Genetic counseling and testing for Breast and Ovarian Cancer: Beyond BRCA

PARP Inhibitors: Where are we now?

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Extended Panel Testing is now Widely Available

• NCCN guidelines to guide who should undergo testing
• How to advise patients found to have a deleterious mutation in a gene, role of the genetic counselor
• Variants of uncertain significance: Use of ClinVar to determine if any of these are called pathogenic mutations by other labs

Who Should Undergo Testing?
NCCN Guidelines version 1.2018

• An individual with ovarian cancer
• Known mutation in the family
• Breast cancer diagnosed ≤ 50
• TNBC diagnosed ≤ 60
• Two breast cancer primaries in a single individual
• Male breast cancer
• Breast cancer at any age with family members (≥ 1) with breast cancer ≤ 50, or ovarian cancer (any age), or ≥ 2 close relatives (1, 2 or 3 degree) with breast, prostate and/or pancreatic cancer
• Ashkenazi Jewish descent with breast, ovarian or pancreatic cancer at any age

March 3, 2018 • Sheraton Hotel Dallas
BRCA1 and BRCA2

- Carrier frequency: 1:400, as high as 1:40 in Ashkenazi Jewish individuals
- Lifetime risk 50-85% for breast cancer, 10-60% for ovarian/fallopian tube cancer
- Associated cancers: male breast cancer, prostate cancer, melanoma, pancreatic cancers (BRCA2)


BRCA1 and BRCA2

- Improved survival with BSO

Domcheck SM et al. JAMA 304:967-975, 2010

PALB2

- Partner and localizer of BRCA2
- Collaboration with BRCA2 in DS Break Repair

**PALB2**

- Association with breast, pancreatic cancers and male breast cancer, not with ovarian or prostate cancer
- Clinical picture more similar to BRCA2 gene mutation carriers
- Lifetime risk of breast cancer: 40-60%

Rainville IR et al Curr Oncol Rep 16:371, 2014

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**TP53**

- 1990: Germline TP53 mutations: cause of Li-Freumeni Syndrome (LFS)
- Ubiquitous tumor suppressor
- Associated with sarcoma, brain tumors, early-onset breast cancers, leukemia and adrenocorticocarcinomas
- Median age of BC in LFS is 33, one third diagnosed under age 30.
- Tumors are predominantly Her2 +/ER+

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**TP53**

- Counseling: lifetime risk of cancers, surveillance starts in childhood, breast cancer surveillance starts at 20-25 or earlier (breast MRI)
- Mastectomy recommended over lumpectomy 2nd to increased risk of radiation induced cancers.
- Screening with total body MRI
**PTEN**

- Tumor suppressor gene phosphate and tensin homologue (PTEN)
- Germline PTEN mutations cause Cowden Syndrome (CS): multiple hamartomatous lesions, facial trichilemmomas, mucosal papillomas, macrocephaly
- Prevalence: < 1:200,000
- Clinical manifestations occur in >90% by age 20
- Cancers seen with CS include early onset breast cancer, thyroid cancers, endometrial cancers
- Increased incidence of benign thyroid lesions (can present with a goiter)
- Surveillance: breast cancer imaging beginning at age 30-35

Alexander EK et al. NEJM 368:2416-24, 2013

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**PTEN: Cowden Syndrome**

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**STK11**

- Tumor suppressor: serine/threonine protein kinase
- Germline mutations cause Peutz-Jeghers syndrome (PJS)
- Clinical Presentation: Hamartomatous GI polyps, mucocutaneous hyperpigmentation and increased risk of cancers: breast, CR, gastric, pancreatic, lung, ovarian and testicular
- Surveillance with mammograms and breast MRI beginning at age 25, colonoscopies and upper endoscopies beginning in late teens.
- De novo mutations account for up to 50% of PJS cancers

Rainville IR et al Curr Oncol Rep 16:371, 2014
Peutz-Jeghers Syndrome

CDH1
- Germline mutations in CDH1 cause hereditary diffuse gastric cancer
- Encodes E-cadherin: calcium-dependent protein involved in epithelial cell adhesion
- Increased lifetime risk of lobular breast cancer: 39-52%
- Lifetime risk of diffuse gastric carcinoma: up to 80%
- Preventive gastrectomy recommended to reduce the high lifetime risk of diffuse gastric cancer.
- Endoscopic surveillance for those who refuse (limited efficacy)

Rainville IR et al Curr Oncol Rep 16:371, 2014

ATM
- DNA damage repair
- Acts with MRN complex: MRE11-RAD50-NBN at site of DS breaks
- Bi-allelic germline mutations: Ataxia telangiectasia
  - Childhood neurodegenerative disease
  - Telangiectasia
  - Immune deficiency
  - Gonadal atrophy
  - Predisposition to malignancy
- Heterozygous ATM carriers: 0.5-1% of population
- Lifetime risk of breast cancer: 20%
Panoply of DNA Repair Mechanisms Maintain Genomic Stability

Base Excision Repair (BER)
- Abnormal base detected and removed
- Excision of several bases around the abnormal base
- DNA polymerase fills in the region
- DNA ligase seals the region

PARP Inhibitors as Targeted Therapy
- PARP1 and PARP2: members of the PARP superfamily [Poly (ADP)ribose polymerase]
- Facilitate DNA repair by binding to DNA breaks and attract DNA repair proteins to site of damage
- PARP Inhibition “works” by leading to persistence of SSBs or inhibiting PARP release from DNA
- Either way, leads to potentially lethal DSBs during the process of DNA replication
PARP Inhibitors as Targeted Therapy

- In normal cells, effect of PARP inhibition is “buffered” by homologous recombination which repairs the DSBs
- However, if BRCA1 or BRCA2 (or potentially other genes in the HR pathway) are defective, as in BRCA1 or BRCA2 mutation carriers, DSBs are left unrepaired, leading to cell death

Synthetic Lethality

- Different single gene defects are compatible with cell viability but the “synthesis” or combination of these gene defects leads to cell death
- BRCA dysfunction is synthetically lethal when PARP is inhibited

DNA Repair: Role of Homologous Recombination and Base-Excision Repair

Iglehart JD and Silver DP, NEJM 361:190-1, 2019
PARP Inhibitors as Targeted Therapy

- Selectively inhibit the growth of cells with defects in either BRCA1 or BRCA2 genes
- In vitro models: cells with BRCA mutations: >1000 times more sensitive to PARP inhibitors than wild-type cells
- Led to development of clinical trials in pts with metastatic breast, ovarian, and other cancers (particularly in those with gBRCA mutations)


Relative Potency of PARP inhibitors

Turner, ASCO 2017

NEJM 2016
NEJM 2017
A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician’s choice of therapy in patients with advanced breast cancer and a germline BRCA-mutation


Study Design: EMBRACA

Phase 3, international, open-label study
431 patients in 16 countries and 145 sites

Primary endpoint: PFS by blinded central review
Key secondary efficacy endpoints:
- Progression-free survival by RECIST by blinded central review
- Overall survival (OS)
- ORR by investigator
- Safety

Exploratory endpoints:
- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

Talazoparib 1 mg PO daily

Physician’s choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine

TALA Overall PCT

<table>
<thead>
<tr>
<th>Event, no. (%):</th>
<th>Median PFS, mo (95% CI)</th>
<th>Hazard ratio (95% CI), 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TALA (n = 287)</td>
<td>8.6 (7.2, 9.3)</td>
<td>0.54 (0.41, 0.71)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Overall PCT (n = 144)</td>
<td>5.6 (4.2, 6.7)</td>
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*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated.
†HER2-positive disease is excluded. 
‡Physician’s choice of therapy must be determined prior to randomization.
PFS: Subgroup Analysis

Interim OS Analysis: Secondary Endpoint

EMBRACA Phase 3 Trial of Talazoparib:

Conclusions

- EMBRACA is the largest randomized trial evaluating a PARP inhibitor in patients with advanced breast cancer and a germline BRCA1/2 mutation
- Talazoparib resulted in prolonged progression-free survival vs physician's choice of therapy by blinded central review
  - HR: 0.54 (95% CI, 0.41, 0.71); P < .0001
- All key secondary efficacy endpoints demonstrated benefit with talazoparib
  - Overall survival is immature (51% of projected events); HR: 0.76 (95% CI, 0.54, 1.06); P = .105
- Global Health Status/Quality of Life showed overall improvement from baseline and a delay in the time to clinically meaningful deterioration in patients receiving talazoparib
  - HR: 0.38 (95% CI, 0.26, 0.55); P < .0001
- Talazoparib was generally well tolerated, with minimal nonhematologic toxicity and few adverse events resulting in treatment discontinuation
FDA Approval for PARP Inhibitors

- On December 19, 2014, the FDA approved olaparib capsules (Lynparza; AstraZeneca) for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.
  - Dose and schedule of olaparib is 400 mg orally twice daily.
- On December 19, 2016, the U.S. Food and Drug Administration granted accelerated approval to rucaparib (RUBRACA, Clovis Oncology Inc.) for treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies.
  - Dose and schedule of rucaparib is 600 mg, orally, twice daily with or without food.
- On March 27, 2017, the FDA approved niraparib (ZEJULA, Tesaro, Inc.) for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.
  - Dose and schedule of niraparib is 300 mg taken once daily with or without food.

FDA Approval and Plans for Expedited Review for olaparib

- On Aug. 17, 2017, the U.S. Food and Drug Administration granted regular approval to olaparib tablets (Lynparza, AstraZeneca) for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.
- On October 18, 2017, the FDA granted priority review to a supplemental New Drug Application (sNDA) for olaparib (Lynparza) for the treatment of patients with germline BRCA-positive, HER2-negative metastatic breast cancer who have previously received chemotherapy in the neoadjuvant, adjuvant, or metastatic settings.
- Anticipate that Pfizer will apply for FDA approval of talazoparib based on the EMBRACA trial. Dose 1 mg orally daily.

What Next?

- Neo-adjuvant therapy with talazoparib: studies underway
- Adjuvant olaparib: OlympiA trial underway
- Metastatic disease:
  - translational studies from EMBRACA planned
  - combinations of PARP inhibitors with other agents: platinis?
  - combinations with PD-L1 inhibitors: trials underway
  - other settings: ATM, CHEK2, PALB2?
  - Overcoming resistance mechanisms