Prostate Cancer Clinical Genomics
6th annual Knight Cancer Network Symposium

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March 18, 2022
Disclosures

• Lantheus (Consulting)
Learning Objectives

• Background
• Who To Test
• Why Test
  – Informs treatment
    • PARP inhibitor
    • Platinum chemotherapy
    • Immune checkpoint inhibitor
    • Clinical trials
  – Informs prognosis
  – May inform family cancer risks
• Take Home Points
Mutations in Metastatic Prostate Cancer

Actionable mutations: 133/150 pts (89%)
Mutations in Metastatic Prostate Cancer

Actionable mutations: 133/150 pts (89%)

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

12% with metastatic prostate cancer vs 5% with localized prostate cancer vs 3% without a known cancer diagnosis

Cancer Genome Atlas prostate cancer study
Exome Aggregation Consortium
Types of Genetic Testing

**Somatic/Tumor**
- tests tumor DNA
  - Tumor tissue
  - ctDNA

**Germline**
- tests DNA patient is born with
  - Saliva
  - Blood
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• **Why Test**
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• **Take Home Points**
Germline Testing—Who to Refer

- Everyone who meets family history criteria
- Consider if intraductal/cribriform histology
- Genes to include: BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2
Germline Testing – Who to Refer

- Personal history of prostate cancer with
  - 1 or more close relatives with
    - Pancreatic cancer
    - Ovarian cancer
    - Breast cancer at 50 or younger
    - Colorectal at 50 or younger
    - Prostate cancer metastatic, high risk or very high risk
  - 1 or more close relatives with
    - Prostate cancer at 60 or younger
  - 2 or more close relatives with
    - Breast cancer at any age
    - Prostate cancer at any age
  - 3 or more close relatives with
    - Lynch syndrome realter cancer: colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, glioblastoma, bile duct or small intestinal cancer
  - Ashkenazi Jewish ancestry
  - A known family history of germline mutation
  - Personal history of breast cancer

NCCN Prostate Cancer Guidelines 3.2022 01/10/2022
Germline Testing – How to Test

- Referral to genetic counselor
- Sending patient for patient-initiated testing (e.g. COLOR, Invitae, around $250)
- Patient facing research:
  - The Gentlemen: [https://redcap.iths.org/surveys/?s=XELDJEX3K3](https://redcap.iths.org/surveys/?s=XELDJEX3K3)
  - PROMISE: [https://www.prostatecancerpromise.org/](https://www.prostatecancerpromise.org/)
Prostate Cancer Genetics at OHSU

• Opened November 2021
• Men w/ Pca eligible to germline testing and with known mutations
• To refer patients:

  Email: oncaccess@ohsu.edu
  Call: 503-494-7999
  Fax: 503-346-6854
Somatic Testing Who to Test

- **BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12:**
  - recommended for all with metastatic PCa,
  - can be considered in men with regional disease

- Microsatellite High (MSI-H) and mismatch repair deficiency (dMMR) testing
  - recommended for men with mCRPC
  - may be considered for men with regional and mCSPC

- Tumor mutational burden (TMB) testing
  - may be considered in mCRPC
Somatic Testing – How to Test Blood vs Tumor

- Multilineage prostate cancer evolution
  - HRD is early truncal event
- ctDNA considered more sensitive if PSA >10 ng/ml

Schweizer et al. Prostate 2019
Woodcock et al. Nature Com 2020
CHIP Interference with ctDNA testing

Sokolova, et al, JNCCN 2020
Somatic Testing – How to Test Blood vs Tumor

- OHSU: GENETRAILS
- Commercial Vendors
- Is generally NOT a substitute for germline testing
- If BRCA1/2 mutations identified on somatic NGS dedicated germline testing is recommended
Learning Objectives

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• Take Home Points
DNA Damage Repair: PARPi

Base excision (PARP*)

PARP inhibitors

HEJ

BRCA mutation carriers

Homologous Recombination

Non-Homologous End Joining

BRCA 1/2, ATM, CHEK2, RAD51

CELL SURVIVAL

CELL DEATH

*PARP – Poly-ADP-ribose polymerase

PARPi Targets

A. PARP1 function in BER
- DNA damage
- SSB
- Base excision repair
- PARPi
- PARP1
- DSB
- HR defect
- DNA damage
- Cell death

B. PARP1 inhibits NHEJ
- DNA damage
- DSB
- Ku 70/80
- DNA-PKcs
- HR defect
- Error-prone DNA repair
- Genomic instability

C. PARP1 trapping on DNA damage
- DNA damage
- PARPi
- PARP1 trapping
- DNA damage
- DNA damage
- Cell death

D. PARP1 recruits DNA repair proteins
- DNA damage
- SSB
- PARPi
- PARP1 recruitment
- Poly ADP ribosylation
- BRCA1, BARD1
- DNA repair defect
- DNA damage

Konstantinopoulos et al, Cancer Discovery, 2015
TRITON 2: Rucaparib in mCPRC with BRCA1/2

- 55% PSA50 response to Rucaparib

Abida W., et al. JCO, 2020
Phase III Trial of PARPi in PCa: 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

Olaparib 300 mg bid
- n=162

Physician’s choice†
- n=83

Cohort B:
- Other alterations*
- N=142

Olaparib 300 mg bid
- n=94

Physician’s choice†
- n=48

2:1 randomization
Open-label

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

*BRD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and/or RAD51L

Hussain M., et al. ESMO, 2019
PROfound: Olaparib Improves rPFS*

*rPFS – radiographic progression free survival

Hussain M., et al. ESMO, 2019
DeBono., et al. NEJM, 2020
PROfound: Olaparib Improves rPFS*

*rPFS – radiographic progression free survival

De Bono., et al. NEJM, 2020
PROfound Gene-by-Gene rPFS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Olaparib</th>
<th>Physician’s choice</th>
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</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>10.84</td>
<td>3.48</td>
</tr>
<tr>
<td>CDK12</td>
<td>5.09</td>
<td>2.20</td>
</tr>
<tr>
<td>ATM</td>
<td>5.36</td>
<td>4.70</td>
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<tr>
<td>BRCA1</td>
<td>2.07</td>
<td>1.84</td>
</tr>
<tr>
<td>CHEK2</td>
<td>5.59</td>
<td>3.35</td>
</tr>
<tr>
<td>PPP2R2A</td>
<td>2.69</td>
<td>NR</td>
</tr>
<tr>
<td>RAD51B</td>
<td>10.89</td>
<td>7.20</td>
</tr>
<tr>
<td>RAD54L</td>
<td>2.41</td>
<td>1.77</td>
</tr>
</tbody>
</table>

Hussain M., et al. NEJM, 2020
PROPel: A Global Randomized Double-Blind Phase III Trial

**Patient population**
- 1L mCRPC
- Docetaxel allowed at mHSPC stage
- No prior abiraterone
- Other NHAs allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG 0–1

**Stratification factors**
- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mHSPC: yes vs no

**Primary endpoint**
- Radiographic progression or death (rPFS) by investigator assessment

**Key secondary endpoint**
- Overall survival (alpha control)

**Additional endpoints**
- Time to first subsequent therapy or death (TFST)
- Time to second progression or death (PFS2)
- Objective response rate (ORR)
- HRRm† prevalence (retrospective testing)
- Health-related quality of life
- Safety and tolerability

**Treatments**

1. Olaparib 300 mg bid + abiraterone 1000 mg qd*
   - n=399
   - Full dose of olaparib and abiraterone used

2. Placebo + abiraterone 1000 mg qd*
   - n=397
   - Full dose of abiraterone used

First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS. Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS. Please access the Supplement via the QR code at the end of this presentation for more details.

*In combination with prednisone or prednisolone 5 mg bid. †HRRm, homologous recombination repair mutation, including 14 genes panel.
ADT, androgen deprivation therapy; bid, twice daily; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone sensitive prostate cancer; qd, daily

Presented by Fred Saad, 2022 ASCO Genitourinary Cancers Symposium
PROOpel: Primary Endpoint: rPFS By Investigator-Assessment

34% Risk Reduction of Progression or Death with Olaparib + Abiraterone
PROpel: Overall Survival

28.6% Maturity; Trend Towards Improved OS with Olaparib + Abiraterone

Events: 228
NR, not reached.

Olaparib + abiraterone (n=399)  Placebo + abiraterone (n=397)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>107 (26.8)</th>
<th>121 (30.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.86 (0.66–1.12)</td>
<td>P=0.29</td>
</tr>
</tbody>
</table>

Pre-specified 2-sided alpha: 0.001
PROPel: Most Common Adverse Events

AE Profile was Consistent with the Known Toxicity Profiles for the Individual Drugs

Safety was assessed through the reporting of AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and laboratory assessments. *Anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythrocytopenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.
Magnitude: Randomized, Double-Blind, Placebo-Controlled Study

Prospectively Selected Biomarker Cohorts Designed to Test HRR BM+ and HRR BM-

Study start: February 2019

Patient eligibility:
- L1 mCRPC
  - ≤4 months prior AAP allowed for mCRPC
  - ECOG PS 0 or 1
  - BPI-SF worst pain score ≤3

Stratifications:
- Prior taxane-based chemo for mCSPC
- Prior ARi for nmCRPC or mCSPC
- Prior AAP for L1 mCRPC
- HRR BM+ cohort only:
  - BRCA1/2 vs other HRR gene alterations

Prescreening for BM status:

<table>
<thead>
<tr>
<th>HRR BM+ Planed N = 400</th>
<th>HRR BM- Planned N = 600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib + AAP</td>
<td>Niraparib + AAP</td>
</tr>
<tr>
<td>Placebo + AAP</td>
<td>Placebo + AAP</td>
</tr>
</tbody>
</table>

Allocation to cohort:

1:1 randomization:

Primary endpoint:
- rPFS by central review

Secondary endpoints:
- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints:
- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM+ status.

Note: Patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator’s choice.

AAP: abiraterone acetate + prednisone/prednisolone, AR, androgen receptor; ARi, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumor deoxyribonucleic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; L1, first line; mCSPC, metastatic castration-resistant prostate cancer; mcPSA, metastatic castration-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; rPFS, progression-free survival; rPFS2, progression-free survival on first subsequent therapy; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival

*Tissue and Plasma assays: FoundationOne tissue test (FoundationOne®CDx). Resolution Bioscience liquid test (ctDNA). AmoyDx blood and tissue assays. Invitae germline testing (blood/saliva), local lab biomarker test results demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel.

Presented by Kim N. Chi, 2022 ASCO Genitourinary Cancers Symposium
Magnitude **HRR BM-**: Prespecified Early Futility Analysis

No Benefit of NIRA + AAP in HRR BM- Patients

- Composite endpoint\(^a\) (N = 233)
  \[ \text{HR} = 1.09^b \quad (95\% \text{ CI } 0.75-1.59) \]
  [futility was defined as ≥1]

- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP

- With added toxicity and no added efficacy in patients with HRR BM- mCRPC, the IDMC recommend stopping enrollment in this cohort

\(^a\)PFS or PSA progression, whichever occurred first

\(^b\)Breakdown of composite endpoint events
  83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
  65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)
Magnitude **BRCA 1/2-Mutated:**

Primary Endpoint

NIRA + AAP Significantly Reduced the Risk of Progression or Death by 47%

**rPFS assessed by central review**

- **HR: 0.53** (95% CI, 0.36-0.79)
- **P = 0.0014**

**rPFS assessed by investigator**

- **HR: 0.50** (95% CI, 0.33-0.75)
- **Nominal P = 0.0006**

Median Follow-up 16.7 months

AAP, abiraterone acetate + prednisone/prednisolone; CI, confidence interval; HR, hazard ratio; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival.

Presented by Kim N. Chi, 2022 ASCO Genitourinary Cancers Symposium
Magnitude **All HRR BM+**: Primary Endpoint

NIRA + AAP Significantly Reduced the Risk of Progression or Death by 27%

Median Follow-up 18.6 months

AAP, abiraterone acetate + prednisone/prednisolone; BM, Biomarker, CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival.

Presented by Kim N. Chi, 2022 ASCO Genitourinary Cancers Symposium
PARPi in Prostate Cancer

- Rucaparib for mCRPC w/ $BRCA1/2$ muts
- Olaparib for mCRPC w/ HRD
- ?PARPi+abiraterone for mCSPC w/ $BRCA1/2$ muts
DNA Damage Repair (DDR): Platinum

Base Excision (PARP*)

PARP inhibitors

Homologous Recombination
BRCA 1/2, ATM, CHEK2, RAD51

Non-Homologous End Joining
NHEJ

BRCA mutation carriers

Platinum DNA Damage

CELL DEATH

CELL SURVIVAL

Biallelic Inactivation of BRCA2 in Platinum-sensitive MCRPC

- 3 pts with mCRPC, who achieved an exceptional response to platinum chemotherapy
- All three patients had biallelic inactivation of BRCA2
Carboplatin in BRCA Carriers Pca

PSA Response

- mCRPC
- carboplatin/docetaxel
- n=141
- 8/141 - gBRCA2 mutation
- 6/8 - PSA$_{50}$
PD1/PDL1 inhibitors

Pan tumor

Pembrolizumab approval:
- 12 different tumor types
- mismatch repair deficiency
- Radiographic response 53%
- Complete response 21%
- 5% of mCRPC MMRd

FDA.gov
Le, et al. Science, 2017
Abida, et al, JAMA Oncol, 2018
Clinical Trial Eligibility

Actionable mutations: 133/150 pts (89%)
Learning Objectives

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• Take Home Points


**gBRCA Increases Risk of PCa**

- *gBRCA2* associated with 4.5- to 8.6-fold increased relative risk of PCa

- PCa with *gBRCA1/2* mutations associated:
  - More advanced stage at diagnosis
  - Metastases at diagnosis
  - Younger age at diagnosis
  - Worse outcomes
  - OS in carriers vs noncarriers 8 vs 13 years

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Active Surveillance: Increased Gleason Grade Upgrade with BRCA1/2, ATM

Carter., et al. Eur Urol, 2019
Learning Objectives

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BRCA Associated Cancers

BRCA 1
- breast cancer
- **ovarian cancer**
- uterine body and cervix (RR = 2.65)
- fallopian tube cancer
- peritoneal cancer
- prostate cancer (<65 yo RR = 1.82)
- pancreatic cancer (RR = 2.26)
- Fanconi anemia (subtype FA-D1)
- acute myeloid leukemia

BRCA2
- breast cancer
- ovarian cancer
- fallopian tube cancer
- peritoneal cancer
- **prostate cancer** (<65 yo RR = 7.33)
- **male breast cancer**
- pancreatic cancer (RR = 3.51)
- malignant melanoma (RR = 2.58)
- gallbladder and bile duct cancer (RR = 4.97)
- stomach cancer (RR = 2.59)
- Fanconi anemia (subtype FA-D1)
- acute myeloid leukemia

For germline **BRCA2** mutation carriers, the relative risk of developing prostate cancer by age 65y is **2-8** fold compared with non-carriers.

J Natl Cancer Inst. 2002 Sep 18;94(18):1358-65
J Natl Cancer Inst 91:1310-6, 1999
Men vs Women *BRCA* testing

Genetic testing for hereditary cancer risk

- Men: 3:1
- Women: 10:1

Genetic testing for *BRCA1* and *BRCA2*

- Men: 10:1
- Women: 3:1

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JAMA Oncol. 2018;4(6):876-879
**Prostate Cancer Early Detection**

### Baseline Evaluation
- **History and physical (H&P)** including:
  - Family cancer history
  - Family or personal history of high-risk germline mutations
  - History of prostate disease and cancer early detection, including prior prostate-specific antigen (PSA) and/or isoforms, exams, and biopsies

### Risk Assessment
- Age 45–75 y for average-risk patients or
- Age 40–75 y for those with:
  - African ancestry
  - Germline mutations that increase the risk for prostate cancer
  - Suspicious family history

- Start risk and benefit discussion about offering prostate cancer early detection:
  - Baseline PSA
  - Strongly consider baseline digital rectal examination (DRE)

### Early Detection Evaluation
- **PSA < 1 ng/mL, DRE normal (if done)** → Repeat testing at 2- to 4-year intervals
- **PSA 1–3 ng/mL, DRE normal (if done)** → Repeat testing at 1- to 2-year intervals
- **PSA > 3 ng/mL** and/or very suspicious DRE → See Further Evaluation and Indications for Biopsy (PROSD-3)
- **PSA < 4 ng/mL, DRE normal (if done), and no other indications for biopsy** → Repeat testing in select patients at 1- to 4-year intervals

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**a** Family or personal cancer history and/or family or personal history of high-risk germline mutations can inform when to begin shared decision-making regarding prostate cancer early detection. Family cancer history includes, but is not limited to, a first- or second-degree relative with metastatic prostate cancer, ovarian cancer, male breast cancer, female breast cancer ≤ 5 y, colorectal or endometrial cancer ≤ 50 y, or pancreatic cancer or two or more first- or second-degree relatives with breast, prostate (but not clinically localized Grade Group 1), colorectal or endometrial cancer at any age. If there is a known or suspected cancer susceptibility gene, referral to a genetics professional is recommended. Mutation carriers have an increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline BRCA2 or HOXB13 mutations occurs earlier and is more likely to be associated with prostate cancer mortality. For men with BRCA1, ATM, or mismatch repair (MLH1, MSH2, MSH6, PMS2) germline gene mutations timing of testing is less clear. Consequently, prostate cancer screening is recommended at age 40 for BRCA2 carriers, and it is reasonable for men with other germline mutations to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (CRIT-1) and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (LS-1). Page EC, Eur Urol 2019;76:831-842; Giri VN, et al. J Clin Oncol 2020;38:2798-2811.
Take Home Points

• ~12% pts w/ metastatic PCa have germline DDR muts
• ~20% w/ metastatic PCa have somatic DDR muts
• Patients w/ PCa and HRD are candidates for PARPi and Platinum
• Patients with PCa and MMRd are candidates for PD1/PDL1 inhibitors
THANK YOU!

To refer patients to Prostate Cancer Genetics Clinic at OHSU:
Email: oncaccess@ohsu.edu
Call: 503-494-7999
Fax: 503-346-6854
Germline Testing– Who to Refer

PROSTATE CANCER STATES

LOCALIZED

BCR

mCSPEC

nmCRPC

mCRPC

WHY TEST

Identify hereditary cancer syndrome, inform family cancer risks, determine clinical trial eligibility

In some cases, may be helpful in active surveillance discussion

Treatment implications are currently evaluated by several clinical trials

PARPi, platinum candidacy

WHO TO TEST

Everyone who meets family history criteria (Table 1)

≥T3a

Grade Group ≥4

PSA >20

N1

Intraductal/ductal histology

NCCN does now specify recommendations for BCR*

Metastatic disease*

WHICH GENES TO TEST

MLH1, MSH2, MSH6, PMS2, BRCA1/2, ATM, PALB2, CHEK2**
Prostate Cancer Genetics at OHSU

To refer patients for Prostate Cancer Genetics Clinic at OHSU:
Email: oncaccess@ohsu.edu
Call: 503-494-7999
Fax: 503-346-6854
NCCN Family History Criteria For Germline Testing

**PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS**

Germline testing is recommended *in patients with a personal history of prostate cancer* in the following scenarios:

- **By Prostate Cancer Stage or Risk Group (diagnosed at any age)**
  - Metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer

- **By Family History and/or Ancestry**
  - ≥1 first-, second-, or third-degree relative with:
    - breast cancer at age ≤60 y
    - colorectal or endometrial cancer at age ≤50 y
    - male breast cancer at any age
    - ovarian cancer at any age
    - exocrine pancreatic cancer at any age
    - metastatic, regional, very-high-risk, high-risk prostate cancer at any age
  - ≥1 first-degree relative (father or brother) with:
    - prostate cancer at age ≤60 y
  - ≥2 first-, second-, or third-degree relatives with:
    - breast cancer at any age
    - prostate cancer at any age
  - ≥3 first- or second-degree relatives with:
    - Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer
    - A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM*
    - Ashkenazi Jewish ancestry
  - Personal history of breast cancer

Germline testing may be considered *in patients with a personal history of prostate cancer* in the following scenarios:

- **By Prostate Cancer Tumor Characteristics (diagnosed at any age)**
  - intermediate-risk prostate cancer with intraductal/cribriform histology

- **By prostate cancer AND a prior personal history of any of the following cancers:**
  - exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract, and small intestinal
Prostate Cancer Background

- Prostate cancer (PCa) is the most common non-cutaneous tumor among men in US
- 192,9300 men estimated to be diagnosed with PCa in 2020

Platinum Mechanism of Action

• 1) Attachment of alkyl groups to DNA  DNA fragmented by repair enzymes in their attempts to replace the alkylated bases  preventing DNA synthesis and RNA transcription

• 2) DNA damage via the formation of cross-links in DNA prevents DNA from being separated for synthesis or transcription

• 3) Induction of mispairing of the nucleotides leading to mutations
PD1/PDL1 inhibitors

Patient survival and clinical response to Pembrolizumab across 12 different tumor types with mismatch repair deficiency Radographic response 53%m Complete response 21%

Le et al. Science, 2017