Therapeutic implications of inherited cancer susceptibility

Susan M. Domchek, MD
Basser Professor of Oncology
University of Pennsylvania
Disclosure

• Honoraria from AstraZeneca, Clovis and Bristol Meyers Squibb
Germline genetic testing as a paradigm for individualized care

- Risk Assessment
- Disease Prevention
- Therapeutics

*BRCA1/2 as the prototype*
Biology of BRCA1/2 and sensitivity of tumors: How do you target loss?

- Everyone has BRCA1 and BRCA2 genes: normal cells have two copies of each gene.
- BRCA1 and BRCA2 play key roles in homologous recombination repair: they repair damaged DNA, specifically double stranded breaks.
- Most BRCA1/2 mutation associated tumors have loss of the second copy of the respective gene and don’t have functional protein.
- BRCA1/2 mutation associated tumors have a decreased ability to repair double stranded breaks.
- Certain drugs cause double stranded breaks, which BRCA1/2 mutation associated cancers can then find very difficult to repair.
Biology of BRCA1/2 can teach us about sensitivity of tumors

Traditional chemotherapy
Carboplatin/cisplatin

Poly ADP ribose polymerase (PARP) inhibitors
Olaparib, rucaparib, niraparib, talazoparib, veliparib
Synthetic lethality

DNA damage

Cell with loss of BRCA HRR defect

Normal cell with intact homologous recombination and base excision repair

PARP inhibitor

Death

Survival

HRR  BER

PARP inhibitor

HRR  BER
A Mechanisms of PARPi linked to BER/HRR nexus for tumors with BRCA mutations or BRCAAness phenotype

1A Synthetic lethality with PARPi
1B PARPi lethality in combination therapy with drugs (e.g., temozolomide)

Endogenous factors (oxidants)

Damaged DNA (abasic site, alkylated damage, SSB)

2 BER
3 DNA replication (collapsed replication fork)

PARPi block BER
PARPi trap PARP-1 on SSB
PARPi block the role of PARP-1 in resolution of DNA replication forks
PARPi block NHEJ

Other PARPi?

PARP-1
PARP-2
PARPi

3 Unrepaired SSB

4 HRR-proficient cells

5 Tumors with BRCA mutations or BRCAAness

6 DNA errors-induced death

7 DSB repair & cell survival

8 DSB-induced death

Shah et al Frontiers in Oncology 2013
2005: Synthetic lethality of PARP inhibitors in BRCA null cells described
Farmer et al Nature
Bryant et al Nature

2009: Phase 1 Study, proof of concept
Fong et al NEJM

2010: Phase II trial
BRCA associated metastatic breast cancer
Tutt et al, Lancet 2010

2014: First Parp inhibitor approval (ovarian cancer)
Kaufman et al, JCO 2014

2018: PARP inhibitor approval for metastatic BRCA breast cancer
Robson et al, NEJM 2017

2014: First Parp inhibitor approval (ovarian cancer)
Kaufman et al, JCO 2014

2018: PARP inhibitor approval for metastatic BRCA breast cancer
Robson et al, NEJM 2017
Current FDA approvals

- **Olaparib:**
  - 2014: *gBRCA*-mutated ovarian cancer who have already received three or more chemotherapy treatments
  - 2017: maintenance therapy in relapsed patients with platinum-sensitive *gBRCA1/2* ovarian cancer
  - 2018: *gBRCA*-mutated metastatic breast cancer

- **Rucaparib:**
  - 2016: advanced ovarian cancer associated with deleterious germline or somatic *BRCA* mutations who have received two or more chemotherapies
  - 2018: maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer

- **Niraparib:**
  - 2017: maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-therapy

- **Veliparib**
  - None to date (of note, drug most tolerated in combination with chemotherapy)

- **Talazoparib**  **THIS WEEK!!** *gBRCA*1/2 metastatic breast cancer
First FDA approval based largely on this Phase II study

Multiple tumor types
- Cisplatin-resistant ovarian cancer
- Breast cancer with ≥3 lines of therapy in metastatic setting
- Pancreatic and prostate cancer

Kaufman et al, JCO 2015
Domchek et al, Gyn Onc 2016
<table>
<thead>
<tr>
<th>BRCA status, n (%)</th>
<th>Ovarian (n=193)</th>
<th>Breast (n=62)</th>
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<td><strong>BRCA1 mutation</strong></td>
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Kaufman et al *JCO*, 2015
Best % change from baseline by genotype

Olaparib 400 mg bid cohort

BRCA status

Increasing tumor shrinkage

Tutt et al, Lancet 2010
Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

Robson et al, NEJM 2017
OLYMPIAD Study Design: Olaparib Monotherapy

- Evidence of metastatic disease
  - gBRCA 1/2
  - 1st, 2nd or 3rd line
  - Prior anthracycline unless contraindicated and taxane in either the neo-adjuvant/adjuvant or metastatic setting
  - TNBC
  - HER2 negative
  - ER/PR positive patients not indicated for further endocrine therapy

Randomise 2:1
Open label
N=310 pts

Olaparib 300 mg po bid daily, continuous
To progression

Physician’s choice:
- Capecitabine 2500 mg/m2 x 14 q 21
- Vinorelbine 30 mg/m2 d 1, 8 q 21
- Eribulin 1.23 mg/m2 or eribulin mesylate 1.4 mg/m2 d 1, 8 q 21

REGISTRATION TRIAL – Randomized Phase III.

Studies with niraparib and talazoparib with nearly identical study design
Objective response by BICR

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<th>Response Type</th>
<th>Olaparib 300 mg bd</th>
<th>Chemotherapy TPC</th>
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<tr>
<td><strong>Partial response</strong></td>
<td>60%</td>
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<td>29%</td>
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<td>Median time to response, days</td>
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<td>66</td>
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<td>Median duration of response, months</td>
<td>6.2 (4.6–7.2)</td>
<td>7.1 (2.8–12.2)</td>
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Primary endpoint: progression-free survival by BICR

Particularly important for 10% of TNBC with BRCA mutations!
EMBRACA: Talazoparib vs SOC Chemotherapy
Primary Endpoint: PFS

1-Year PFS 37% vs 20%    Median follow-up time: 11.2 months

Litton et al, NEJM 2018
OLYMPIA: Adjuvant olaparib in breast cancer patients with gBRCA mutations at high risk of recurrence

Post neoadjuvant BRCA TNBC, Non-PathCR pts,
Assumptions:
- Control arm 3 year EFS ~ 60%
- ER positive now allowed CPG>3

Post adjuvant gBRCA
TNBC: Patients with node positive disease (any tumour size) or node negative, primary tumour > 2cm
   ER positive >3 LN
Assumptions:
- Estimated Control arm 3 year EFS ~ 75%

Randomise 1:1
Double blind
N=1800

Olaparib 300 mg bd
12 month duration

Placebo 12 month duration

IDFS

Distant DFS; OS
### BRCA associated pancreatic cancer

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Kaufman et al *JCO*, 2015
### Rucaparib and BRCA1/2 associated pancreatic cancer

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<tr>
<th>Patient Number</th>
<th>Patient</th>
<th>BRCA Mutation</th>
<th>Number of Prior Regimens</th>
<th>Received Prior Platinum</th>
<th>Platinum Refractory</th>
<th>Rucaparib Treatment</th>
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**Legend:**
- **Rucaparib treatment**
- **Stable disease**
- **Complete response**
- **Partial response**
- **Progressive disease**
- **Progressive disease reported on last day of treatment**

*CR 19 weeks, PR 25 weeks, PR 36 weeks, PR 5 weeks**

Domchek et al, in press JCO PO 2018
**RUCAPANC2**

**UPCC 05217**

Metastatic or Locally Advanced PDAC

1. ≥16 week stability on platinum-containing regimen.
2. ECOG ≤1
3. Deleterious BRCA1, BRCA2 or PALB2 mutation

ENROLL

- **Research** blood collections for ctDNA TMLS - Baseline, C3D1, tumor progression

Biopsy → Rucaparib → Progression → Biopsy

WES of tumor tissue

Survival endpoint

Kim Reiss Binder, MD
NCT03140670
Immunology and Inherited Genetics

- Pembrolizumab with approval by the FDA in tumor with mismatch repair deficiency REGARDLESS of tumor type
  - Mismatch repair deficiency can be due to either inherited (germline) or acquired (somatic factors)
  - These tumors are immunologically “hot” at baseline

- Germline: Lynch Syndrome due to mutations in MLH1, MSH2, MSH6, PMS2 with risk of colon, uterine, ovarian and other cancers

- Pembrolizumab activates the immune system

- Inherited cancer susceptibility may be particularly amenable to “basket” trials: doesn’t matter the cancer type, as long as the germline susceptibility is the same
Combinations to turn ‘cold tumors’ into ‘hot tumors’

Vonderheide, Domchek and Clark, Clin Cancer Res; 2017
Mediola: PARPi + PD-L1 antibody

Included germline BRCA1/2 mutation cohorts in breast and ovarian cancer

Domchek et al, SABCS 2017
Mediola: BRCA-metastatic breast cancer

<table>
<thead>
<tr>
<th>Receptor status</th>
<th>BRCAm</th>
<th>Prior platinum</th>
<th>No. of prior lines of chemotherapy</th>
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Legend:
- PR
- SD
- Confirmed PD RECIST
- NE
- Treatment discontinuation
- Death
- On study without progression
- Clinical progression
- Unconfirmed PD RECIST

Domchek et al, SABCS 2017
Time to progression or treatment discontinuation (N=32)

DCR at 12 weeks: 81% (90% CI 66%, 92%)

Drew et al, SGO 2018
Benjamin Franklin
Signatory, Declaration of Independence
Founder, University of Pennsylvania
Cancer immune prevention

1. Immune prevention (of infection) was the PREVIOUS great immune revolution
   - Childhood vaccines are for prevention, not treatment
   - Post-exposure vaccination generally does not work

2. “Cancer vaccines” as therapy have had a poor clinical track record
   - Very safe and even immunogenic, but minimal efficacy (ORR <4%)
   - Patients are immunosuppressed from tumor, TME, and treatment

3. The new breakthrough cancer immunotherapies are not amenable to use in prevention
   - Toxicity unacceptable for healthy individuals
   - Therapy depends on cancer: patients must be patients; neoantigens are not shared
Prospect of hTERT as a universal tumor antigen

- Immunogenic protein expressed in (nearly) all human cancer
  - But restricted expression in normal cells

- Critical functional role in oncogenesis
  - Limits mutation/deletion as a means of immune escape

- Clinical trials using hTERT peptides in metastatic breast cancer
  - Robust immune response without toxicity
  - Immune response correlates with overall survival
    - Domchek et al, Cancer Res, 2007; Rech et al, Science Translational Med,

IND sponsor, Vonderheide
PI, Fox
Next generation TERT vaccine: DNA/Electroporation with cytokine adjuvant

Key advances

1. Optimized DNA construct
2. Inclusion of DNA cytokine, esp IL-12
3. Electroporation

Yan et al, Cancer Immunol Res, 2013 (David Weiner, Penn)
Phase I study of TERT DNA +/- IL-12 DNA in patients with high-risk solid tumors in remission after surgery and (neo)adjuvant therapy

N= first 75
Breast cancer cohort: N=9
• Stage III or Stage II/LN-positive s/p surgery and 4-24 weeks after completion of definitive adjuvant therapy;
• TNBC any stage s/p surgery but residual microscopic cancer following neoadjuvant therapy

Vaccination starting 4-24 weeks after completion of adjuvant therapy
• TERT DNA (INO-1400, 1401) +/- IL-12 DNA (INO-9012) q4weeks x 4 im with electroporation (CELLECTRA ®-5P)
• Sponsor, Inovio

<table>
<thead>
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<th>Arm</th>
<th>Dosing</th>
<th>INO-1400</th>
<th>INO-9012 (IL-12)</th>
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<td>1</td>
<td>Day 0, Weeks 4, 8, and 12</td>
<td>2 mg</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Day 0, Weeks 4, 8, and 12</td>
<td>8 mg</td>
<td>–</td>
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</table>

Shields et al, SITC Annual Meeting, 2017
TERT/IL-12 DNA immunogenicity

Cellular Responses to TERT Prior to and at Peak Magnitude of Response After Treatment by Arm

Arm 1
n=10

Arm 2
n=10

Arm 3
n=9

Arm 4
n=9

Arm 5
n=8

Arm 6
n=2

Shields et al, SITC Annual Meeting, 2017
Future directions

• PARP inhibitor combinations in trials
  • PARPi plus PDL1 antibody
  • PARPi plus ATR inhibitor
  • Olaparb plus palbociclib plus fulvestrant

• Expansion in other BRCA1/2 tumors

• Expansion into other genes (Olaparib extended: TBCRC, Tung)

• Prevention!
Basser Center
- Katherine Nathanson
- Bob Vonderheide
- Payal Shah
- Kara Maxwell
- Angela Bradbury
- Kim Reiss-Binder
- Beth Stearman

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- Stacy Pundock

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- Jacquelyn Powers
- Kelsey Spielman