Demystifying Clinical Trials and some exciting new directions

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I have no disclosures.
Progress in gynecologic cancers: made by clinical trials

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

OVARIAN CANCERS
1960 - CISPLATIN
1970 - CISPLATIN & CTX
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1990 - BEV
2010 - PARPis
Progress in gynecologic cancers: *made by clinical trials*

- **ALKYLATORS**
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  - 2000: PARPis
  - 2010: IO?

- **ANGIOGENESIS INHIBITION**
  - 2000: CARBO/TAX, BEV, PARPis
Getting started...
What is a clinical trial?

The World Health Organization (WHO) definition for a clinical trial is:

'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'
Why clinical trials?

• Clinical trials allow progressive assessment of clinical interventions. These may include all or some of: drugs, radiation, imaging, surgery, complementary and alternative agents/modalities, intervention delivery...

• Clinical trial phases were developed to formalize types of objectives and assessment, while also minimizing the number of patients needed so as to maximize patient safety and contribution.

• Clinical trials provide evidence that can be applied by treating physicians in making individual patient level decisions.
Who performs/supports clinical trials?

• Any investigator can perform a trial provided s/he follows regulatory and safety guidelines.
• The National Institutes of Health funds grants and contracts for clinical trials in many disciplines of medicine.
• Clinical investigators who work at the NIH may also run clinical trials. Those are often done at the NIH Clinical Center, the NIH research hospital, in Bethesda, MD.
• Pharma, clinical research organizations (CRO), and academic investigators also run clinical trials.
Who participates in clinical trials?

Anyone who

• Is interested

• Fulfills the eligibility criteria
Who participates in clinical trials?

Anyone who
• Is interested
• Fulfills the eligibility criteria

Who should participate in clinical trials?

EVERYONE!
What is a clinical trial phase?

- Clinical trial phases test different questions.
- They ask progressive questions.

Depending upon the question, may lead to regulatory review and/or change in clinical practice.
What do different clinical trial phases do?

- **Phase 1 clinical trials**
  - ask questions regarding safety and side effects to help define the best dose(s) for further study
  - may often be open to a wide array of cancer types
  - do not have benefit as a primary endpoint
What do different clinical trial phases do?

- **Phase 1 clinical trials**
  - ask questions regarding safety and side effects to help define the best dose(s) for further study
  - may often be open to a wide array of cancer types
  - do not have benefit as a primary endpoint

- **Phase 2 clinical trials**
  - treat a more homogeneous population of patients
  - use a predefined and consistent dose and schedule
  - look for signs of activity as the primary endpoint of therapy
  - may be randomized, between regimens or with placebo controls
What do different clinical trial phases do?

- **Phase 3 clinical trials**
  - compare a new promising approach to standard therapy(s)
  - have intent to change clinical practice patterns (e.g., FDA registration)
  - may do so by showing superiority or non-inferiority to the standard of care
  - May commonly use blinded treatment and placebo controls
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What goes into designing a clinical trial?

• Scientific justification: because “it’s there” or are there data?
Defining your hypothesis...

• Scientifically justified: because “it’s there” or are there data?

• Potential to make a clinically meaningful finding

'Ditto,' said Tweedlaedum. 'Ditto, ditto!' cried Tweedledee.

Lewis Carroll, *Through the Looking Glass*
Defining your hypothesis...

- Scientifically justified: because “it’s there” or are there data?
- Potential to make a clinically meaningful finding
- Interesting to the community

Francesca's feet had enough of impractical footwear. They made a silent, but assertive vote.
What goes into designing a clinical trial?

- Scientific justification: because “it’s there” or are there data?
- Potential to make a clinically meaningful finding
- Interesting to the community
- Feasible
Exciting new directions in ovarian cancer
Exciting new directions in ovarian cancer

• Making PARPi active for everyone: the olaparib/cediranib story

• Leveraging immunotherapy for ovarian cancer: novel combinations

• The cell cycle front and center in ovarian cancer: prexasertib
Exciting new directions in ovarian cancer

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• The cell cycle front and center in ovarian cancer: prexasertib
Making PARPi active for everyone: the olaparib/cediranib story

Reducing local oxygen (hypoxia) can cause genes, like BRCA1, to be reduced. This makes the tumor BRCA-like and maybe more susceptible to PARPi. This is mimicked by use of an angiogenesis inhibitor like cediranib.
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Human blood vessel cells exposed to olaparib and cediranib cannot form blood vessel tubes in culture.
Adding cediranib to olaparib is active activity strongest in patients without BRCA mutation

<table>
<thead>
<tr>
<th>BRCA Mutation Carrier</th>
<th>BRCA Non-carrier/Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>Ced/Olap</td>
</tr>
<tr>
<td>PFS events</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Median PFS</td>
<td></td>
</tr>
<tr>
<td>16.5 mo</td>
<td>19.4 mo</td>
</tr>
<tr>
<td>p=0.16</td>
<td>p=0.008</td>
</tr>
<tr>
<td>HR 0.55 (95% CI: 0.24-1.27)</td>
<td>HR 0.32 (95% CI: 0.14-0.74)</td>
</tr>
</tbody>
</table>

Liu et al, Lancet Oncology, 2014
NRG GY004: Testing olaparib + cediranib
No chemotherapy!

PlatS
HGSOC
Stratify by gBRCAm

Platinum-based
SoC

Olaparib

Olaparib + Cediranib

Fully accrued
Anticipate final results 1/2Q19
Using cediranib to make PARPi active for women with platinum-resistant ovarian cancer

Platinum Sensitive
Reconfirms activity in all women

Platinum Resistant
Higher number of women without BRCA mutation will have platR cancer. This is first evidence that the combination works here too

RR = 74%

RR = 7/35 (20%) +4 unconfirmed
NRG GY005:
A phase 2/3 study comparing olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy in women with recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer

NRG PI: Jung-min Lee
Phase 2: completed

Phase 3: anticipated to open 3/4Q18
Exciting new directions in ovarian cancer

- Making PARPi active for everyone: the olaparib/cediranib story

- Leveraging immunotherapy for ovarian cancer: novel combinations

- The cell cycle front and center in ovarian cancer: prexasertib
The molecular background of the ovarian cancer may predispose it to further injury by PARPi.

This further injury on a messy genomic background may cause more “not self” proteins that activate the immune system.

Using a drug that ”wakes up” the immune system may then enhance the effects of the PARPi.
Phase I study of durvalumab and olaparib
durable response in BRCA wild type ovarian cancer

Durvalumab + olaparib

Durvalumab + cediranib

(below the red line and/or a long horizontal line is good)  
Lee et al, JCO 2017
PARPi + immunotherapy: *a promising start*

**Before Treatment**

**On Treatment – 3+ years, now CR**

*Data cut-off Oct 13, 2016*

NCT02484404

Lee et al, JCO 2017
Encouraging an immune response
‘inflammatory’ vs. ‘immune desert’ tumors

ImmunoHOT tumor in a patient without BRCA mutation and a 3+ year response

ImmunoCOLD tumor in a patient without BRCA mutation and rapid progression on treatment

Lee et al, JCO 2017
If 2 is good, are 3 better?

Durable clinical activity of D+O+C in women’s cancers

By patient

**BRCA1 mutation**

*Updated: Data Cut off date 1/3/2018*

R: platinum resistant HGSOC/ S: platinum sensitive HGSOC

*TNBC **Endometrial Ca

Lee et al, ESMO 2017
An open-label, Phase II basket study of olaparib and durvalumab (MEDIOLA):
Results in germline BRCA-mutated, platinum-sensitive relapsed ovarian cancer

Yvette Drew,1 Maja de Jonge,2 Sook-Hee Hong,3 Yeon Hee Park,4 Anita Wolfer,5 Jennifer Brown,6 Michelle Ferguson,7 Martin E Gore,8 Ricardo Alvarez,9 Christopher Gresty,10 Helen Angell,10 Kassondra Meyer,11 Maria Learoyd,10 Mei Tang,12 Mark Lanasa,11 Pia Herbolsheimer11 and Susan M Domchek13

Funded by AstraZeneca; ClinicalTrials.gov number NCT02734004

1Northern Centre for Cancer Care, Newcastle-upon-Tyne, UK; 2Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands; 3Seoul St Mary’s Hospital, Catholic University of Korea, Seoul, South Korea; 4Samsung Medical Center, Seoul, South Korea; 5Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland; 6Beatson West of Scotland Cancer Centre, Glasgow, UK; 7NHS Tayside, Dundee, UK; 8The Royal Marsden Hospital, London, UK; 9Cancer Treatment Centers of America, Augusta University, Augusta, GA, USA; 10AstraZeneca, Cambridge, UK; 11AstraZeneca, Gaithersburg, MD, USA; 12Medimmune Oncology, Inc., Gaithersburg, MD, USA; 13Basser Center for BRCA, University of Pennsylvania, Philadelphia, PA, USA
MEDIOLA: Study schema

Initiation of therapy at the time of relapse

PSR OC 2L+ gBRCAm PARPi and IO naïve

Olaparib 300 mg po bid

Durvalumab 1.5 g IV q4w

Target DCR at 12 weeks: 90%*
→ N=31

4 week run-in

Tumor assessments

Optional biopsies

*Target based on olaparib monotherapy efficacy

- Primary endpoints: DCR at 12 weeks, safety
- Secondary endpoints: DCR at 28 weeks, ORR, DoR, PFS, OS, PD-L1 expression
- Exploratory endpoints: TILs

DCR, disease control rate; DoR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; po, oral; TILs, tumor-infiltrating lymphocytes
Patient later achieved a PR after receiving durvalumab + olaparib combination

AE, adverse event; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Prior lines of chemo

Time to progression or treatment discontinuation (N=32)

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

*[Patient later achieved a PR after receiving durvalumab + olaparib combination
AE, adverse event; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease]
MEDIOLA RESULTS (SGO 2018)

Tumor responses

<table>
<thead>
<tr>
<th></th>
<th>1 prior (2L)</th>
<th>2 prior (3L)</th>
<th>3+ prior (4L)</th>
<th>All lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>10/13=77%</td>
<td>6/9=67%</td>
<td>7/10=70%</td>
<td>23/32=72%</td>
</tr>
<tr>
<td>95% CI</td>
<td>(46%, 95%)</td>
<td>(30%, 93%)</td>
<td>(35%, 93%)</td>
<td>(53%, 86%)</td>
</tr>
</tbody>
</table>

Best percentage change in target lesion size

- Best change (%)
  - 1 prior line of chemotherapy
  - 2 prior lines of chemotherapy
  - 3 or more prior lines of chemotherapy

(below the blue line is good)
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Pushing cells through the cell growth cycle: a new technique to drive cancer cell death

Cells in growing tumors go divide into daughter cells.

Cells undergo DNA injury by chance during the cell cycle, and more often when under chemo(radio)therapy stress.

Injured cells must arrest to repair.

If cells cannot stop the growth cycle, they will accumulate injury and die.
Prexasertib: a new drug that pushes cells through the cell cycle

Surprising activity in platinum-resistant ovarian cancer patients

J-m Lee et al, Lancet Oncology 2018
Where we were…some cell death, but not cure
DNA damaging agents

- radiation
- gemcitabine
- PLD
- platinums

DNA repair inhibitors

- CHEKi
- wee-i
- ATR/ATMi
- PARPi

Where we may be now…
And, where we can go…

- DNA damaging agents
  - radiation
  - gemcitabine
  - PLD
  - platinums

- DNA repair inhibitors
  - CHEKi
  - wee-i
  - ATR/ATMi
  - PARPi

- Tissue targets
  - immuno check-i
  - angio-i

+
And, where we can go…

DNA damaging agents
- radiation
- gemcitabine
- PLD
- platinums

DNA repair inhibitors
- CHEKi
- wee-i
- ATR/ATMi
- PARPi

Tissue targets
- immuno
- check-i
- angio-i
And, where we can go...
Questions?

“I go home today. They cured me using this new miracle drug. I’m afraid it’ll be years before it’s approved for humans.”