fall</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Mental Impairment</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Fatigue with darolutamidde not different from placebo when adjusted for duration of exposure

** Mental impairment for darolutamidde reported as the sum of cognitive disorder and memory impairment

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Does nmCRPC Still Exist, and Does it Matter?

- 200 patient retrospective study of PSMA-PET in nmCRPC
  - 98% had a detectable lesion
  - 55% distant metastases
  - 44% pelvis only
  - 29% oligo-metastatic
The Opportunity of Better Imaging

• Identify oligometastatic disease
  – Study metastases-directed strategies

• Monitor response to therapy
  – Identify site-specific heterogeneity of response
  – Investigate the biology of resistant disease sites

• Consider theranostic strategies that combine imaging with treatment

• Molecular imaging for treatment targets beyond PSMA
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

• Is this disease state going to diminish with increasingly sensitive imaging?

• Relatively similar MFS across studies
• Potential toxicity differences from enzalutamide:
  – Apalutamide
    • Thyroid dysfunction and rash
  – Daralutamide
    • Appears to have no increase in falls or cognitive function and little increase in fatigue and hypertension
    – Toxicity differences not confirmed
• 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?
METASTATIC CASTRATE RESISTANT DISEASE
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(^1)</td>
<td>2004</td>
<td>mCRPC</td>
<td>?</td>
<td>✓</td>
</tr>
<tr>
<td>Sipuleucel-T(^2)</td>
<td>2010</td>
<td>Asymptomatic or minimally symptomatic mCRPC</td>
<td>No</td>
<td>✓</td>
</tr>
<tr>
<td>Cabazitaxel(^3)</td>
<td>2010</td>
<td>Post-docetaxel mCRPC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Abiraterone(^4,5)</td>
<td>2011 and 2012</td>
<td>mCRPC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Enzalutamide(^6)</td>
<td>2012 and 2014</td>
<td>mCRPC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Radium-223(^7)</td>
<td>2013</td>
<td>Symptomatic bone predominant mCRPC</td>
<td>SSRE</td>
<td>✓</td>
</tr>
</tbody>
</table>

Long-term Survival from PREVAIL

Subsequent Therapy, no. (%)  

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ENZA (N=872)</th>
<th>PBO (N=845)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients taking ≥ 1 of the 6 subsequent therapies below</td>
<td>583 (66.9)</td>
<td>695 (82.2)</td>
</tr>
<tr>
<td>Abiraterone acetate</td>
<td>362 (41.5)</td>
<td>456 (54.0)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>151 (17.3)</td>
<td>210 (24.9)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>481 (55.2)</td>
<td>546 (64.6)</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>53 (6.1)</td>
<td>364 (43.1)</td>
</tr>
<tr>
<td>Radium-223</td>
<td>57 (6.5)</td>
<td>65 (7.7)</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>20 (2.3)</td>
<td>12 (1.4)</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.
NEW: PARP INHIBITORS
Integrative Landscape Analysis of Somatic and Germline Aberrations in Metastatic CRPC

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 available tumors had second allele affected by loss-of-function mutation or copy loss
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Olaparib in DDR-Deficient CRPC

TOPARP-A Phase 2 Trial: OS

Overall Survival

P = 0.05 by log-rank test

Biomarker-positive, median: 13.8 mo

Biomarker-negative, median: 7.5 mo

Lynparza Phase III PROfound trial in HRR* mutation-selected metastatic castration-resistant prostate cancer met primary endpoint

7 August 2019 07:00 BST

AstraZeneca and MSD’s Lynparza met the primary endpoint of significantly increasing the time patients selected for BRCA1/2 or ATM mutations live without radiographic disease progression vs. standard of care treatment
Kaplan–Meier Estimates of Imaging-Based Progression-free Survival and Interim Overall Survival.

**A** Imaging-Based Progression-free Survival in Cohort A

- **Olaparib**
  - Median mo: 7.4
  - Value at 6 mo: 0.60
  - Value at 12 mo: 0.28
  - Value at 21 mo: 0.09

- **Control**
  - Median mo: 3.6
  - Hazard ratio for progression or death: 0.34 (95% CI: 0.25–0.47)
  - P=0.001

**B** Interim Overall Survival in Cohort A

- **Olaparib**
  - Median mo: 18.5
  - Value at 6 mo: 0.91
  - Value at 12 mo: 0.73
  - Value at 18 mo: 0.56

- **Control**
  - Median mo: 15.1
  - Hazard ratio for progression or death: 0.64 (95% CI: 0.43–0.97)
  - P=0.02

**C** Imaging-Based Progression-free Survival in Cohorts A and B

- **Olaparib**
  - Median mo: 5.8
  - Value at 6 mo: 0.50
  - Value at 12 mo: 0.24

- **Control**
  - Median mo: 3.5
  - Value at 6 mo: 0.50
  - Value at 12 mo: 0.22

Hazard ratio for progression or death: 0.49 (95% CI: 0.38–0.63)

P<0.001

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# The Mutation Matters

## PFS in the PROFound Trial by Gene Alteration

<table>
<thead>
<tr>
<th>Gene</th>
<th>PFS Olaparib</th>
<th>PFS Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>10.84 (91.7, 13.08)</td>
<td>3.48 (1.74, 3.65)</td>
</tr>
<tr>
<td>CDK12</td>
<td>5.09 (3.61, 5.52)</td>
<td>2.20 (1.71, 4.83)</td>
</tr>
<tr>
<td>ATM</td>
<td>5.36 (3.61, 6.21)</td>
<td>4.70 (1.84, 7.26)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>2.07 (1.38, 5.52)</td>
<td>1.81 (1.71, 3.71)</td>
</tr>
<tr>
<td>CHEK2</td>
<td>5.59 (1.64, 11.99)</td>
<td>3.35 (1.38, NR)</td>
</tr>
<tr>
<td>PPP2R2A</td>
<td>2.69 (1.77, 3.91)</td>
<td>NR</td>
</tr>
<tr>
<td>RAD51B</td>
<td>10.89 (1.61, 14.75)</td>
<td>1.77</td>
</tr>
<tr>
<td>RAD54L</td>
<td>7.20 (3.71, 7.39)</td>
<td>2.41 (1.81, 3.02)</td>
</tr>
</tbody>
</table>

## PSA and Objective Response to Olaparib by Gene Classification in the TOPARP-B Trial

<table>
<thead>
<tr>
<th>Gene Group</th>
<th>BRCA 1 &amp; 2</th>
<th>ATM</th>
<th>CDK12</th>
<th>PALB2</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA/Objective Response</td>
<td>80%</td>
<td>10.4%</td>
<td>0</td>
<td>57.1%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Conclusions – PARP Inhibitors

• Two agents currently approved
• About 20% of patients may harbor a qualifying mutation
  – Half of these are inherited and can be detected in the blood
  – Half are cancer specific
    • May be detectable in the blood but may require a sample of tumor
• Not all mutations are associated with really good response
  – BRCA2 stands out
• Side effects remain a consideration, including a rare risk of myelodysplastic syndrome/leukemia
ON THE HORIZON:
TARGETING PSMA
PSMA

THANK YOU

OHSU KNIGHT CANCER INSTITUTE
PROSTATE CANCER RESEARCH PROGRAM
Promising New Treatments on the Horizon

Celestia (Tia) S. Higano, MD, FACP
Affiliate Professor
Department of Urologic Sciences
University of British Columbia
Vancouver, BC CANADA

Biography:
Celestia (Tia) S. Higano, MD, FACP, was a Professor in the Departments of Medicine and Urology, Division of Medical Oncology at the University of Washington and a Member of the Clinical Division of Fred Hutchison Cancer Research Center. She is an adjunct Professor in the Department of Urologic Sciences at the University of British Columbia and Medical Director of the Prostate Cancer Supportive Care Program at the Vancouver Prostate Centre. She recently retired from the University of Washington and plans to continue her practice in Seattle.

Dr. Higano received her medical degree from University of Massachusetts Medical School and completed her residency at the Mayo Graduate School of Medicine in Rochester, MN. She was an oncology fellow under E. Donnall Thomas and Robert B. Livingston at the Fred Hutchison and University of Washington.

Dr. Higano is a practicing oncologist, an internationally renowned expert and clinical researcher focusing on prostate cancer. At UW, she led the prostate cancer clinical research group that participated in the development of agents such as zoledronic acid, sipuleucel-T, enzalutamide, apalutamide, abiraterone, radium 223. Over these years, her clinical research has impacted the standards of care for patients with prostate cancer. She is also an educator and mentor and has guided the career development of many fellows and young faculty at the University of Washington and others outside of her institution who have chosen an academic career in GU Oncology.
Disclosures

- **Institutional research funding**: Aptevo, Aragon, Astellas, AstraZeneca, Clovis, Dendreon, eFFECTOR Therapeutics, Emergent, Ferring, Genentech, Hoffman-Laroche, Medivation, Pfizer

- **Consulting, scientific advisory boards**: Astellas, Bayer, Blue Earth Diagnostics, Clovis, Dendreon, Ferring, Hinova, Janssen, Merck, Orion, Pfizer, Tolmar, Carrick Therapeutics, Novartis, Genentech

- **Other**: spouse holds stock and former officer of CTI Biopharma
Goals of talk

• To understand the importance of genetic testing
• To learn what “actionable targets” in 2020 have an impact of therapy choice and new research approaches
  - DNA repair defects
  - MSI-high
  - TMB-high
  - PTEN loss
• Lu-PSMA therapy and future trials
What are “actionable targets”, where and how do we find them?

- An “actionable target” is a mutation present in some tumors that a new drug is designed to target.
- The presence of an “actionable target” may guide the therapeutic decision if the drug is effective.

<table>
<thead>
<tr>
<th></th>
<th>Germline Mutations</th>
<th>Somatic Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starts in:</td>
<td>Germ cells (egg, sperm)</td>
<td>Cancer cells arising from specific tissue</td>
</tr>
<tr>
<td>Present in:</td>
<td>All cells in the body including cancer cells</td>
<td>Cancer cells only</td>
</tr>
<tr>
<td>Inherited?:</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

Which patients should be tested for germline mutations?

• Men with prostate cancer, even if no family history, and:
  • Intermediate- or high-risk localized prostate cancer
  • Biochemical relapse
  • Metastatic prostate cancer (GENTleMEN study, www.gentlemenstudy.org)
  • Those with intraductal/cribiform pathology

• Those with a positive family history for cancer regardless of stage of disease

• Those with known “DNA damage repair” mutations in family member (eg, BRCA2)
How do you test for germline mutations?

• Saliva or blood

• Examples of commercial tests available: Ambry, Color Genomics, Foundation One, Invitae, Myriad (not “23 and me”, etc)

• Results back in 2-4 weeks

• Test results and interpretation:
  - “Negative”- 85-90%, means no known pathogenic mutations found
  - “Positive”- 10-15%, means there is a risk of inheritable cancer and patient should be referred for genetic counseling, “cascade” testing of family members
  - “VUS” stands for variant of unknown clinical significance: treat as negative until further information is available
How are DNA mutations in tumor found?

• “Archival” tissue such as prostate biopsy or surgery specimen
• Biopsy of “fresh” tumor tissue such as lymph node, liver or lung, bone
• Liquid “biopsy” of circulating tumor DNA in blood
  • Guardant360, Foundation One, examples of commercial tests available
Why is it important to understand genetic changes in 2020?

The drugs that are FDA approved* to treat specific “actionable targets” are not ordinarily used to treat “run of the mill” prostate cancer

- DNA damage repair mutations
  - PARP inhibitors: olaparib, rucaparib*
  - Platinum chemotherapy: carboplatin
- MSI-high
  - PD1 inhibitors: pembrolizumab*
- TMB-high
  - Pembrolizumab FDA approved June 2020*
- PTEN loss (no drugs approved for prostate cancer yet)
  - PI3K inhibitors: ipatasertib, others
DNA damage repair mutations

- DNA repair pathways protect our cells from daily damage to DNA
- If there is a **germline** mutation of the repair pathway such as *BRCA2*, there is a predisposition to cancer.
- These mutations can arise in the cancer cells over time, either independently or in addition to a germline mutation.

![BRCA2 Family Pedigree](image-url)
PARP inhibitors are active against tumors with DNA damage repair mutations

- Olaparib, rucaparib already FDA approved
- Other PARP inhibitors in clinical trials
  - Niraparib
  - Talazoparib
  - Veliparib
- May have different activity, may be more potent
- May have different side effect profile
- Combination studies with other agents may demonstrate further benefit
Microsatellite instability, “MSI”

• “MSI-high” indicates a high level of DNA mismatch repair.

• In prostate cancer, it is not common, 3-6%

• In 2017 the FDA approved pembrolizumab for any tumor type that showed MSI-h in patients who had exhausted standard treatments

• Pembolizumab is an anti-PD-1 antibody that has effects on immune T cells

• Other PD-1 inhibitors include:
  • Atezolizumab (Tecentriq®)
  • Avelumab (Bavencio®)
  • Cemiplimab (Libtayo®)
  • Durvalumab (Imfinzi®)
  • Pembrolizumab (Keytruda®)
  • Nivolumab (Opdivo®)
Keynote 199 phase 2 study of pembrolizumab in mCRPC patients

Pembrolizumab alone has anti-tumor activity in heavily pretreated men with mCRPC

Antonarakis et al JCO 2019
Studies of **PD-1 inhibitors** in combination with other drugs

- **KEYNOTE-921**: Docetaxel +/- **pembro** in prior ARSI setting (n=1000)
- **KEYLYNK-010**: Olaparib + **pembro** vs. second line ARSI (n=780, 2:1)
- Keynote 641: Enza +/- **pembro** (n=1200) (first or second line)
- **KEYNOTE-991**: ADT/Enza +/- **pembro** (n=1232) in mHSPC setting
- **CheckMate-7DX**: ADT/Docetaxel +/- **nivolumab** (n=984)
Ongoing phase 3 combination PD-1 inhibitor trial

- Cabozantinib and atezolizumab
- Phase 2 study of 44 heavily pretreated patients who received this combination showed promising activity
- This combination now in a phase 3 trial with results due in 2021

Cabozantinib alone
Tumor mutational burden, TMB

- If mutational burden is greater than 10%, then tumor is considered “TMB-high”
- TMB-h is also uncommon in prostate cancer, 3%
- June 2020, FDA approved pembrolizumab for prostate cancer with TMB-h
PTEN loss and PI3K pathway activation

• The PI3K/AKT pathway is overactive in 40-50% of prostate cancer patients and results in increased cancer cell turnover
• PTEN ordinarily puts a break on this pathway
• Loss of PTEN means cancer cells multiply unchecked,
  • 40% of prostate cancer patients
• Drugs that inhibit the PI3K pathway have not been active alone, the combination of abiraterone and a PI3K inhibitor, ipatisertib, was effective in those with loss of PTEN with improved median survival compared to abiraterone alone
• Phase 3 trial overall survival results are imminent
PSMA Targeted Therapy

PSMA is expressed on many prostate cancer cells

Can be used as a target for drug delivery

Attachment of a radioactive particle delivers radiation directly to PSMA on tumor cells
Lu-PSMA Trial, n=30

- Tumors must have PSMA target as measured on PSMA PET/CT
- Tumor must not have a lot of cells that do not have PSMA target as measured by FDG PET
- 57% had a PSA$^{50}$ decline
- 29% had complete response on scans
- 53% had partial response on scans
- 41% progressed within 3 months of stopping therapy
- Median overall survival 13.5 mo

Hofman et al, Lancet Oncol 2018
Vision Phase 3 Trial

- Enrollment of 1180 patients completed September 2020
- Results are anticipated in 2021
TheraP ANZUP 1603 Phase 2 Trial, n=200

- Compares cabazitaxel to Lu-PSMA
- $\text{PSA}^{50}$ responses better for Lu-PSMA arm
- Overall, toxicities were greater with cabazitaxel than Lu-PSMA
- Lu-PSMA had more dry mouth and dry eyes, more low platelet counts
- Overall survival results are pending
Take Home Messages

- Identification of actionable mutations can open up treatment options for men with prostate cancer
  - *BRCA* and other DNA repair genes (28%)
  - MSI-h (3-6%)
  - TMB-h (3%)

- Much of current research is combining drugs with known benefit with targeted agents

- Targets that still require demonstration of survival benefit
  - PSMA
  - Loss of PTEN (40%)
  - Others

- Consider participation in a clinical trial, clinicaltrials.gov
On-going research-Vancouver, BC

BRCA2

Abiraterone +/- niraparib (PARPi)

Targeted therapy

PC BETS: ctDNA “liquid biopsy” directed therapy*

ADT + abiraterone +/- AKT inhibitor for PTEN deficient (mHSPC)

PSMA

Bispecific antibody to CD3-PSMA

BITE to CD3 and PSMA

KEYLYNK Pembrolizumab + olaparib vs abiraterone or enzalutamide
On-going trials for mCRPC at UW/SCCA

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Thank you for your attention

Stay safe, wear a mask, stay away from crowds and practice good hand hygiene!

Stay out of the smoke!