Tumor Testing:
The Good, the Bad, and the Ugly

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Disclosures

- I work for the federal government (NCI, NIH).
- I have no financial conflicts to disclose.
Tumor Testing and Targeted Therapy: Some Perspective

• We have been testing tumors for decades.
  • Immunohistochemistry
    • Standard stains for pathologic assessment
  • Specific stains for different proteins
    • 1980s Estrogen Receptor (ER)
    • 2000s Human Epidermal growth factor Receptor 2 (HER2)

• As the tools change, new “markers” emerge for us to “target” therapy
  • Tamoxifen targets ER
  • Herceptin targets HER2
  • Imatinib targets BCR-ABL in Chronic Myelogenous Leukemia (CML)
  • Erlotinib targets EGFR for Lung Cancer
Overview of Talk

• Precision medicine
  • Basic review of mutations and cancer
  • Testing tumors to identify treatment options

• Ovarian cancer as an example

• Please do ask questions:
  • I will periodically pause along the way to see if there are questions
Mutations and Cancer

“It’s Complicated”
Cancer arises from gene mutations

**Germline mutations**
- Mutation in egg or sperm
- Present in egg or sperm
- Present in all cells
- Are inherited
- Cause cancer family syndromes

**Somatic mutations**
- Somatic mutation
- Occur in non germline tissues
- Not stable, may appear or disappear over time
- Are not inherited
What is DNA?

- Building blocks of our genes
- Two complementary strands (double helix, Rosalind Franklin)
- Each chromosome contains 2 copies of each gene, one on each strand
- Germline (what we are born with) mutations, affect only one strand.
- Cancer needs another (second) hit to happen.

From: evolution.berkeley.edu
DNA Encodes Genes

- Genes encode proteins
- Proteins tell cells what to do
  - Grow
  - Move around
  - Produce stimulatory cell factors
  - Produce inhibitor factors
  - Interact with other cells
  - Etc…

From: http://fajerpc.magnet.fsu.edu
DNA Damage

HOW?
- Spontaneous injury
- UV light
- Chemicals
- Radiation
- Chemotherapy
- Additives

WHAT HAPPENS?
- Many types of repair
- Each type of repair has separate genes/proteins
- If the repair pathway is wrong or doesn’t work, errors happen
- Either repair occurs or the cell dies
Genetic Overlap

Multiple genes can increase the risk of a single cancer

Multiple cancers can be associated with a single gene
Tumor Testing
Example: TAILORx Clinical Trial

- Prospective clinical trial evaluating 10,273 women with hormone positive, HER 2 negative, lymph node negative breast cancer
  - Recruited patients (4/2006 to 10/2010)
- Tumors were tested with a 21 gene breast cancer assay *(OncotypeDX)* to predict benefit of chemotherapy
  - Low Scores women received hormones only
  - High Scores women received chemotherapy also
  - Intermediate Scores
    - Women were randomly assigned to chemotherapy or not with their hormone therapy

- Results 2018
  - Breast cancer with intermediate score
  - Women don’t need chemotherapy
Tumor Testing: New Tools

• With the Human Genome Project, we can efficiently and effectively identify many genes and mutations
  • We can identify genetic mutations in cancers

• What kind of tools?
  • Panel of markers (genetic, protein, etc)
    • Examples:
      • Oncotype Dx (21 genes), Pam50 (50 genes), Mammoprint (70)
  • Next-Gen Sequencing
    • Rapidly examines hundreds of hotspots in cancer genomes
  • Pyro Sequencing
    • Detects and quantified mutations, methylation, other genetic modifications through sequencing
## Tumor Testing: Many Different Platforms  
(courtesy Shannon Westin)

<table>
<thead>
<tr>
<th>Platform</th>
<th># Genes</th>
<th>Tissue Required</th>
<th>Turn Around</th>
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<td>14 days</td>
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<td>10-14 days</td>
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<tr>
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<td>14 days</td>
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<tr>
<td>Cancer Plex (Kew Group)</td>
<td>~400</td>
<td>10 days</td>
<td>7-10 days</td>
</tr>
</tbody>
</table>
Driver and Passenger Mutations

- Cancer cells typically have many mutations
  - Most mutations have no functional advantage
    - *Passenger* mutations are along for the ride

- A few mutations contribute to the tumor’s growth
  - Driver mutations confer a functional growth advantage
    - *Driver* mutations move the growth forward

- Challenge: *How to tell the passenger from the driver*

- Some mutations transform normal cells into tumor cells
  - Gatekeeper mutations are seen in many tumor types
    - Retinoblastoma (Rb)
Targeted Therapy

Tissue Matters
What is Targeted Therapy?

The development of agents designed to interrupt or inhibit a molecular event in a way that is thought to change the biology of the cancer.
Survival, Growth, and Invasion Pathways

Inhibitors of EGFR, MET, PDGFR, IGFR, ...

Neutralizing MoAbs to VEGF, IGF1, met

Dasatinib

Sorafenib, etc

AZD6244, etc

enzastaurin

Cell Survival

Gene Expression Cell Proliferation

Angiogenesis

Endothelial Cell
Example: Non-Small Cell Lung Cancer (NSCLC)

- Precision Diagnosis and Treatment for Advanced Non-small Cell Lung Cancer (NEJM August 2017)
  - Biopsy of tumor
  - Tumor testing for specific driver mutations
    - EGFR, ALK, BRAF V600E
  - If no driver mutations present in biopsy, stain for immuno-checkpoint presence. (PD-L1)

- Choice of therapy depends upon presence of mutations
Treatment Algorithm for NSCLC

A

Non-squamous NSCLC
EGFR M+

19Del
EGFR TKI: afatinib preferred

L858R
EGFR TKI: afatinib, gefitinib, erlotinib

Uncommon mutations
EGFR TKI: afatinib preferred

Progressive disease
plasma cf DNA

T790M -
Tumour rebiopsy

T790M -
Chemotherapy Doublet

T790M +
Third generation EGFR TKI

Chemotherapy Doublet

1st Line

2nd Line

3rd Line

B

Non-squamous NSCLC
ALK rearrangement

Crizotinib
1st Line

Maintenance

Ceritinib or Alectinib
2nd Line

Chemotherapy doublet
Pemetrexed based preferred
3rd Line

*The new umbrella screening protocol will simply be referred to as LUNGMAP. It is a major revision that will allow Lung-MAP to expand to include all NSCLC histologies and include more patients.

*Only new sub-studies will be open to all NSCLC histologies. The rest of the current sub-studies are for patients only with squamous cell carcinoma.
Tissue Matters

*Not every mutation has the same effect in different tissues*
EGFR overexpressed in 50-70% Ovarian Cancer
Rare to have mutations
Some studies ↑EGFR associated w/ poor prognosis

**EGFR in Ovarian Cancer**

- **gefitinib**: negative
- **GOG170C neg; NCI neg** (Schilder, ClinCaRes 2005; Posadas, CANCER 2007)
- **erlotinib**: OR 6%
  (Gordon, IJGC 2005)
- **lapatinib**: GOG170G closed early
- **cetuximab/matuzumab**: no single agent studies found
NCI-MATCH Tumor Gene Testing

Gene sequencing will look for changes in 143 genes.

If a patient's tumor has a genetic abnormality that matches one targeted by a drug used in the trial, the patient will be eligible to join the treatment portion of NCI-MATCH.
NCI-MATCH Central Screening Summary

- Overall match rate: 18%
  - Patients with a tumor gene abnormality that matched to one of the 30 treatment arms (992/5560 with testing completed)

- Enrollment rate: 69%
  - Patients with a treatment assignment who enrolled (689/992)
Ovarian Cancer(s)
Epithelial Ovarian Cancer Incidence Rates* by Age and Race/ethnicity, US, 2010-2014

NH White  Asian/Pacific Islander  NH Black  Hispanic

NH = non-Hispanic. Asian/Pacific Islander includes persons of Hispanic ethnicity.
*Age adjusted to the 2000 US standard population.
Progress in Gynecologic Cancers

OVARIAN CANCERS

- 1960: ALKYLATORS
- 1970: CISPLATIN
- 1980: CISPLATIN COMBOS
- 1990: CARBO/TAX
- 2000: ANGIOGENESIS INHIBITION
- 2010: DNA REPAIR INHIBITION

New agents combos:
- OLAPARIB
- NIRMARIB
- RUCAPARIB

CISPLATIN & CTX
- CARBO
- TAX
- BEV
Survival, Growth, and Invasion Pathways

Neutralizing MoAbs to VEGF, IGF1, met

Inhibitors of EGFR, MET, PDGFR, IGFR, ...

Dasatinib

Sorafenib, etc

AZD6244, etc

enzastaurin

Cell Proliferation
Vasopermeability

Cell Survival

Gene Expression
Cell Proliferation

Angiogenesis

Endothelial Cell

SIGMA-ALDRICH
<table>
<thead>
<tr>
<th>STUDY</th>
<th>AGENT</th>
<th>N</th>
<th>RESPONSE RATE</th>
<th>PFS AT 6 MONTHS</th>
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<tbody>
<tr>
<td>170-C</td>
<td>Gefitinib</td>
<td>27</td>
<td>3.7%</td>
<td>14.8%</td>
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<tr>
<td>170-D</td>
<td>Bevacizumab</td>
<td>62</td>
<td>21%</td>
<td>40.3%</td>
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<tr>
<td>170-E</td>
<td>Imatinib</td>
<td>56</td>
<td>1.8%</td>
<td>16.1%</td>
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<tr>
<td>170-F</td>
<td>Sorafenib</td>
<td>59</td>
<td>3.4%</td>
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<tr>
<td>170-G</td>
<td>Lapatinib</td>
<td>26</td>
<td>0.0%</td>
<td>7.7%</td>
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<tr>
<td>170-H</td>
<td>Vorinostat</td>
<td>27</td>
<td>3.7%</td>
<td>7.4%</td>
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<tr>
<td>170-I</td>
<td>Temsirolimus*</td>
<td>54</td>
<td>9.3%</td>
<td>24.1%</td>
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<tr>
<td>170-J</td>
<td>Enzastaurin</td>
<td>27</td>
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<td>11.1%</td>
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<tr>
<td>170-K</td>
<td>Mifepristone</td>
<td>22</td>
<td>4.5%</td>
<td>13.6%</td>
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<tr>
<td>170-L</td>
<td>AMG706</td>
<td>22</td>
<td>Closed due to possible drug related AEs</td>
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<tr>
<td>170-M</td>
<td>Dasatinib</td>
<td></td>
<td>Closed after first stage</td>
<td></td>
</tr>
<tr>
<td>170-N</td>
<td>A6</td>
<td></td>
<td>Closed after first stage</td>
<td></td>
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<tr>
<td>170-P</td>
<td>AMG-102</td>
<td></td>
<td>First stage accrual in progress</td>
<td></td>
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<tr>
<td>170-Q</td>
<td>EGEN-001</td>
<td></td>
<td>First stage accrual in progress</td>
<td></td>
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</tbody>
</table>

*1-3 priors
Thresholds: RR - 10%, 25%; PFS – 15%, 35%
Why Use Molecular Tumor Testing?

- Multiple subtypes for ovarian cancer
  - Subtype specific driver mutations

- FDA approval for pembrolizumab for any tumor with mutations in microsatellite instability or mismatch repair (MSI+ or MMR)

- Participation in clinical trials
  - MATCH or other
Ovarian Carcinoma: Multiple Subtypes

- **Low-grade**
  - Slow growing
  - Encompass all histologies, including:
    - low-grade serous carcinoma
    - low-grade endometrioid carcinoma
    - mucinous carcinoma
    - and some clear cell carcinomas
  - They likely evolve through a step-wise progress from borderline tumors
  - Usually chromosomally stable

- **High-grade**
  - Evolve rapidly
  - Include:
    - high-grade serous carcinoma
    - high-grade endometrioid carcinoma
    - carcinosarcoma
    - undifferentiated carcinoma
    - and some clear cell carcinomas
  - No recognizable precursors in the ovary
  - Widespread DNA copy number changes

Jones PM *Front Oncol* 2013
PARP Inhibitors and Ovarian Cancer

How to use the defect in ability to repair DNA damage to treat the cancer
What are PARP Inhibitors?

• Agents that target the enzyme poly ADP ribose polymerase (PARP)

• PARP is a protein involved in repairing single-strand breaks in DNA

• Inhibitors of PARP prevent DNA repair and allow the accumulation of single-strand breaks
Why and How do they work?

• Tumors have ongoing DNA error events.
  • (develop mutations)

• Typically this results from an inherent dysfunction in recognition and/or repair of DNA injury.

• Propagation of dysfunctional DNA repair can introduce new strengths and susceptibilities.

• BRCA1/2 mutations alter the repair system and can introduce DNA errors.
Responses to PARP Inhibition in Ovarian Cancer with BRCA mutation (both germline & somatic)
PARP maintenance: recurrent platinum-sensitive OvCa

**NOVA: niraparib maintenance**

- **A. Germline BRCA Mutation**
  - Progression-free survival (%)
  - Hazard ratio, 0.27 (95% CI, 0.17–0.41)
  - P = 0.001
  - Niraparib vs Placebo
  - No. at Risk:
    - Niraparib: 131, 125, 107, 98, 90, 83, 75, 68, 61, 54, 46, 39, 32, 24, 18, 10, 8, 4, 1
    - Placebo: 65, 52, 53, 42, 32, 34, 31, 22, 21, 12, 6, 3, 1

- **B. No Germline BRCA Mutation**
  - Progression-free survival (%)
  - Hazard ratio, 0.45 (95% CI, 0.34–0.61)
  - P = 0.001
  - Niraparib vs Placebo
  - No. at Risk:
    - Niraparib: 234, 188, 145, 113, 88, 85, 75, 57, 41, 23, 16, 7, 3
    - Placebo: 116, 88, 52, 33, 23, 19, 10, 8, 4, 1

**SOLO2: olaparib maintenance in gBRCA**

- **SOLO2**
  - Events (%):
    - Olaparib (n=196): 81 (41.3)
    - Placebo (n=99): 70 (70.7)
  - Median PFS, months:
    - Olaparib: 30.2
    - Placebo: 5.5
  - HR: 0.25
  - 95% CI 0.18 to 0.35
  - P < 0.0001

- **Progression-free survival**
  - Months since randomization
  - No. at risk:
    - Olaparib: 1, 1, 1, 1, 1, 10, 8, 8, 3, 2, 3, 1
    - Placebo: 9, 7, 4, 2, 1, 3, 8, 2, 0, 8, 0, 0

M. Mirza et al, NEJM 2016

E. Pujade-Lauraine, et al, SGO 2017
Blocking PARP affects BRCA mutant cancers more

two hits are better than one

- DNA in the BRCA mutant cancer cell is not properly repaired
- It gets worse with addition of DNA repair inhibitors
- Triggers cancer cell death
What have we learned from PARP inhibitors in BRCA1/2 mutation carriers?

- Losing both functional copies of BRCA1 or BRCA2 is important in associated breast and ovarian cancer.
- BRCA1/2 mutation predicts potential for benefit from PARP1 inhibitors.
- Together work to reduce tumor burden in BRCA1/2 mutation carriers.
Development of a biomarker that predicts BRCA-like behavior and benefit to PARPi: *the HRD score*

**BRCA1/2 deficiency**
- Training
- Validation #1
- Validation #2

**Intact BRCA1/2**
- Training: $p=9 \times 10^{-11}$
- Validation #1: $p=2 \times 10^{-7}$
- Validation #2: $p=9 \times 10^{-7}$

**HRD score and survival**

Gordon Mills, with thanks, Abkevich et al, BJC, 2012

Public/private partnership: academia/Myriad
**Survival benefit**

**ARIEL3: Rucaparib maintenance analysis of PFS by HRD type**

- **Germline (g) or somatic (s) BRCA1/2 mut**
- **g or sBRCA1/2**
- **BRCA wildtype/LOH↑ (≥16% genomic LOH prespecified)**
- **p₂<0.05**
- **g or sBRCA1/2**
- **BRCA wildtype/LOH↑**
- **p₂<0.05**
- **Intent to treat population**
  - **10.8 v 5.4**

**ARIEL3: Rucaparib maintenance analysis of PFS by HRD type**

- **gBRCA\text{mut}**
  - **16.6 v 5.4 mo**
- **gBRCA\text{mut} + HRD**
  - **13.6 v 5.4 mo**

**BRCA1/2 mutation/HRD:**
- **Foundation Medicine T5 NGS assay**
- **Coleman et al, The Lancet, 2017**
Immune system recognizes proteins

Logic for combinations

Recognizes mutant proteins better

Snyder et al, NEJM, 2014

Group of biomarker peptides identified
Logic for combinations

Chemo and PARPi tx can increase DNA mutations

Immune system recognizes proteins

Recognizes mutant proteins better

More mutations may mean more clinical benefit

Group of biomarker peptides identified

Snyder et al, NEJM, 2014
Logic for combinations: Better benefit with more mutations (in melanoma)

peptide signature predicted benefit to ipi in melanoma

Snyder et al, NEJM, 2014
Olaparib and Cediranib: Inhibition of DNA repair and angiogenesis is synergistic

<table>
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<tr>
<th></th>
<th>Olaparib</th>
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<tr>
<td>PFS events</td>
<td>28</td>
<td>19</td>
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<tr>
<td>Median PFS</td>
<td>9.0 mo</td>
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<tr>
<td>p</td>
<td>=0.005</td>
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<tr>
<td>HR</td>
<td>0.42 (95% CI: 0.23-0.76)</td>
<td></td>
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Liu et al, Lancet Oncol, 2015; Lee et al, Front Womens Cancers, 2015; Liu et al ASCO 2017
Immune checkpoint therapy in ovarian cancer: *not a panacea*

<table>
<thead>
<tr>
<th>Total (n)</th>
<th>Total</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>DCR</th>
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<tr>
<td>Brahmer et al. (α-PD-L1)</td>
<td>17</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4/17 (23%)</td>
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<tr>
<td>Hamanishi et al. (α-PD-1, nivolumab)</td>
<td>18</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>8/18 (44%)</td>
</tr>
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</table>

**Ongoing Studies:**

**NRG GY-003:** nivolumab v. nivolumab + ipilimumab (platS ovarian cancer)

**NRG GY-009:** Doxil/bev v. Doxil/atezolizumab v. Doxil/bev/atezolizumab (platR ovarian cancer)

Phase I dose finding durvalumab combinations
*enriched for gyne cancer patients*

Subjects Received Study Drugs

- Durvalumab/Olaparib
- Durvalumab/Cediranib

Duration of study:

- DL 1
- DL 2
- DL 3
- Still on study

- Partial Response
- Ovarian Cancer

Months

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

Phase 2 expansions in TNBC and ovarian cancer ongoing.

Lee et al, JCO, 2017
Data cut-off Aug 2016
Prevention…
Or
Risk Reduction
Germline (*Risk*) vs Somatic (*Target*)
Could there be a benefit to having a disease-causing mutation?

**Imatinib hypothesis:**

Constitutively activated fusion protein *causes* CML.

It also *creates* a novel druggable target site.
Putative driver events

## Genetic/Familial High-Risk Assessment: NCCN Guidelines

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk</th>
<th>Ovarian Cancer Risk</th>
<th>Other Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Increased</td>
<td>No increase</td>
<td>Unknown</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Increased</td>
<td>Increased</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Increased</td>
<td>Increased</td>
<td>Pancreas, Prostate, Melanoma</td>
</tr>
<tr>
<td>BRIP 1</td>
<td>No increase</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td>Increase in Lobular BC</td>
<td>No increase</td>
<td>Diffuse gastric cancer</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Increased</td>
<td>No increase</td>
<td>Colon</td>
</tr>
<tr>
<td>NBM</td>
<td>Increased</td>
<td>Insufficient Information</td>
<td>Insufficient Info</td>
</tr>
<tr>
<td>NFI</td>
<td>Increased</td>
<td>No increase</td>
<td>Gastric Stromal Tumor</td>
</tr>
</tbody>
</table>
# Genetic/Familial High-Risk Assessment: NCCN Guidelines

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk</th>
<th>Ovarian Cancer Risk</th>
<th>Other Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALB2</td>
<td>Increased</td>
<td>Insufficient Info</td>
<td>Unknown</td>
</tr>
<tr>
<td>PTEN</td>
<td>Increased</td>
<td>No increase</td>
<td>Cowden Syndrome</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Unknown</td>
<td>Increased risk</td>
<td>Unknown</td>
</tr>
<tr>
<td>RAD51D</td>
<td>Insufficient Info</td>
<td>Increased</td>
<td>Unknown</td>
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<tr>
<td>STK11</td>
<td>Increase</td>
<td>Increase of non-epithelial OC</td>
<td>Colorectal</td>
</tr>
<tr>
<td>TP53</td>
<td>Increased</td>
<td>No increase</td>
<td>Li-Fraumeni Syndrome</td>
</tr>
</tbody>
</table>
Ovarian Carcinogenesis

- Incessant ovulation
- Steroid hormones and gonadotropins
- Talc, endometriosis, pelvic inflammation

Hysterectomy/Tubal ligation
- Elevated inflammation markers
- Release of growth factors
- Oxidative stress
- DNA damage
- Inhibition of apoptosis & cell growth arrest

Anti-inflammatory medications

Ovarian Carcinogenesis

Modified from Ness RB & Cottreau C, JNCI 1999
Abnormal cells leave the fallopian tube and shed onto the ovary, progressing from precancer cells to cancer.
Approximately 50% of high-grade serous EOCs have alterations in HR repair genes.

OVERVIEW OF TOXICITIES ASSOCIATED WITH DIFFERENT TKI TARGETS

- **VEGFR**: Nausea/vomiting, Diarrhea, Elevated AST/ALT, Pneumonitis
- **MET**: Nausea / vomiting, Elevated amylase / lipase, Peripheral edema
- **PDGFR**: Skin rash, Diarrhea, Mucositis, Pneumonitis
- **HER2**: Nausea/vomiting, Diarrhea, Elevated AST/ALT, Pneumonitis
- **ALK**: Diarrhea, Rash, LV dysfunction
- **EGFR**: Cytopenia, LV dysfunction, QT prolongation, Hypothyroidism, PAOD/PAH
- **BCR-ABL**: Anemia, Thrombocytopenia, Fatigue, Diarrhea
- **JAK**: N/A

Other toxicities include:
- Hypertension
- Proteinuria
- Wound healing complications
- HFSR
- Arterial TE
- LV dysfunction
- QT prolongation
- Hemorrhage
- Dysphonia
- Mucositis
- Diarrhea
- Hypothyroidism

Date: 10/12/2018
<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>EOC Overall</th>
<th>High Grade</th>
<th>Low Grade</th>
<th>Clear Cell (Type I)</th>
<th>Endometrioid (Type I)</th>
<th>Mucinous (Type I)</th>
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<tbody>
<tr>
<td>BRAF</td>
<td>11% (Kurman and Shih 2011)</td>
<td>&lt;1% (TCGA 2011)</td>
<td>24–33% (Nakayama et al. 2006; Singer et al. 2003)</td>
<td>1% (Kuo et al. 2009)</td>
<td>24% (Singer et al. 2003)</td>
<td>50–75% (Gemignani et al. 2003)</td>
</tr>
<tr>
<td>KRAS</td>
<td>11% (Kurman and Shih 2011)</td>
<td>&lt;1% (TCGA 2011)</td>
<td>33% (Nakayama et al. 2006; Singer et al. 2003)</td>
<td>&lt;1–7% (Kuo et al. 2009; Singer et al. 2003)</td>
<td>&lt;1% (Singer et al. 2003)</td>
<td>50–75% (Gemignani et al. 2003)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>6.7% (Campbell, Russell, and Phillips 2005; Levine et al. 2005; Wang et al. 2005)</td>
<td>&lt;1% (TCGA 2011)</td>
<td>5% (Nakayama et al. 2006)</td>
<td>20–33% (Campbell et al. 2004; Kuo et al. 2009)</td>
<td>20% (Campbell et al. 2004)</td>
<td>Rare</td>
</tr>
<tr>
<td>PTEN</td>
<td>20% (Kurman and Shih 2011)</td>
<td>&lt;1% mutation (TCGA 2011)</td>
<td>20% (Landen, Birrer, and Sood 2008)</td>
<td>&lt;1–5% (Kuo et al. 2009; Willner et al. 2007)</td>
<td>20–31% (Kurman and Shih 2011; Willner et al. 2007)</td>
<td>Rare</td>
</tr>
</tbody>
</table>
PARP Inhibition Prevents DNA Repair

- Tumors have ongoing DNA error events.
  - Development of mutations

- Typically this results from an inherent dysfunction in recognition and/or repair of DNA injury.

- BRCA1/2 mutations alter the repair system and can introduce DNA errors
  - Want those errors that result in lack of further growth
PARP Inhibitors for Prostate Cancer

• An estimated 15-20% of metastatic prostate cancers have deficiencies in DNA repair.

• One phase 2 trial of olaparib in 50 patients with metastatic prostate cancer showed a 30% response rate.

• A larger trial of 171 patients with metastatic prostate cancer who had previously received docetaxel, were randomized to receive abiraterone alone or with olaparib
  • Improved Progression Free Survival with the combo

• Need to refine the understanding
  • Is DNA repair deficit necessary for response to olaparib?
  • Would need to test the tumor first