New strategies in ovarian cancer treatment

Enhancing, informing and improving treatment

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I have no disclosures.
New Strategies in Ovarian Cancer Treatment

- Targeting the morphomolecular type
- New designs
- New agents
- Novel combinations
- Targeting the TME not just the tumor
- Improved therapeutic delivery
**Targeting the morphomolecular type**

**EZH2* is synthetically lethal with ARID1A**

EZH2 inhibition is > 10x more potent in ARID1A mutant TOV21 OCCC cells than ARID1A replete cells.

EZH2 inhibition causes loss of tumor size and number of nodules in OCCC.

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*repressive methyltransferase

EZH2 is synthetically lethal with ARID1a\textsuperscript{mut}
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**Targeting the morphomolecular type**

Homeostasis (viable)  
ARID1A  
EZH2

ARID1A mutation  
EZH2 active  
Malignant, proliferating
EZH2 is synthetically lethal with ARID1a\textsuperscript{mut}

Homeostasis (viable)

ARID1A mutation
EZH2 active
Malignant, proliferating

ARID1A mutation
EZH2 inhibited
Proliferation inhibited
Apoptosis induced

Targeting the morphomolecular type
Testing the ARID1A clinical synthetic lethality

NRG GY014 pending activation:
Tazemetostat in clear cell & endometrioid ovca

Recurrent ovarian or endometrial clear cancer
Measurable disease
Platinum-resistant
At least 1 prior regimen
ARID1A\textsuperscript{mut} status integrated endpoint

Targeting the morphomolecular type

Tazemetostat 800mg daily
NSGO-OV-UMB1/ENGOT-OV30: phase II umbrella trial in relapsed ovarian cancer

New designs

Part 1

Cohort A n=25
MEDI9447+Durva NSGO

Cohort B n=25
ATR+Durva (SGCTG)

Cohort C n=25
ATR+Durva+Olaparib (PMHC)

Relapsed ovarian cancer

Days: 1 15 29 43 57

biopsy Day: < 1
blood, serum samples

CT, blood, serum samples
**NSGO-OV-UMB1/ENGOT-OV30**: phase II umbrella trial in relapsed ovarian cancer

**Part 1**
- **Cohort A** \( n=25 \)
  - MEDI9447 + Durva NSGO
- **Cohort B** \( n=25 \)
  - ATR + Durva (SGCTG)
- **Cohort C** \( n=25 \)
  - ATR + Durva + Olaparib (PMHC)

**GO-NO GO**
Evaluation of results of each cohort (overall and biomarker-defined subgroups) proceed to part 2

**Part 2**
- **MED19447 + Durvalumab**
  - Standard of Care
- **ATR + Durvalumab**
  - Standard of Care
- **ATR + Durvalumab + Olaparib**
  - Standard of Care

Days: 1 15 29 43 57

- CT, blood, serum samples
- Biopsy
  - Day: < 1
  - Day: < 1
A tale of two DNA repair inhibitors: Pushing cells through cell cycle driving cancer cells to death

Cells in growing tumors divide into daughter cells.

DNA injury occurs by chance during the cell cycle, and more often when cells are under treatment stress.

Injured cells must arrest to repair. P53 activates the G1 repair checkpoint.

Cells that cannot stop the growth cycle, accumulate injury and die.
Prexasertib: CHK1/2 inhibition in parallel with endogenous $TP53^{\text{mut}}$

$p53^{\text{mut}}$ is endogenous--blocks cell cycle arrest promoting replication stress
New agents

Prexasertib: CHK1/2 inhibition in parallel with endogenous $TP53_{\text{mut}}$
79% (19/24) had $\uparrow$ CCNE
63% with $\uparrow$ CCNE had PFS >6mo
BRCA\textsuperscript{mut} and BRCA\textsuperscript{wt} ovca cells have very different responses to PARP inhibition with IFN\textgreek{g} and TNF\textgreek{a}.

Higuchi, ... Adams et al. Cancer Immunol Res 2015

Novel combinations

Immunotherapy: are we using the right approach?
Novel combinations

Immunotherapy: are we using the right approach?

BRCA^{mut} and BRCA^{wt} ovca cells have very different responses to PARP inhibition with IFNγ and TNFα.

Interrupting PARPi and CTLA-4 signaling synergistically induces IFNγ and TNFα.

Only anti-CTLA4 works in BRCA\textsuperscript{mut} OVCA in vivo

Testing this hypothesis: NRG GY021 tremelimumab/olaparib

PlatS HGSOC

Stratify by gBRCAm v wt/unkn
Prior PARPi exposure

1\textsuperscript{st}: 50 pt safety lead in, DLT through cycle 3
2\textsuperscript{nd}: 40 additional safety lead in, DLT through cycle 3
Total: 150, randomized 1:1
Targeting the TME not just the tumor

Hypoxic creates DNA damage liabilities

- Hypoxia downregulates expression of key DNA repair genes, eg CHK1/2, BRCA1
- Local hypoxia generation by angiogenesis inhibitors
- Local hypoglycemia and acidosis and may cause similar effects

Ivy and Kohn, Trends Cancer, 2017
Liu et al, Lancet Oncol, 2015
Glazer et al, Yale Journal, 2013
Targeting the TME not just the tumor

**PFS benefit with olaparib/cedarinib**

All women N=90
16.5 vs. 8.2 mo
HR 0.50; p = 0.007

- **gBRCA (N=47)**
  - 23.7 vs 5.7 mo
  - p = 0.002

- **BRCAwt/unk (N=43)**
  - 23.7 vs 5.7 mo
  - p = 0.002

Liu et al, Annals Oncol, 2019
Targeting the TME not just the tumor

OS benefit of doublet for wild type/unknown BRCA

All women  N=90
44.2 vs. 33.3 mos
HR 0.64; p = 0.11

BRCAwt/unk (N=43)
37.8 v 23.0, p=0.047

Liu et al, Annals Oncol, 2019
Targeting the TME not just the tumor

Olaparib and cediranib: *Clinical synthetic lethality*

Hypoxia and DNA repair inhibition: preliminary proof of concept

Circulating endothelial cells (CEC) are induced during hypoxia
Increase in CECs correlates directly with PFS

Lee et al, Front Womens Cancers, 2015
NRG GY004

PhatS
HGSOC
Stratify by gBRCAm

Platinum-based SoC

Olaparib

Olaparib + Cediranib

Fully accrued
Anticipate final results 2Q19

NRG PI: Joyce Liu
Targeting the TME not just the tumor

Phase 3 registration studies

More BRCAwt women will have PlatR ovca.

Phase 3 opened 12/18
Dropping single agent olaparib arm

NRG PI: Jung-Min Lee
Antibody-directed conjugates: bringing the toxin to the tumor

- Mirvetuximab soravtansine with high affinity to FRα.
- Lysosomal processing releases active maytansinoid derivatives.
- DM4 catabolites inhibit tubulin polymerization/microtubule assembly.
- DM4 metabolites can diffuse into neighboring cells for bystander killing.

Moore et al, Future Oncol 2018
Improved therapeutic delivery

Mirvetuximab sorvetansine + carboplatin safety phase I

**ELIGIBILITY**
- Recurrent ovca (all prior carbo/paclitaxel)
- PFI up to 12 mo
- Safety tested in with carboplatin (AUC 5, 6)
- Minimum 25% cells with ≥2+ FRα staining

**RESULTS**
- **Toxicity:** nausea (67%)
  - thrombocytopenia (61%, 3 gr3)
  - diarrhea (61%, 1 gr3)
  - blurred vision (61%)
  - fatigue (56%, 1 gr3)
- **Confirmed ORR:** 71%
  - 3 CR
  - 9 PR
  - PFSm 15 mos

Moore et al, Gyn Oncol, 2018
Improved therapeutic delivery

Mirvetuximab sorvetansine + carboplatin sensitivity phase I

Moore et al, Gyn Oncol, 2018
New Hope in Ovarian Cancer Treatment

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Novel targets and agents: EZH2 methyltransferase

The next horizon is therapeutic manipulation of epigenetic marks

Gene silencing can be beneficial or detrimental

Generic demethylation has not been active in solid tumors. Agents are now under development for focused action

EZH2 is a trimethylater generally resulting in target downregulation

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