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12th International Symposium
ADVANCED
OVARIAN
CANCER
Optimal Therapy. Update

# New strategies in ovarian cancer treatment

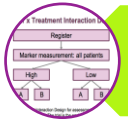
## *Enhancing, informing and improving treatment*

Elise C. Kohn, MD
*National Cancer Institute*

**I have no disclosures.**

# New Strategies in Ovarian Cancer Treatment

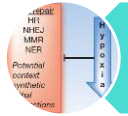
Targeting the morphomolecular type



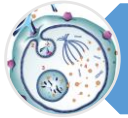

New designs

New agents

Novel combinations




Targeting the TME not just the tumor

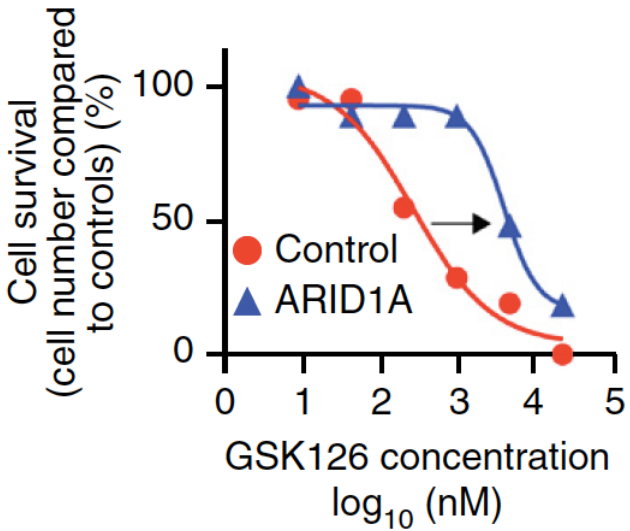


Improved therapeutic delivery

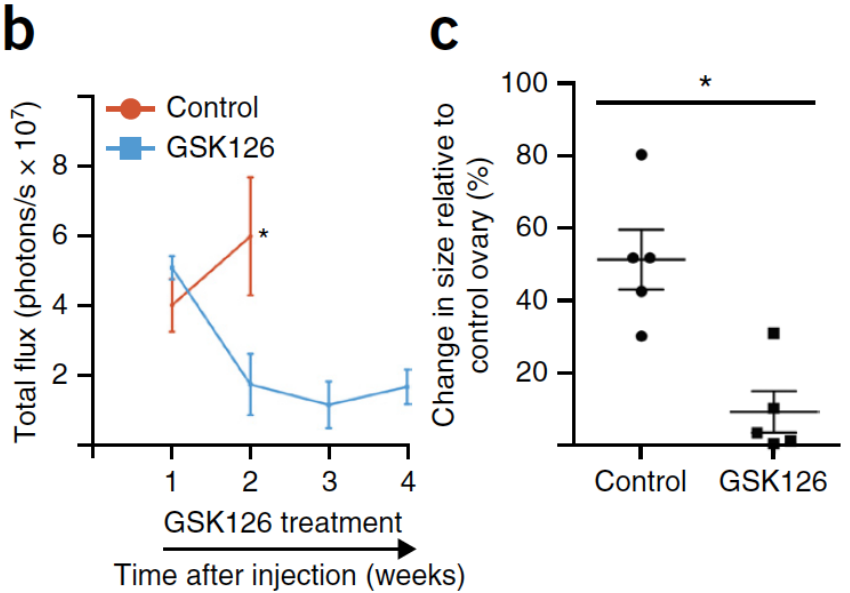
# Targeting the morphomolecular type

## EZH2* is synthetically lethal with ARID1A$^{mut}$

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

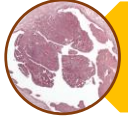



**EZH2 inhibition causes loss of tumor size and number of nodules in OCCC**



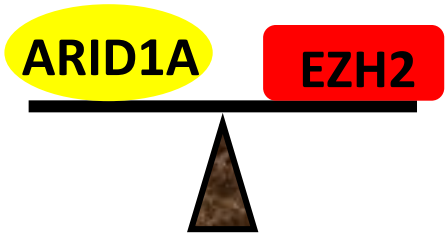

*repressive methyltransferase

Bitler, et al. Nat Med, 2015

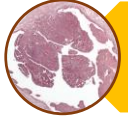


# Targeting the morphomolecular type

## EZH2 is synthetically lethal with ARID1a$^{mut}$




Homeostasis (viable)



# Targeting the morphomolecular type

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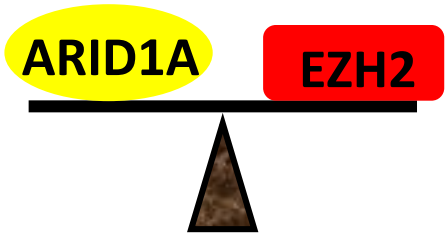


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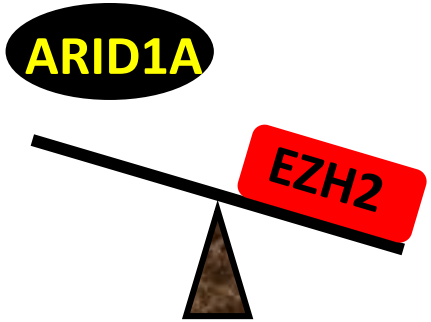
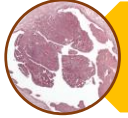
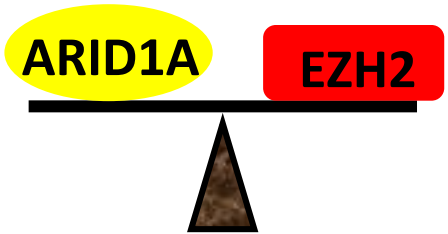



ARID1A mutation
EZH2 active
Malignant, proliferating



# Targeting the morphomolecular type

## EZH2 is synthetically lethal with ARID1a$^{mut}$

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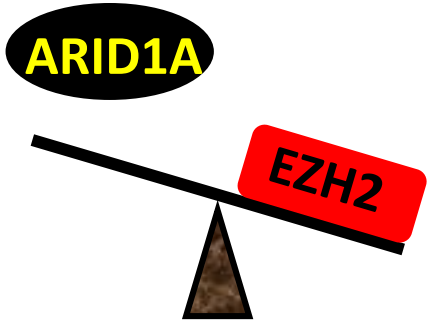


ARID1A mutation
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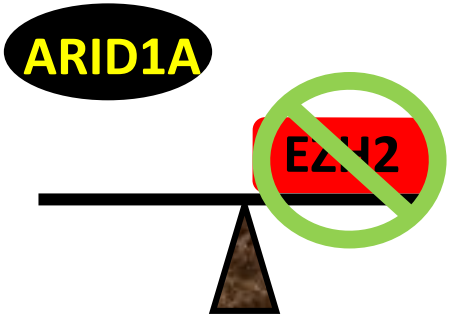
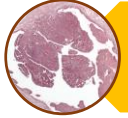



ARID1A mutation
EZH2 inhibited
Proliferation inhibited
Apoptosis induced



## Targeting the morphomolecular type

# Testing the ARID1A clinical synthetic lethality

### NRG GY014 *pending activation:*

### Tazemetostat in clear cell & endometrioid ovca

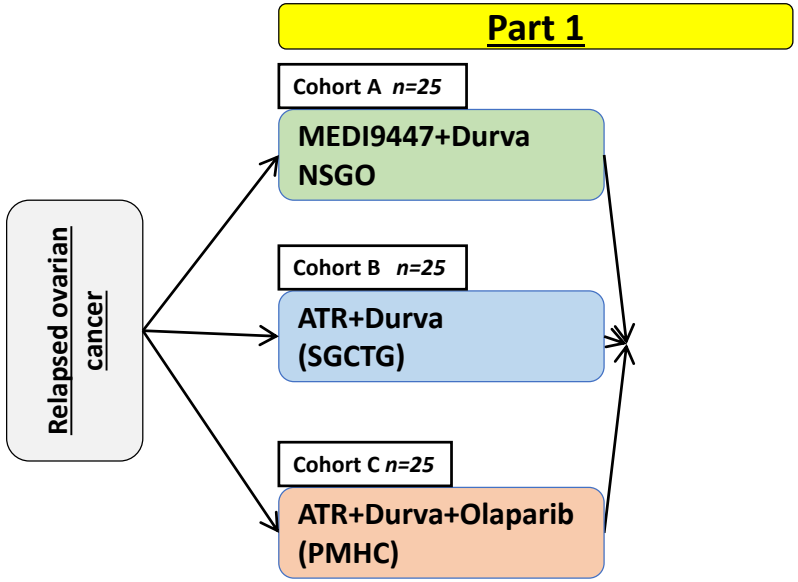
**Recurrent ovarian or endometrial clear cancer**
**Measurable disease**
**Platinum-resistant**
**At least 1 prior regimen**
**ARID1A$^{mut}$ status integrated endpoint**

→ **Tazemetostat 800mg daily**

NRG GY014, Eskander

# New designs

## NSGO-OV-UMB1/ENGOT-OV30: phase II umbrella trial in relapsed ovarian cancer



# New designs

## NSGO-OV-UMB1/ENGOT-OV30: phase II umbrella trial in relapsed ovarian cancer

**Part 1**

Relapsed ovarian cancer

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

2:1

**Part 2**

MED19447 + Durvalumab
Standard of Care

ATR + Durvalumab
Standard of Care

ATR + Durvalumab + Olaparib
Standard of Care

Days: 1 15 29 43 57

biopsy Day: < 1
CT, blood, serum samples

blood, serum samples

biopsy Day: < 1
CT, blood, serum samples

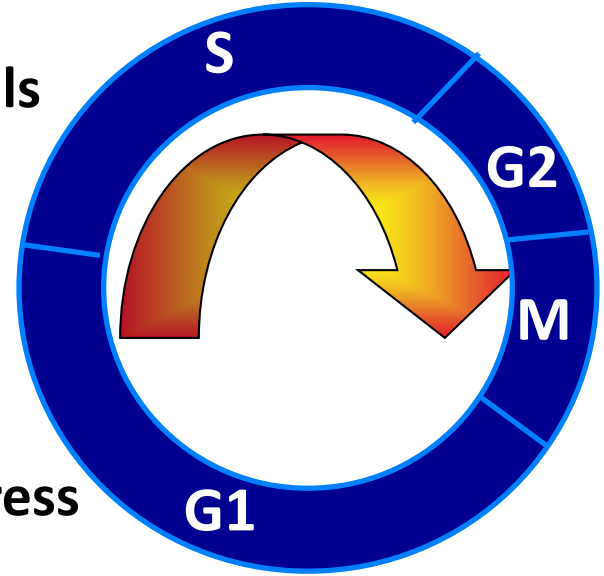
New agents

# 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

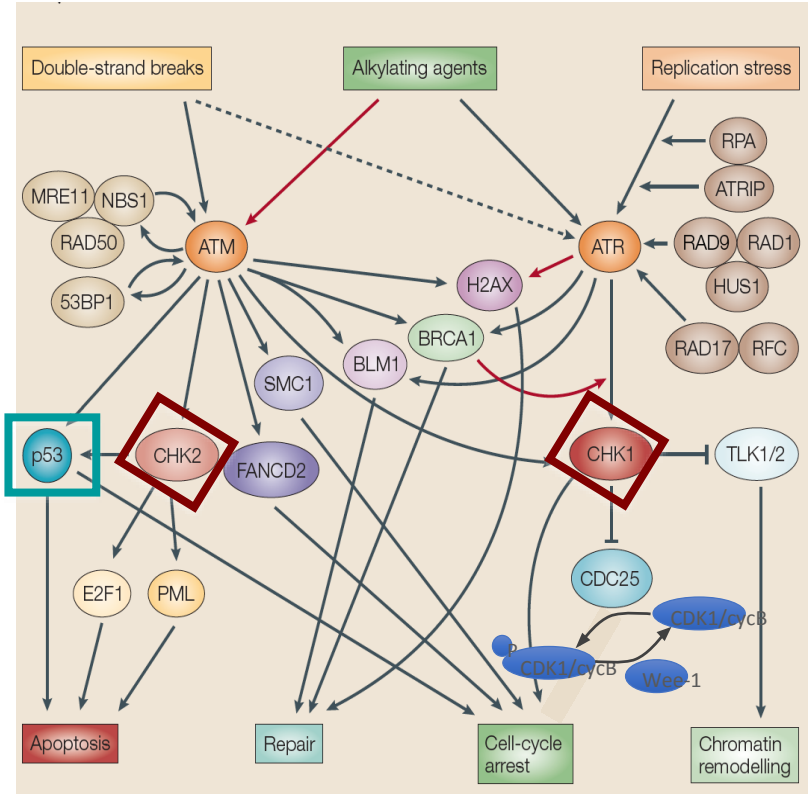
Cells that cannot stop the growth cycle, accumulate injury and die

# New agents

## Prexasertib: CHK1/2 inhibition in parallel with endogenous *TP53*$^{mut}$

**p53$^{mut}$ is endogenous--**

***blocks cell cycle arrest promoting replication stress***



# New agents

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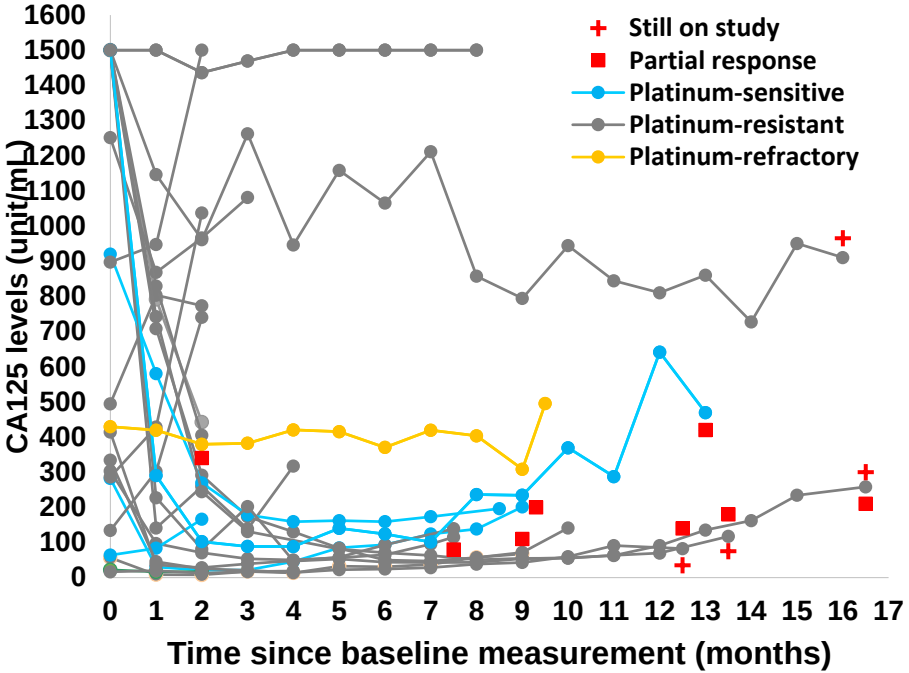


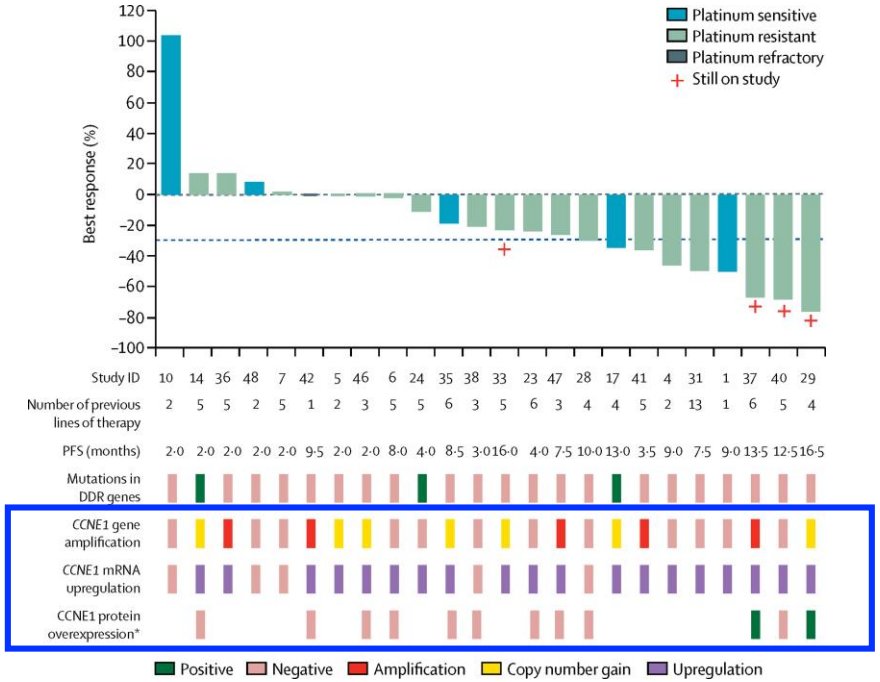

J-m Lee et al, *Lancet Oncol* 2018

# New agents

## Prexasertib: CHK1/2 inhibition in parallel with endogenous *TP53*$^{mut}$

**79% (19/24) had ↑*CCNE***

**63% with ↑*CCNE* had PFS >6mo**

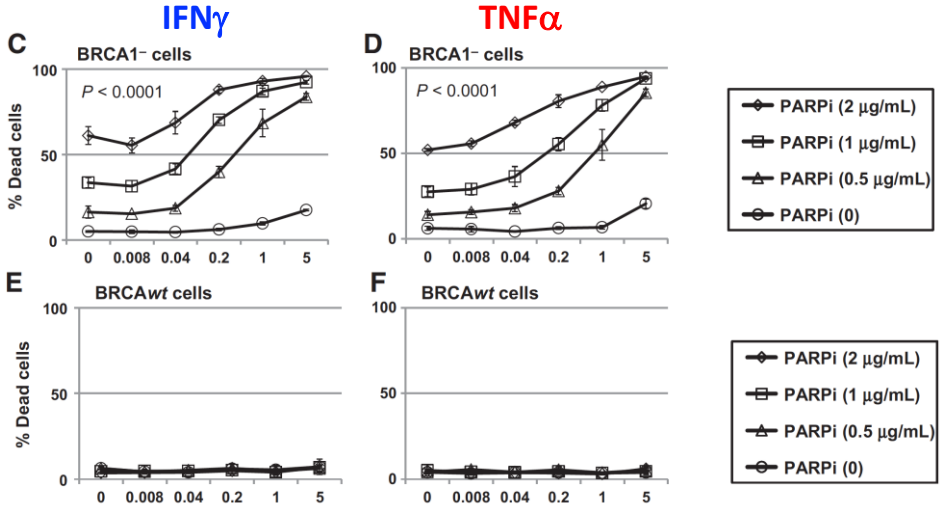



J-m Lee et al, *Lancet Oncol* 2018

# 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**




Higuchi,… Adams et al. Cancer Immunol Res 2015

# Novel combinations

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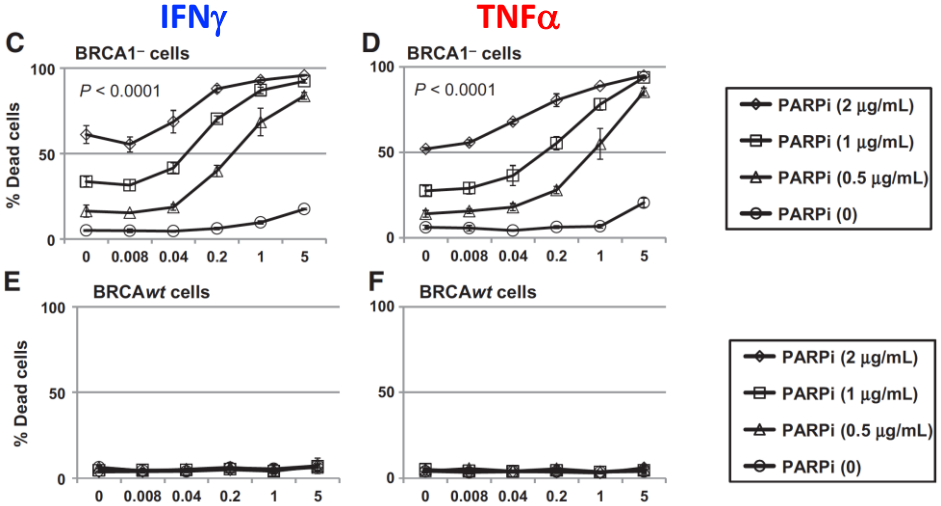
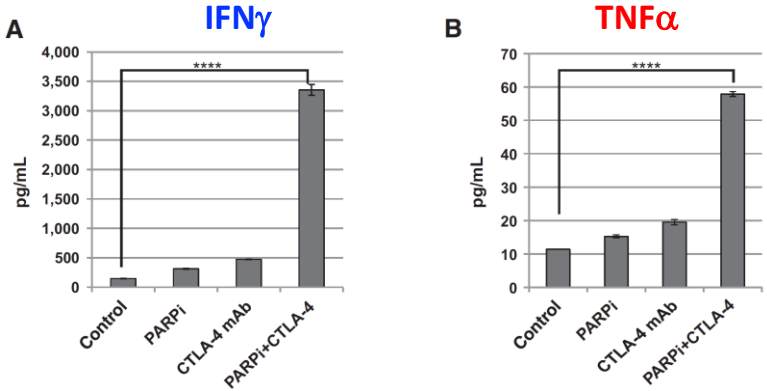


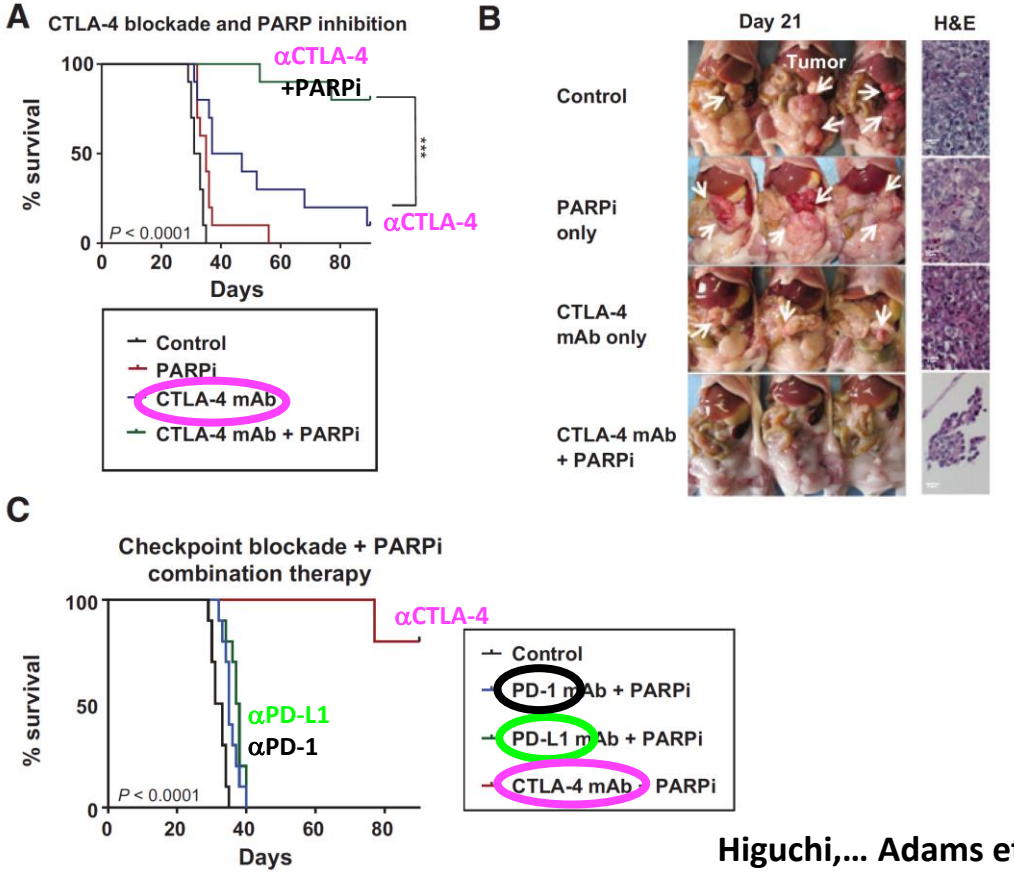




**Interrupting PARPi and CTLA-4 signaling synergistically induces IFNγ and TNFα**

Higuchi,… Adams et al. Cancer Immunol Res 2015

# Novel combinations

## Only anti-CTLA4 works in BRCA$^{mut}$ OVCA in vivo




Higuchi,… Adams et al. Cancer Immunol Res 2015

# Novel combinations

## Testing this hypothesis: NRG GY021 tremelimumab/olaparib

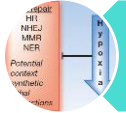
**PlatS HGSOC** — **R**

Stratify by gBRCAm v wt/unkn
Prior PARPi exposure

- **Tremelimumab 10mg/kg q4w x4→ every 12w to 2 yrs**
  **Olaparib 300mg po bid continuously**
- **Olaparib 300mg po bid continuously**

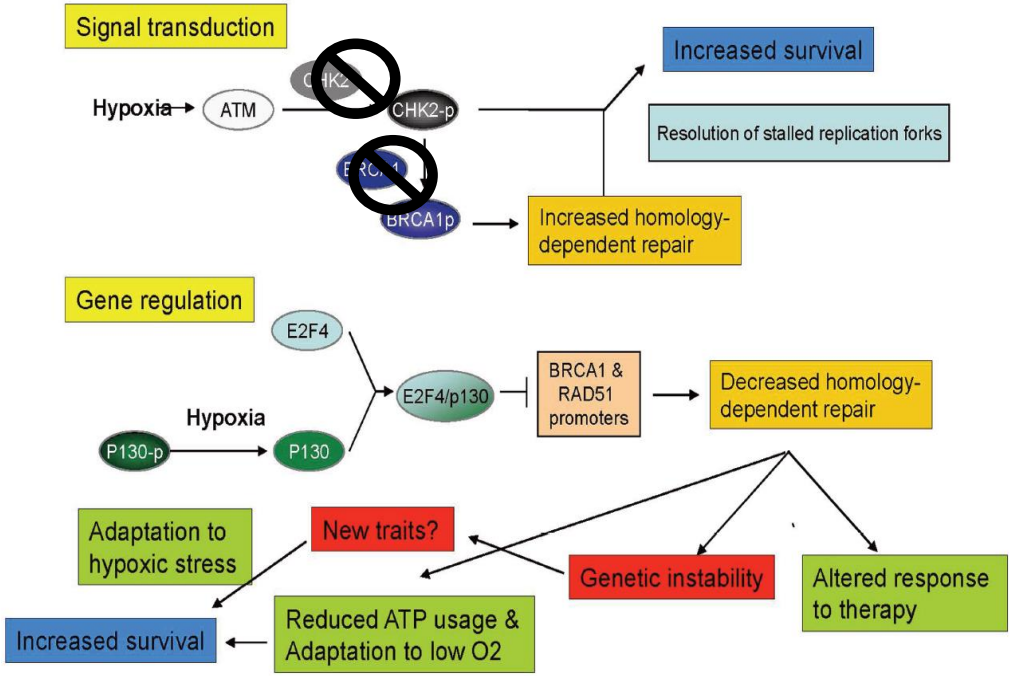
**1st: 50 pt safety lead in, DLT through cycle 3**
**2nd: 40 additional safety lead in, DLT through cycle 3**
**Total: 150, randomized 1:1**

S. F. Adams, PI , protocol under development



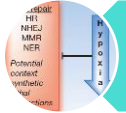
# Targeting the TME not just the tumor

# Hypoxic creates DNA damage liabilities



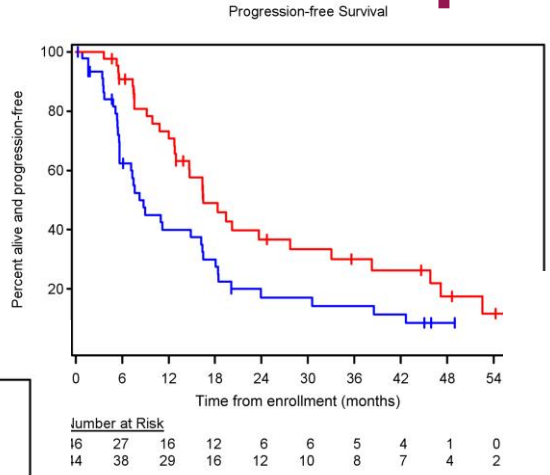

- Hypoxia downregulates expression of key DNA repair genes, eg CHK1/2, BRCA1
- Local hypoxia generation by angiogenesis inhibitors
- Local hypoglycemia and acidosis and may cause similar effects

Ivy and Kohn, Trends Cancer, 2017
Liu et al, Lancet Oncol, 2015
Glazer et al, Yale Journal, 2013



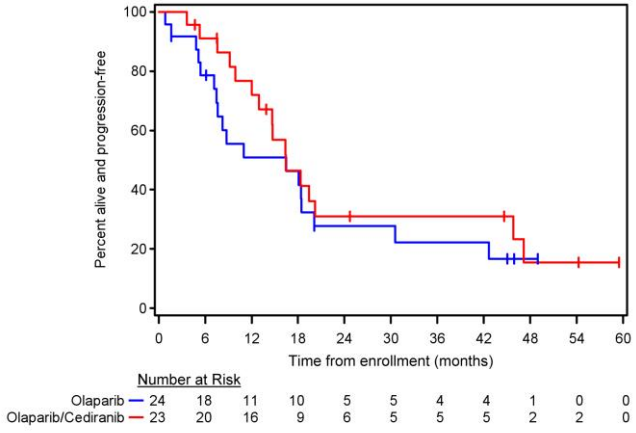

# Targeting the TME not just the tumor

## PFS benefit with olaparib/cedarinib

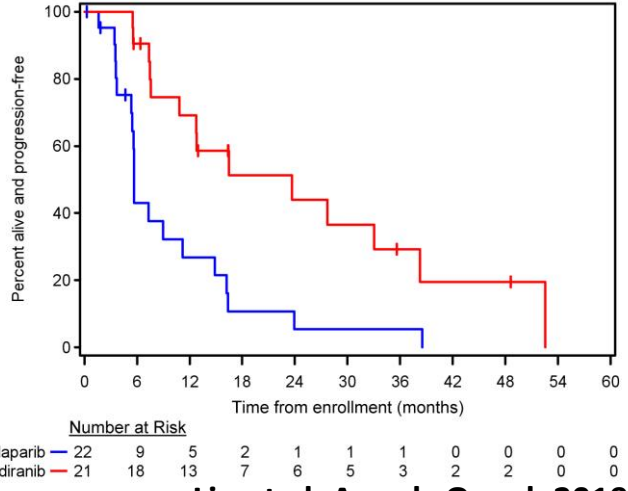



**All women N=90**
**16.5 vs. 8.2 mo**
**HR 0.50; p = 0.007**

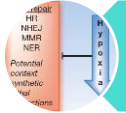
**gBRCA (N=47)**




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




Liu et al, Annals Oncol, 2019



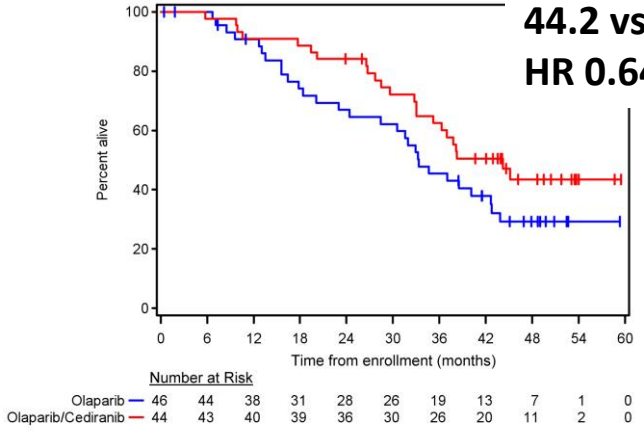
# Targeting the TME not just the tumor

## OS benefit of doublet for wild type/unknown BRCA

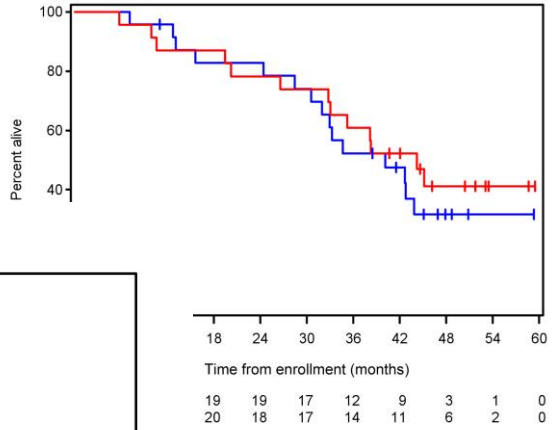
**All women** N=90

44.2 vs. 33.3 mos

HR 0.64; p = 0.11

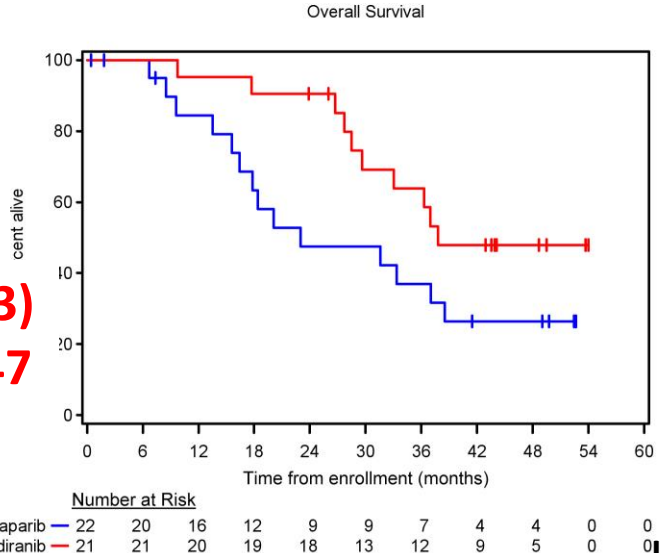



**gBRCA (N=47)**

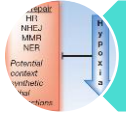



**BRCAwt/unk (N=43)**

**37.8 v 23.0, p=0.047**




Liu et al, Annals Oncol, 2019

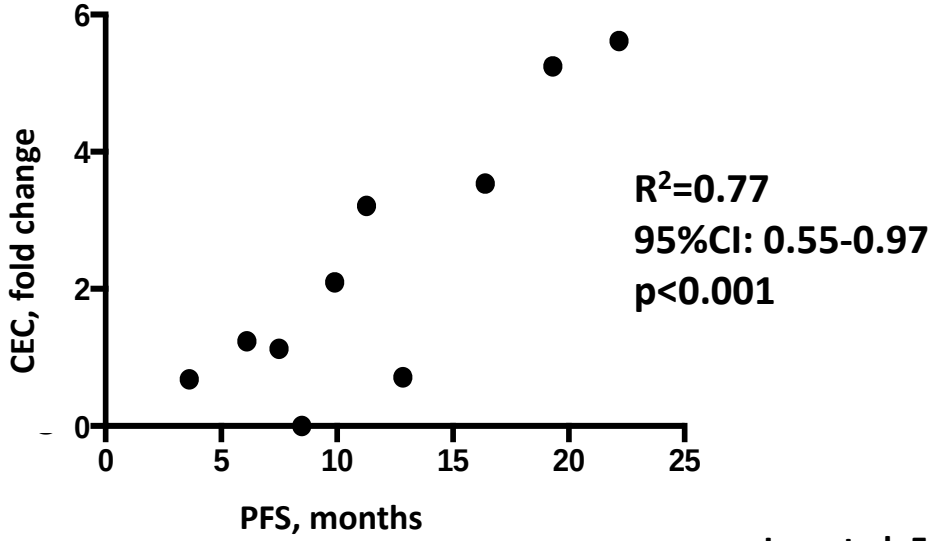


# Targeting the TME not just the tumor

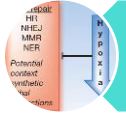
## Olaparib and cediranib: *Clinical synthetic lethality*

### Hypoxia and DNA repair inhibition: preliminary proof of concept

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



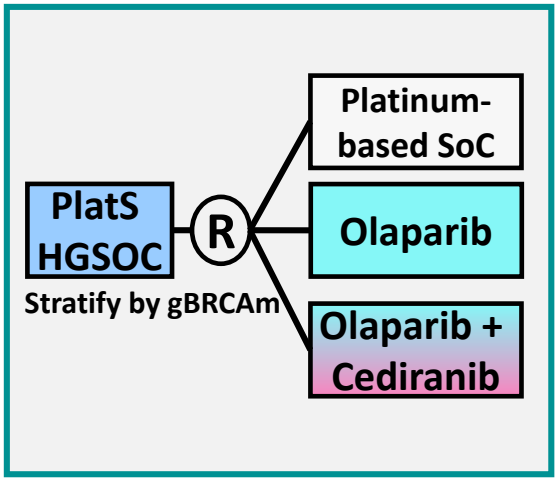

Lee et al, Front Womens Cancers, 2015



# Targeting the TME not just the tumor

## Phase 3 registration studies

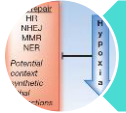
**NRG GY004**




**Fully accrued**

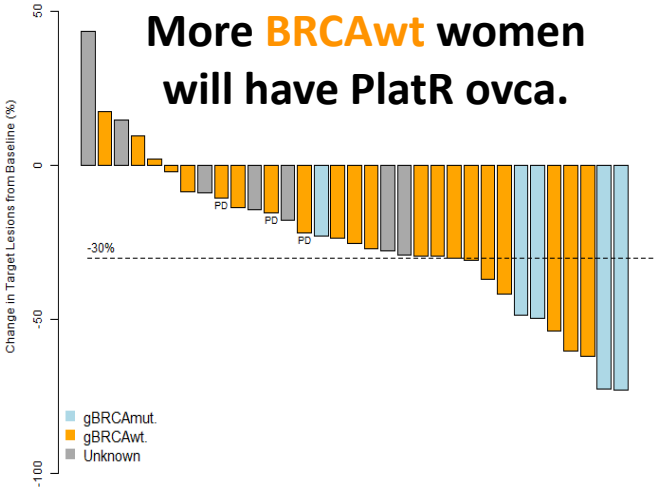
**Anticipate final results 2Q19**

**NRG PI: Joyce Liu**

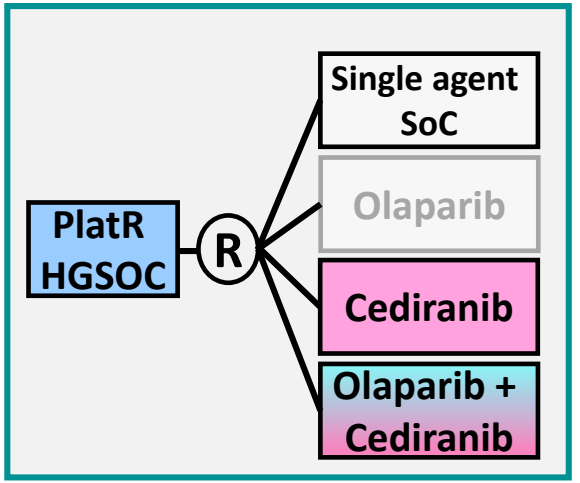


# Targeting the TME not just the tumor

## Phase 3 registration studies




**NRG GY005**



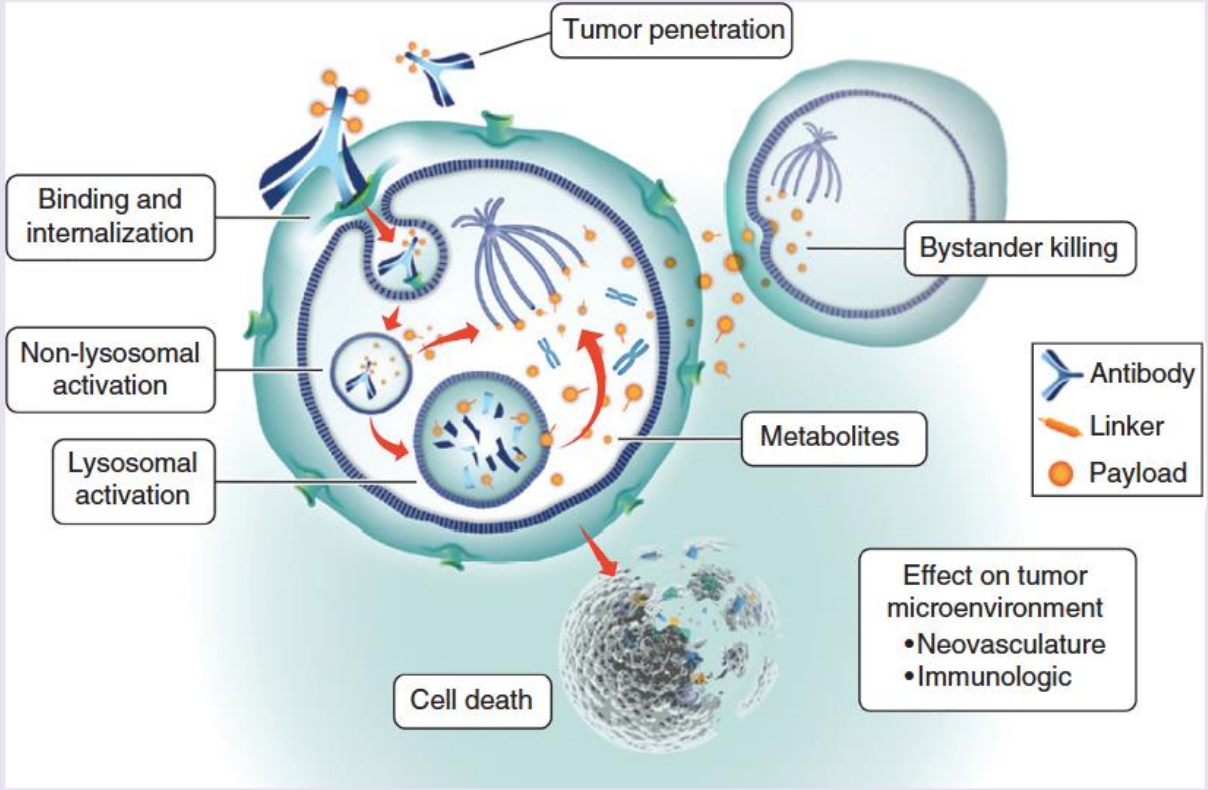

**Phase 3 opened 12/18**

**Droppping single agent olaparib arm**

**NRG PI: Jung-Min Lee**

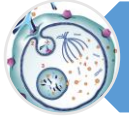
# Improved therapeutic delivery

## Antibody-directed conjugates: bringing the toxin to the tumor




- Mirvetuximab soravtansine 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+ FR$\alpha$ staining

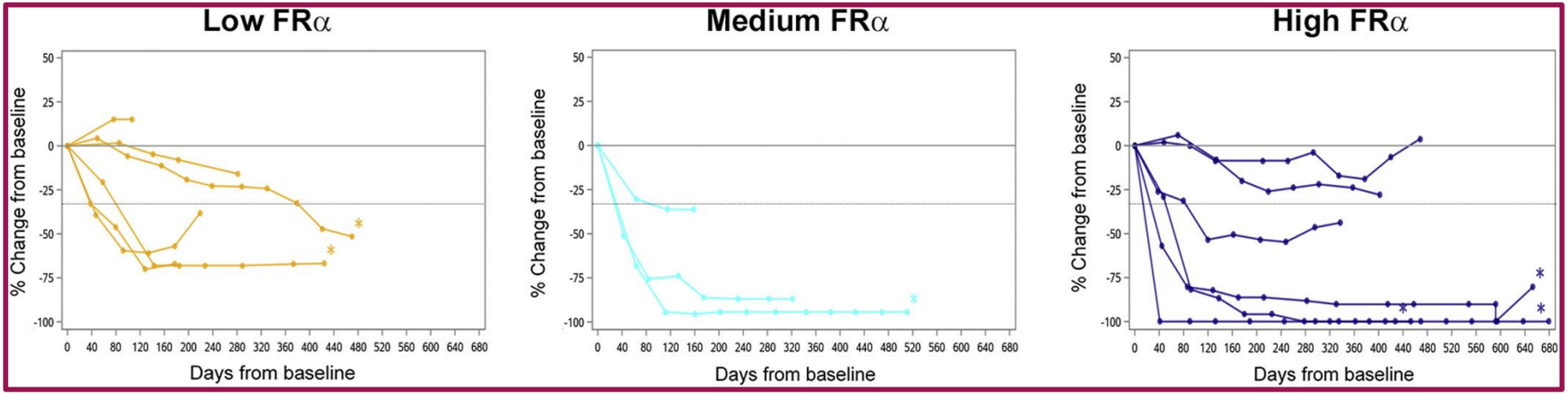
**RESULTS**

- 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

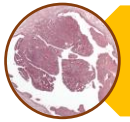
# Improved therapeutic delivery

## Mirvetuximab sorvetansine + carboplatin safety phase I

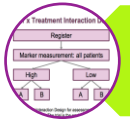



Moore et al, Gyn Oncol, 2018

# New *Hope* in Ovarian Cancer Treatment



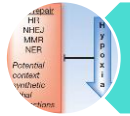
Targeting the morphomolecular type



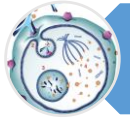

New designs

New agents

Novel combinations




Targeting the TME not just the tumor



Improved therapeutic delivery

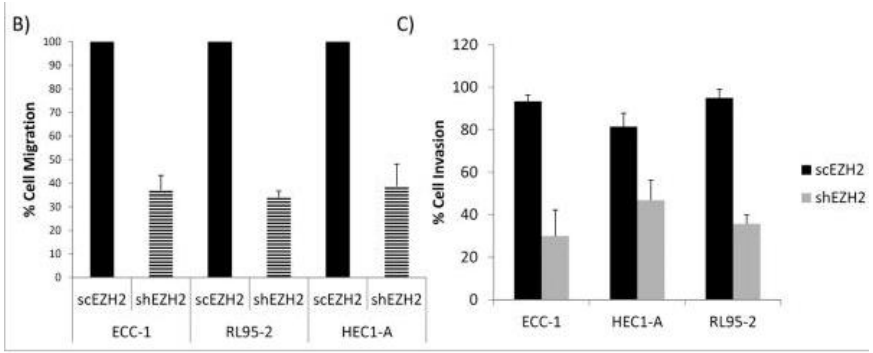
NATIONAL CANCER INSTITUTE

www.cancer.gov

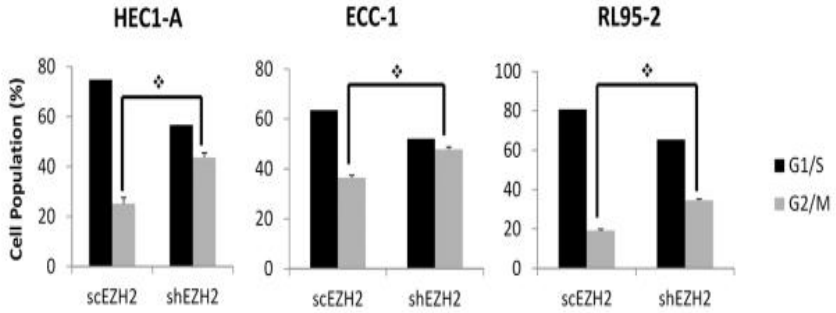
www.cancer.gov/espanol

# Novel targets and agents: EZH2 methytransferase

**Inhibition of migration/invasion in EC cells**




**G2/M accumulation with shEZH2**




- 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

Eskander, et al. Int J Gyn Cancer, 2013

# New Strategies in Ovarian Cancer Treatment

## *Enhancing, informing and improving treatment*

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