Cancer Precision Medicine: A Primer
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OUTLINE

• Background
  • Where we are
  • Where we have been
  • Where we are going
• Targeted Therapy in Ovarian Cancer
• How to Individualized Targeted Therapy
• Personalized Medicine Initiative at UAB
• The Future of “Personalized or Precision Medicine”
  • We have a long way to go

Ovarian Cancer Statistics and Standard of Care in 2015

• 21,290 new cases, 14,180 deaths
• State of Alabama: 350 cases, 260 deaths
• 5th in cancer deaths among women
• More deaths than any other cancer of the female reproductive system
• ~75% diagnosed at late stage (stage III/IV)
• Most treated with surgical cytoreduction and adjuvant platinum-taxane based chemotherapy
• Most patients recur within 2 years and receive multiple rounds of chemotherapy
**Ovarian Cancer - Progress in Outcome**

![Graph showing progress in ovarian cancer outcome with key drugs and years marked](image_url)

Modified from David Spriggs

**FDA approved drugs for Ovarian Cancer - Timeline**

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>1990</td>
<td>Altretamine</td>
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<tr>
<td>1991</td>
<td>Carboplatin</td>
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<tr>
<td>1992</td>
<td>Paclitaxel</td>
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<tr>
<td>1996</td>
<td>Topotecan</td>
</tr>
<tr>
<td>1999</td>
<td>Liposomal Doxorubicin (Accelerated)</td>
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<tr>
<td>2005</td>
<td>Liposomal Doxorubicin (Full)</td>
</tr>
<tr>
<td>2006</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>2014</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>2014</td>
<td>Olaparib (BRCA mutation carriers)</td>
</tr>
</tbody>
</table>

**New Chemotherapy Approaches in Advanced Ovarian Cancer**

- Intraperitoneal chemotherapy
- Neo-adjuvant chemotherapy
- Dose dense taxanes
- Anti-angiogenic therapy
- PARP inhibitors
Anti-angiogenic therapy: Targeted Therapy

VEGF Inhibition

Biologically-Targeted Drugs (Ovarian Cancer)

FDA Approval: November 2014
Bevacizumab

- FDA approved for use in combination with chemotherapy in the treatment of women with platinum-resistant, recurrent ovarian cancer
- Studied as primary therapy and consolidation with paclitaxel and carboplatin showed modest improvement in PFS and OS
- Not FDA approved

PARP inhibitors: Individualized Targeted Therapy

Poly ADP ribose polymerase inhibitor that blocks enzymes in repairing damaged DNA

BRCA and PARP
Olaparib approved for women with advanced ovarian cancer with defective BRCA genes

Proportion Of Hereditary Ovarian Cancer

Ovarian Cancer

15%

Sporadic Hereditary

Can we combine an anti-angiogenic and Parp Inhibitor?
A Randomized Phase 2 Trial Comparing Efficacy of the Combination of the PARP-inhibitor Olaparib and the Anti-angiogenic Cediranib Against Olaparib Alone in Recurrent Platinum-sensitive Ovarian Cancer

Presented By Joyce Liu at 2014 ASCO Annual Meeting

Primary Outcome: Cediranib/olaparib significantly increased PFS compared to olaparib alone

Presented By Joyce Liu at 2014 ASCO Annual Meeting

Cediranib/olaparib significantly increased PFS in patients without a BRCA mutation

Presented By Joyce Liu at 2014 ASCO Annual Meeting
Conclusions

• Combination of cediranib + olaparib more active than olaparib alone
• Activity observed in both BRCA mutation carriers and BRCA non-carrier/unknown patients
• Toxicity profile was acceptable
• Degree of activity supports additional clinical evaluation of cediranib/olaparib combination in ovarian cancer
• Perhaps if you hit two pathways at once this will lead to “synthetic lethality”

Specific Pathways

Other targeted agents....

Can we use one drug to target multiple pathways?
Multi-kinase Inhibitor

- Randomized double-blind, phase III trial of pazopanib (oral multikinase inhibitor) versus placebo in women who have not progressed after first-line chemotherapy

Results:

- 940 patient randomized (91% had Stage III/IV disease)
- Median PFS: 17.9 months vs. 12.3 months ($p=0.0021$)
  - HR 0.766 (95% CI: 0.64 – 0.91)
- Adverse events:
  - Not surprisingly, pazopanib was associated with more AE
- Pazopanib improved PFS in patients following primary therapy. OS data is immature.

How do we individualize treatment?

Can we use Genetic Sequencing?
Ovarian cancers are molecularly heterogeneous

- 489 tumors: Genomic alterations observed in nearly every chromosome
- Any one genomic alteration is found in only a small fraction of patient tumors (except TP53)
  - One drug is unlikely to be effective for all patients
  - Drugs must be developed for specific molecular tumor types
  - Profiling of individual tumors using a broad profiling panel is necessary

Data provided by Dr. D. Levine [TCGA study: Nature 474, 609-615 (2011)]

Personalized Medicine Initiative
Division of Gyn Oncology at UAB

Background on OVCA PMI Project at UAB

- Tumor Cancer Genome Atlas (TCGA) -> heterogeneity of high grade papillary serous ovarian cancer
- Chemo-refractory recurrent ovarian cancer (n=48) identified 67 “actionable” genomic alterations
  - predicted sensitivity or resistance to a FDA approved drug or standard therapy OR
  - one that was either inclusion or exclusion criteria for a specific experimental therapy in an NCI registered clinical trial
- Genotype-guided therapy: significantly improved lung cancer outcomes
Aim

- Capture patients that have a potential molecular target that may allow for the “off-label” use of targeted therapy against these “actionable” aberrations
- This number will continue to grow within the 3 years
- Phase 1 Trial Center also starting to grow

Recurrent Ovarian Cancer ~250/year

Next Generation Sequencing (NGS)
Recurrent Ovarian Cancer ~250/year
Next Generation Sequencing (NGS)
Electronic Medical Record (EMR)

1. FDA approved targeted agent

FDA approved targeted agent
Clinical Trial
Recurrent Ovarian Cancer ~250/year

Next Generation Sequencing (NGS)

FDA approved targeted agent

Clinical Trial

Clinician drug of choice

Electronic Medical Record (EMR)

Outcomes followed

PMI Patient Example
NGS Report

Publically available Databases

Specific Pathways
Review the Literature

KRAS or BRAF mutation status is a useful predictor of sensitivity to MEK inhibition in ovarian cancer.

Clinical Trials

A phase II study of MEK112 plus BLY176 in adult patients with selected advanced solid tumors.

Combination MEK inhibitor/PI3K inhibitor
Specific Pathways

![Diagram of specific pathways]

Other Examples: Two Patients

- Patient with Somatic BRCA mutation → started on a PARP inhibitor
  - *Germline = inherited in ALL the cells of your body*
  - *"BRCA positive patient" = Germline*
  - *Somatic = Not inherited only in the TUMOR cells*
  - *Most patients with a Germline BRCA mutation will have Somatic germline mutations in their TUMOR cells*
  - *...But there are TUMORS/patients that could benefit from a Parp Inhibitor*

Conclusions/Future

- Program is just starting
- Outcomes are TBD
- Cost-effectiveness is an issue
- US-based cohorts and networks
  - ORIEN (The Oncology Research Information Exchange Network)
    - *Now multi-institutional with 120,000 pts*
THANK YOU....

Questions?