

Ovarian Cancer

Ovarian cancer

Advances in clinical and translational research

TRACO lecture

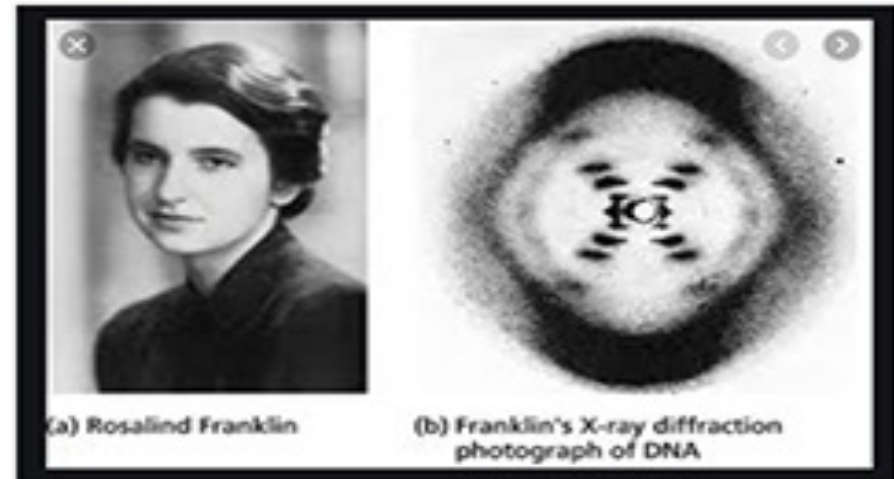
Jung-Min Lee, MD

Women's Malignancies Branch, CCR, NCI

Rosalind Franklin

Rosalind Franklin

- Received her PhD from Cambridge in 1945
- Early 1950s, discovery of DNA structure
- 1956, diagnosed with ovarian cancer
- 1958, died in London



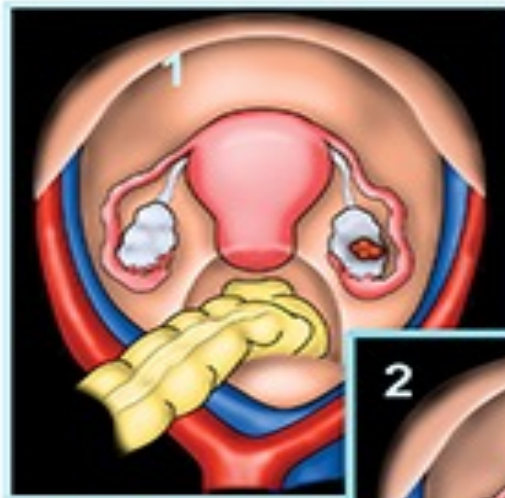
Ovarian cancer

Ovarian cancer

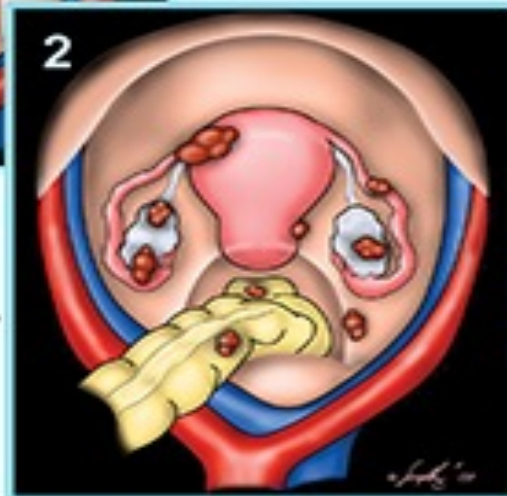
- Most lethal gynecologic malignancy in the US
 - >16,000 deaths/year
 - 5th most common cancer death for women
- 70% diagnosed with advanced disease

FIGO staging

Ovarian cancer FIGO staging



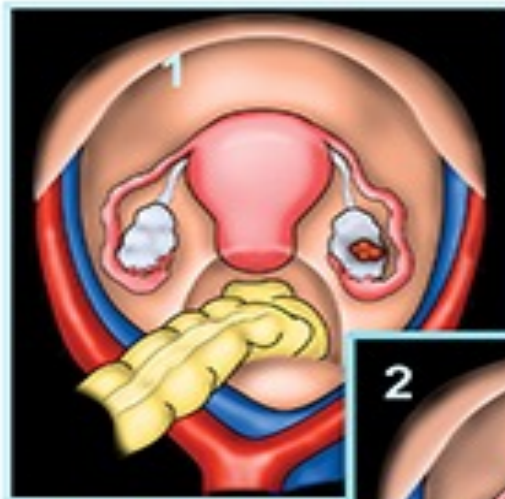
Tumor confined to ovaries
1A unilateral
1B bilateral
1C surface/ascites/rupture/
surgical spill



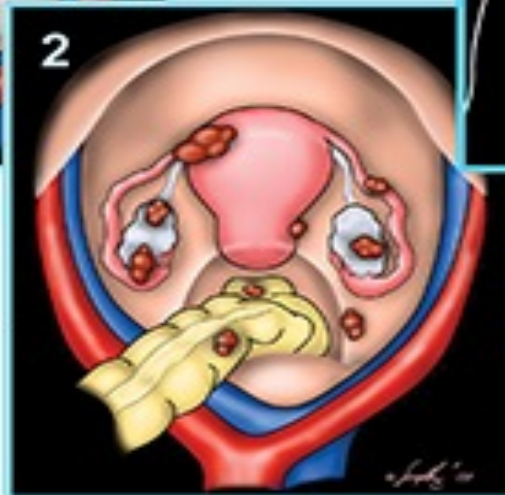
Tumor involves 1 or both ovaries with pelvic extension or PPP
2A local pelvis
2B side walls/bowel surfaces

FIGO staging

Ovarian cancer FIGO staging



Tumor confined to ovaries
1A unilateral
1B bilateral
1C surface/ascites/rupture/
surgical spill



Tumor involves 1 or both ovaries with pelvic extension or PPP
2A local pelvis
2B side walls/bowel surfaces



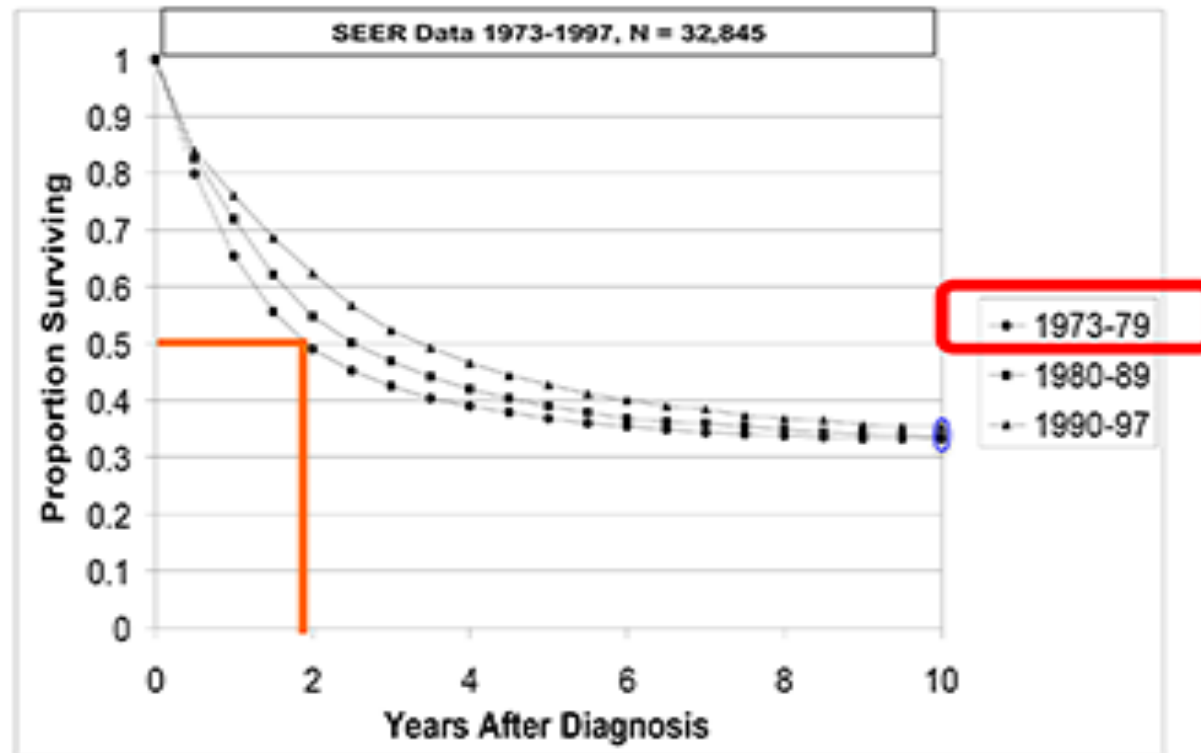
Spread to peritoneum outside the pelvis and/or mets to the RP nodes
3A microscopic spread to abdomen
3B largest ≤ 2 cm
3C largest > 2 cm



Distant mets excluding peritoneal mets
4A pleural effusion
4B parenchymal disease

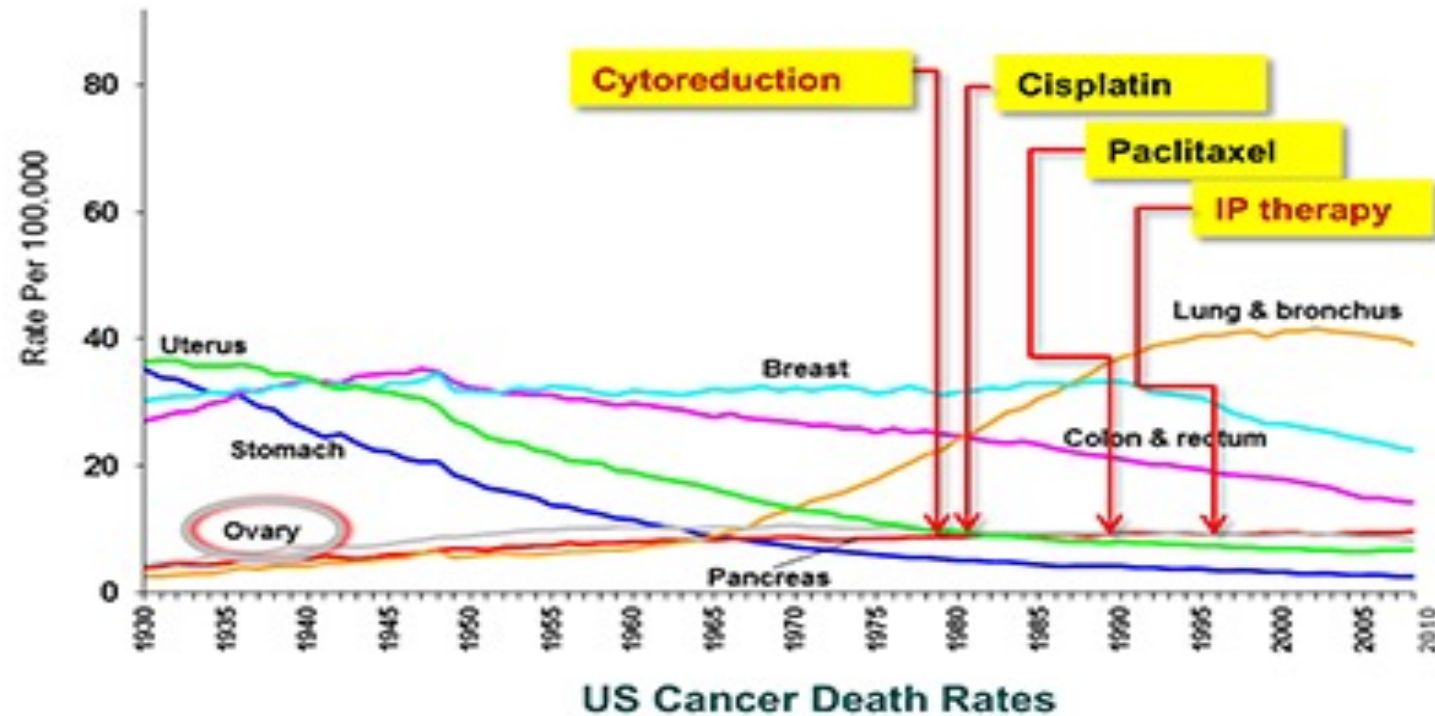
Cancer survival

Ovarian cancer survival trends



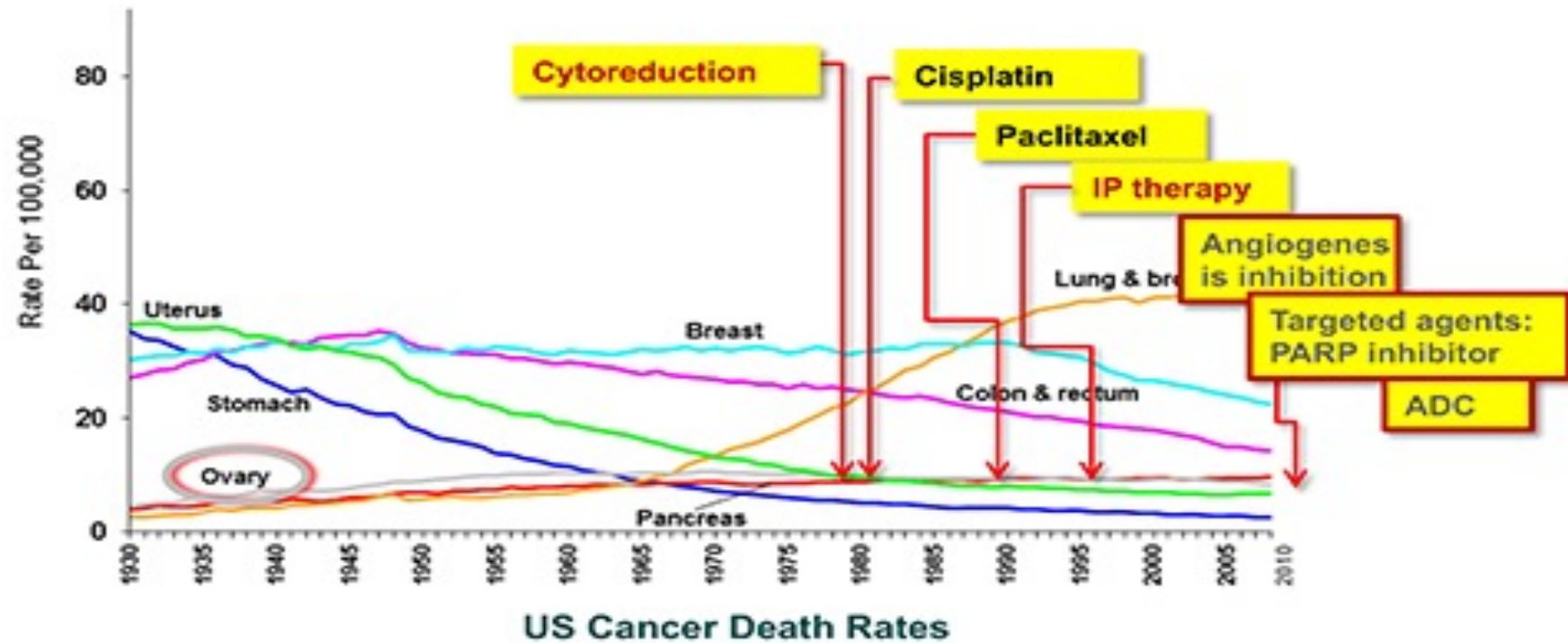
Cancer treatment

Treatment evolution for ovarian cancer



Evolution

Treatment evolution for ovarian cancer



Treatment

Treatment for newly diagnosed ovarian cancer

- Complete surgical staging
- Optimal reductive surgery
- Chemotherapy
- *Clinical Trials*

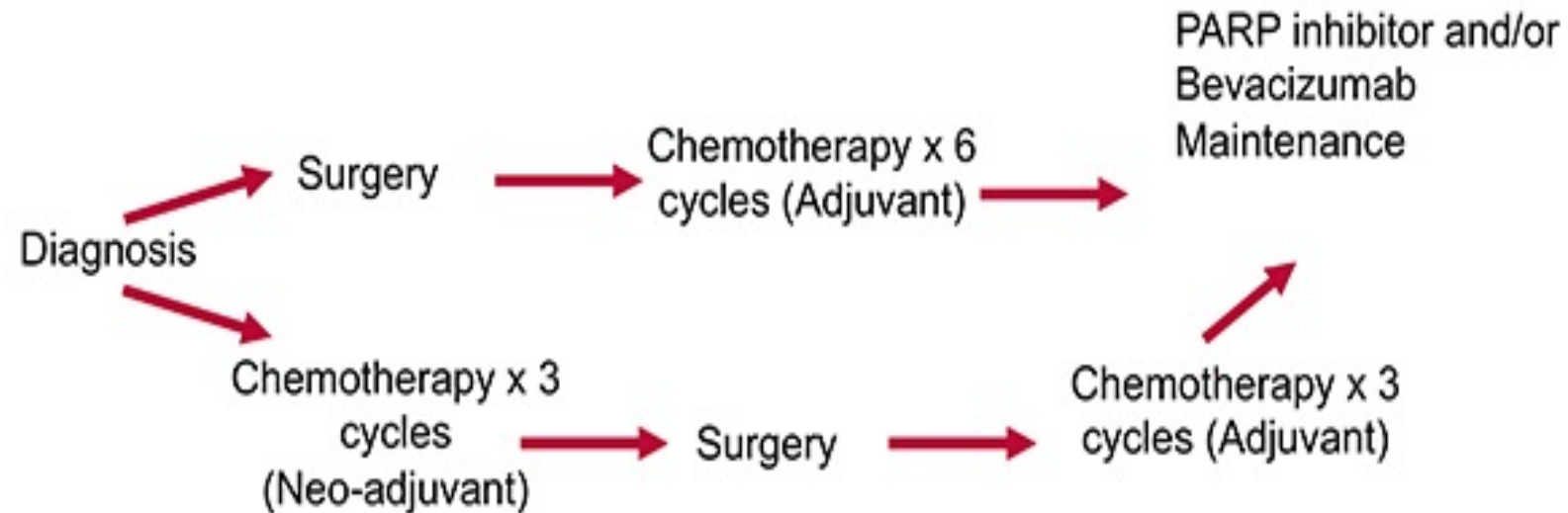
Treatment

Treatment for newly diagnosed ovarian cancer

- Complete surgical staging
- Optimal reductive surgery
- **Chemotherapy**
 - Platinum = cisplatin or carboplatin
AND
 - Taxane = paclitaxel or docetaxel
 - *Intraperitoneal if Stage III, optimal reduction*
- *Clinical Trials*

Ovarian cancer treatment

Treatment paradigm for ovarian cancer

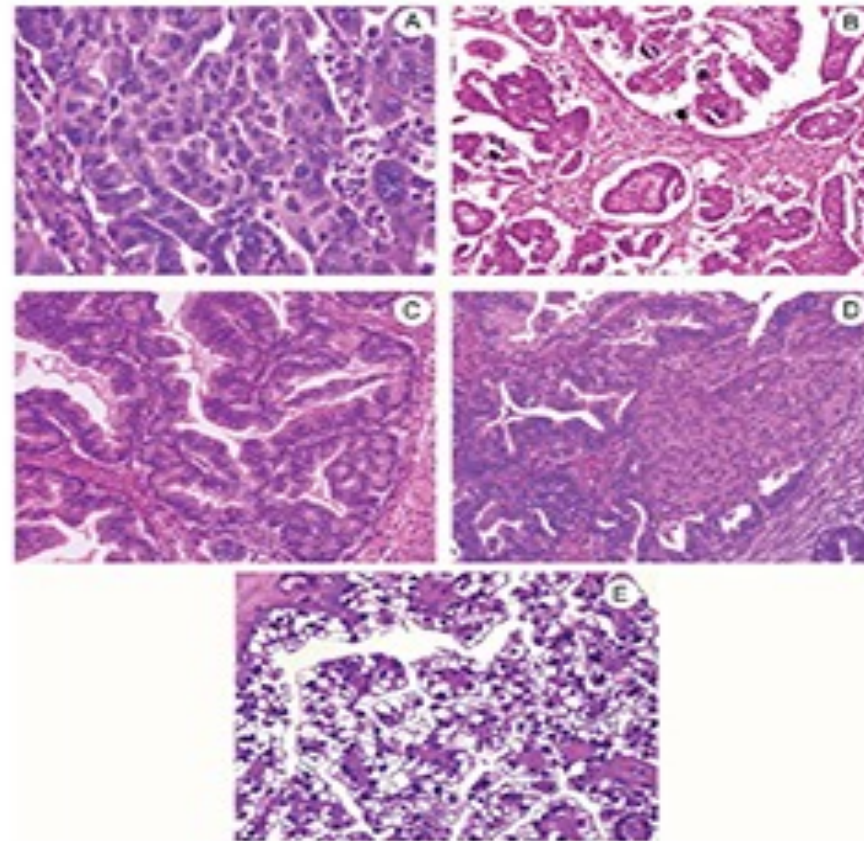


Ovarian cancer types

Ovarian cancer

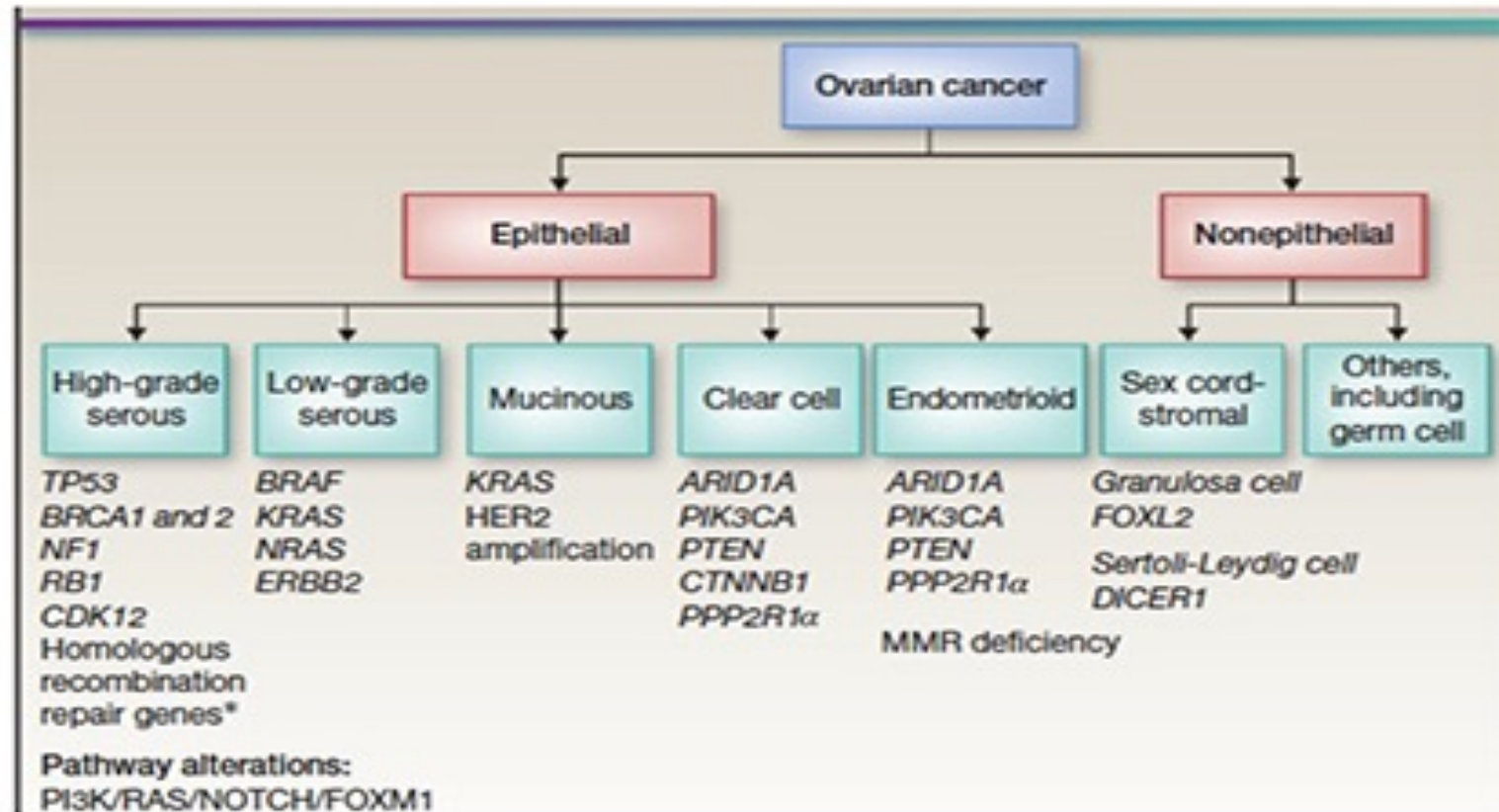
Prevalence

- Serous – 75%
- Endometrioid – 10%
- Clear cell – 8%
- Mucinous – 3%
- Low grade serous – 2%
- Other – 2%



Genomics

Ovarian cancer genomics



Serous ovarian cancer

High grade serous ovarian carcinoma
(HGSOC)

TCGA

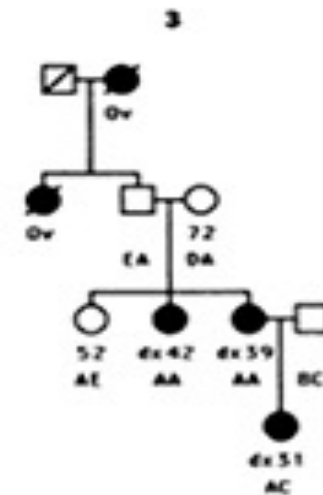
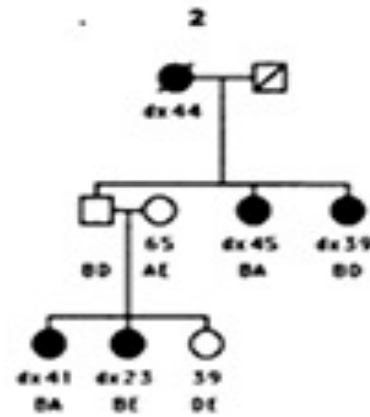
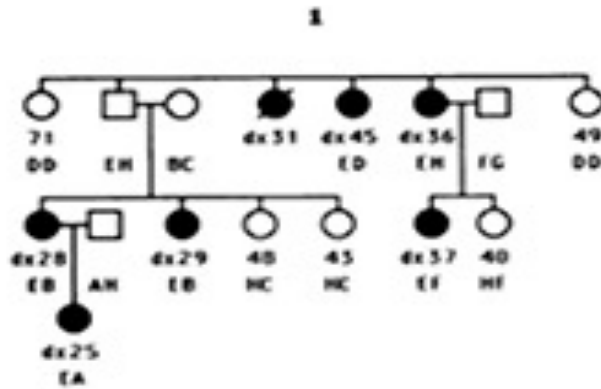
TCGA in HGSOc



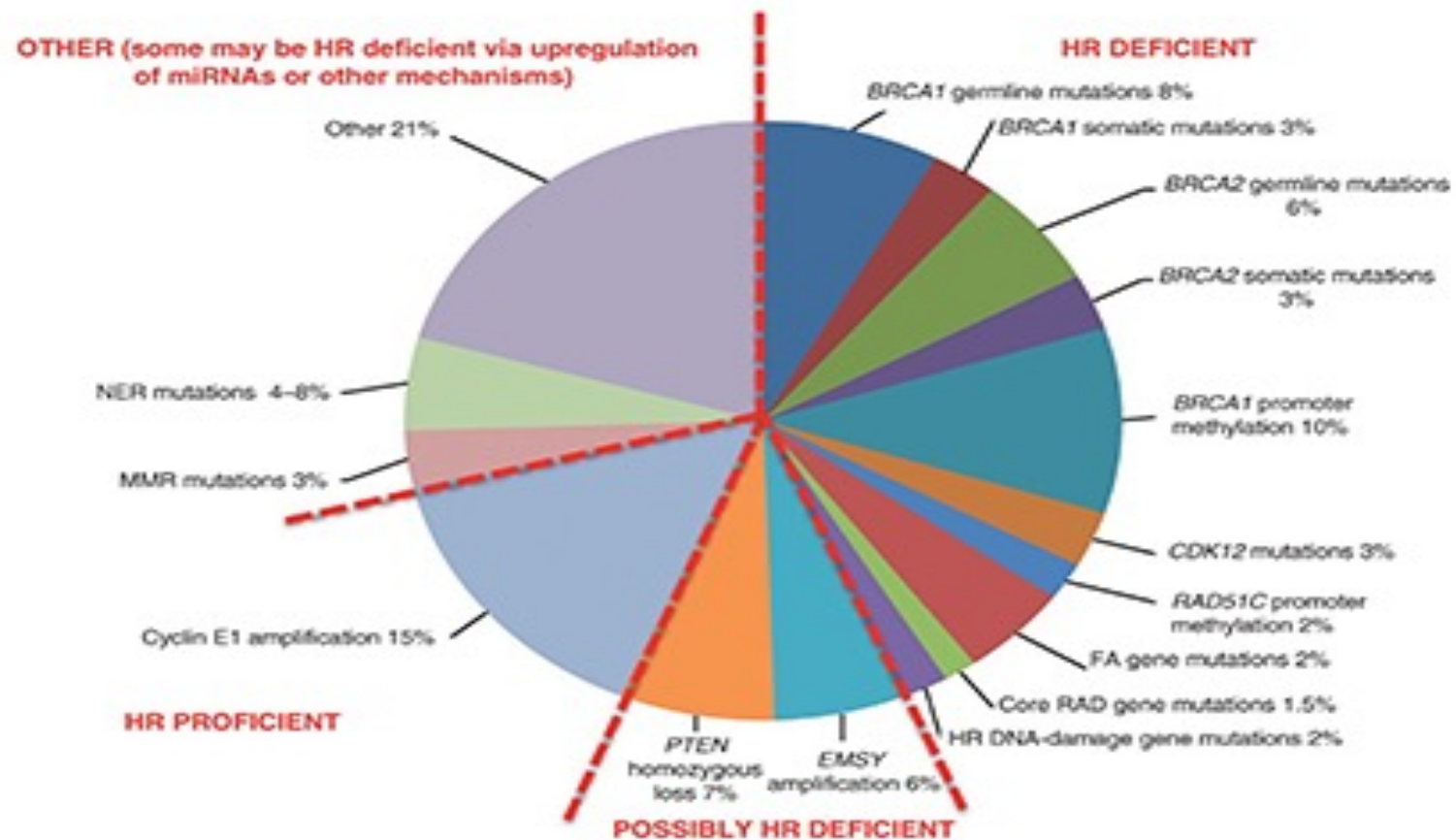
BRCA mutations

BRCA mutations

- Hall...King, *Science*, 1990

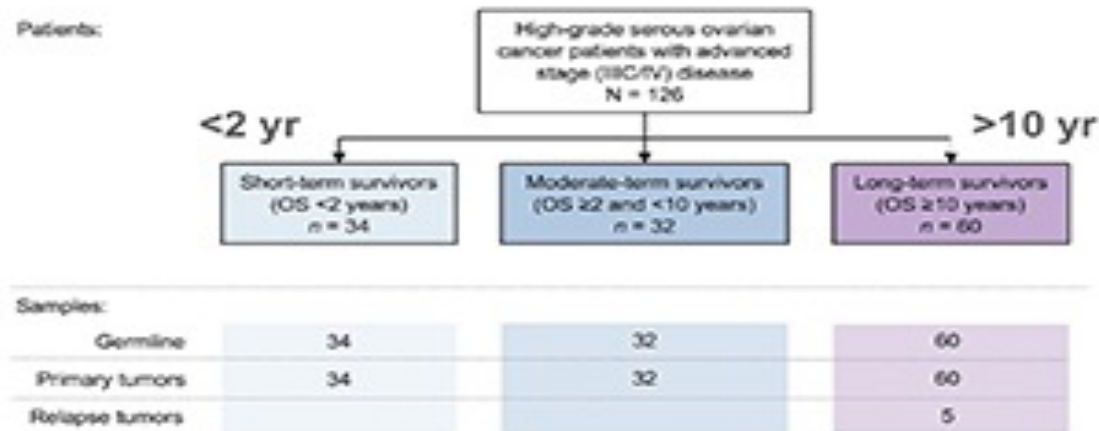


Genetic mutations



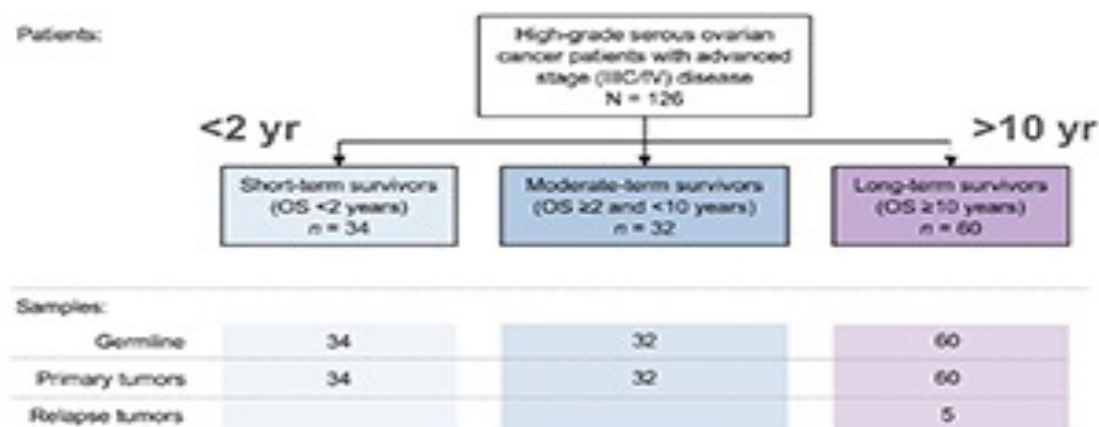
Molecular characteristics

Molecular characteristics of long term survivors

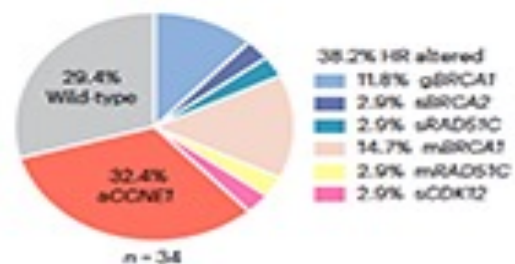


Molecular characteristics

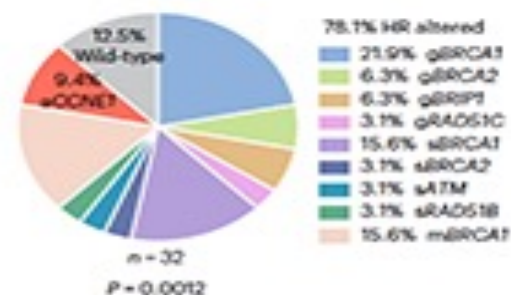
Molecular characteristics of long term survivors



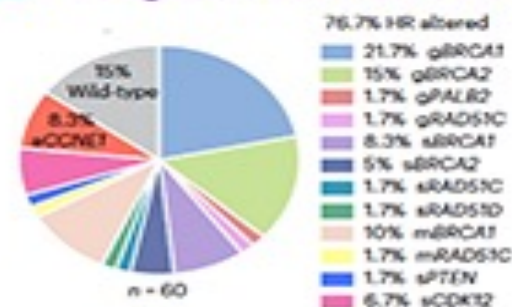
Short term survivor: 38.2% HRD



Moderate term survivor: 78.1% HRD

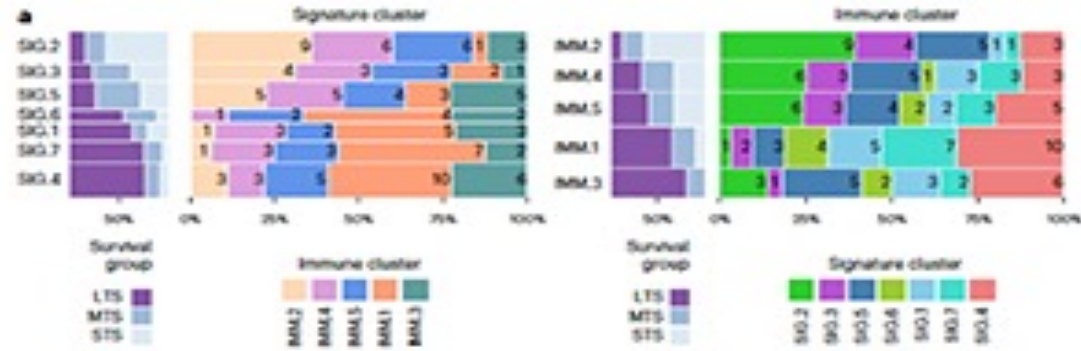


Long term survivor: 76.7% HRD



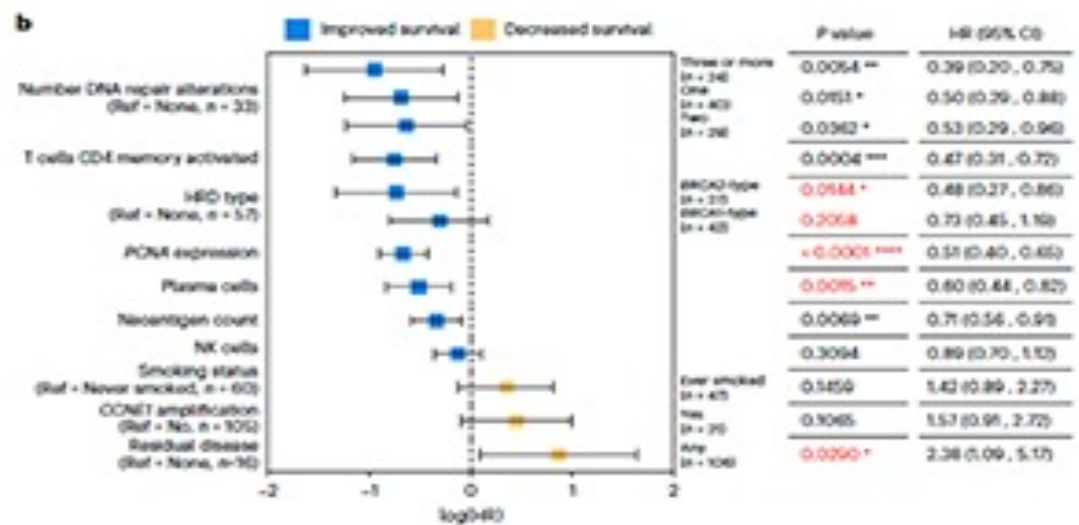
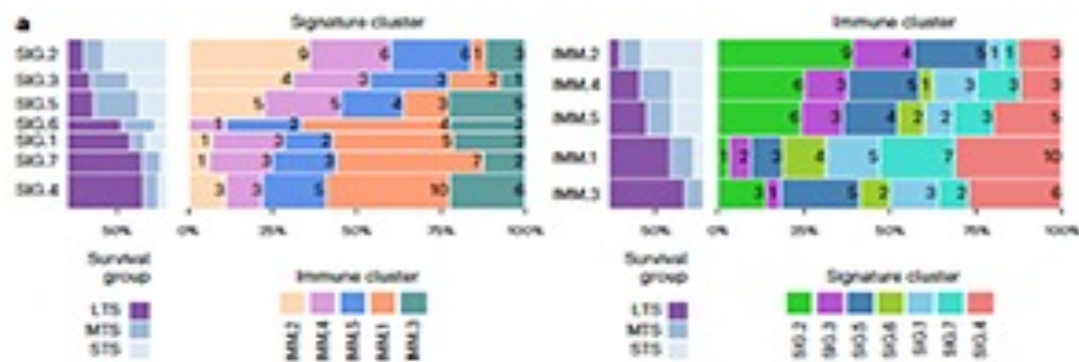
Immunological characteristics

Molecular and immunological characteristics of long term survivors



Immunological characteristics

Molecular and immunological characteristics of long term survivors



PARP inhibitors

Targeting Homologous Recombination
Deficiency
PARP inhibitors

DNA repair

How is DNA repaired?

- Homologous recombination **(HR)**
- Undamaged DNA is the guide
- Replaces damaged part with the “correct” code
- **Uses BRCA**
- Base excision repair **(BER)**
- Cuts out damaged DNA
- Joins cut end with another piece
- **Uses PARP**

DNA repair

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PARP inhibitors

PARP inhibitors approved for ovarian cancer

- Olaparib (Lynparza)
- Rucaparib (Rubraca)
- Niraparib (Zejula)

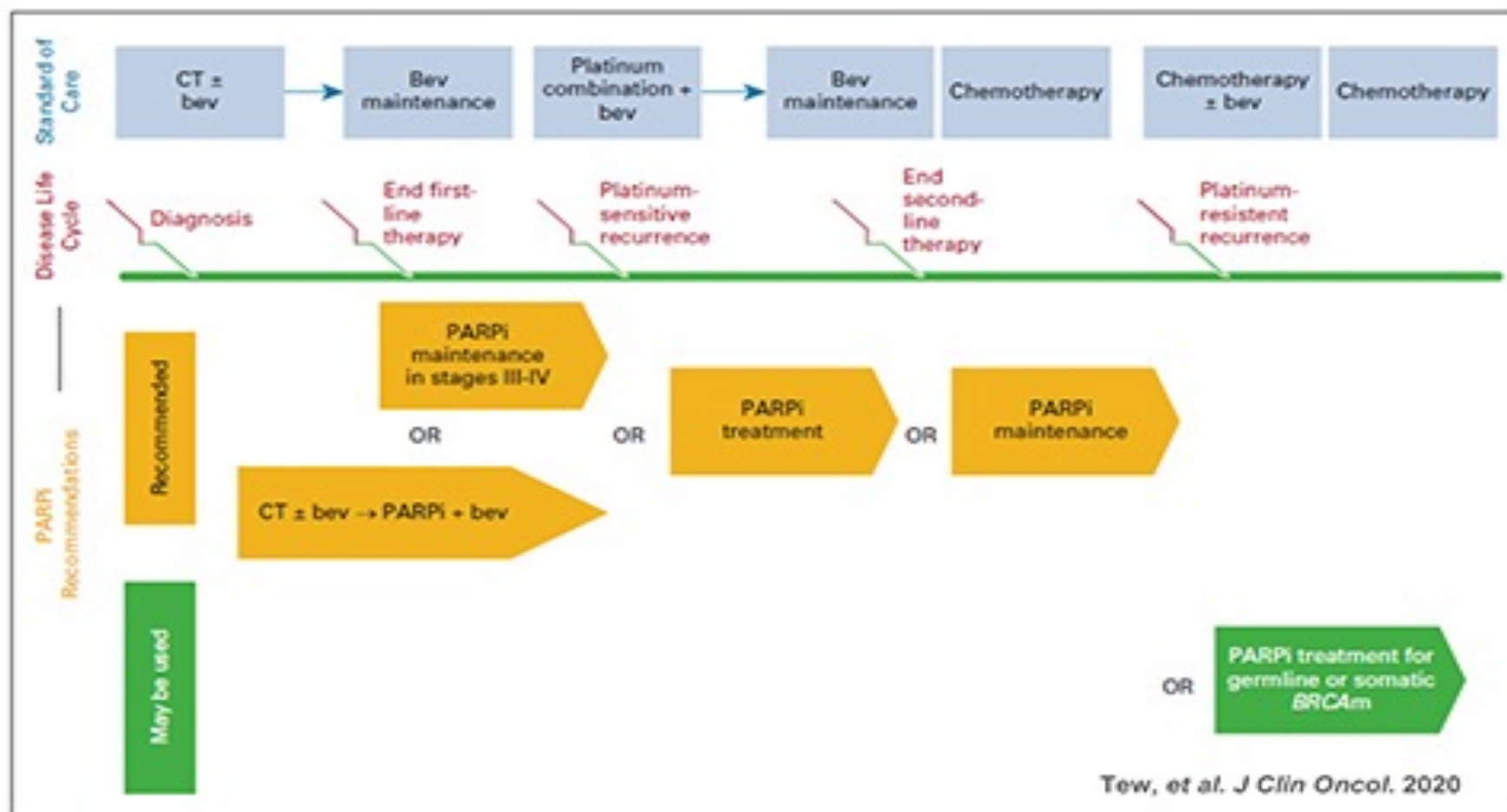
PARP inhibitors

PARP inhibitors – when to use

- First-line maintenance
 - BRCA mutation – germline (hereditary) or somatic (tumor only)
 - BRCA wild type/HR deficiency (HRD) – mutations in particular genes or changes in DNA
 - As monotherapy or in combination with bevacizumab for BRCA mutation and BRCAwt/HRD only
- Second-line maintenance
 - Response to second round of carboplatin/cisplatin
 - If no prior PARP inhibitor..
- Treatment
 - Not currently recommended

PARP inhibitors

PARP inhibitors in clinical practice – ASCO guideline



Relapsed ovarian cancer

Relapsed ovarian cancer

Recurrent ovarian cancer

Treatment for recurrent ovarian cancer



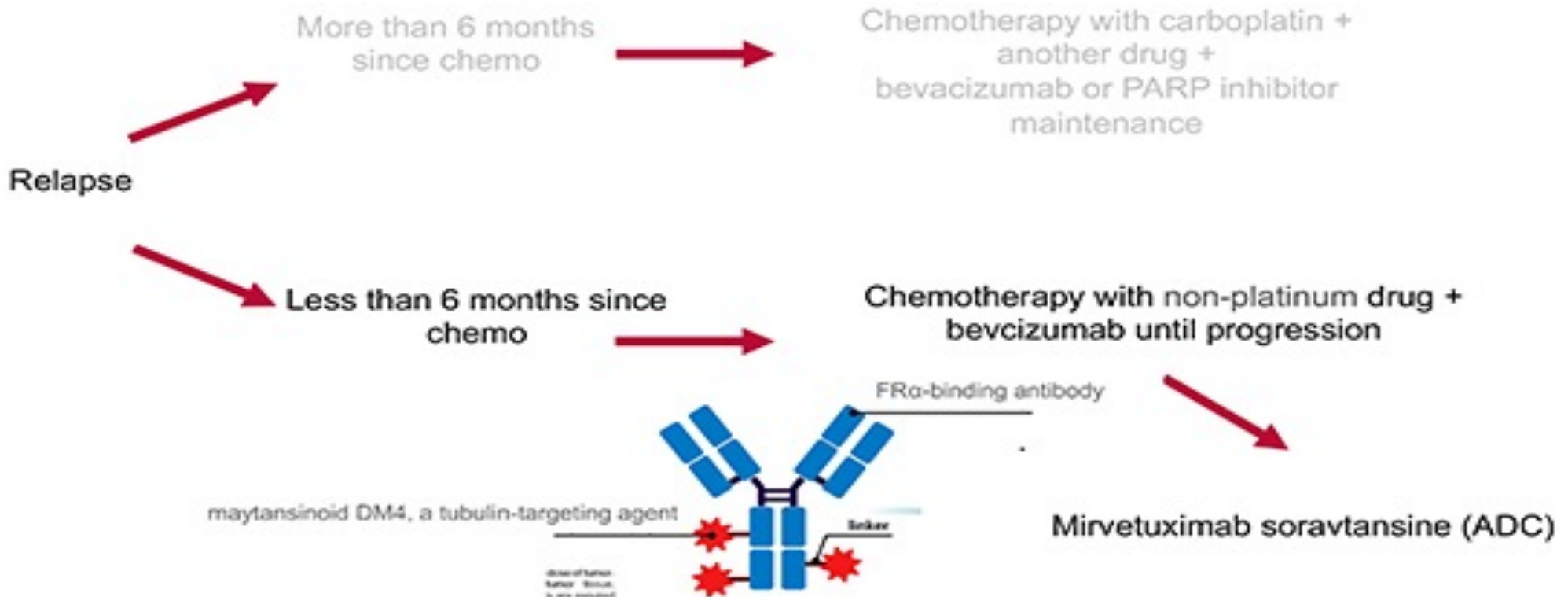
Platinum resistant cancer

Treatment for platinum-resistant ovarian cancer



Platinum resistant cancer

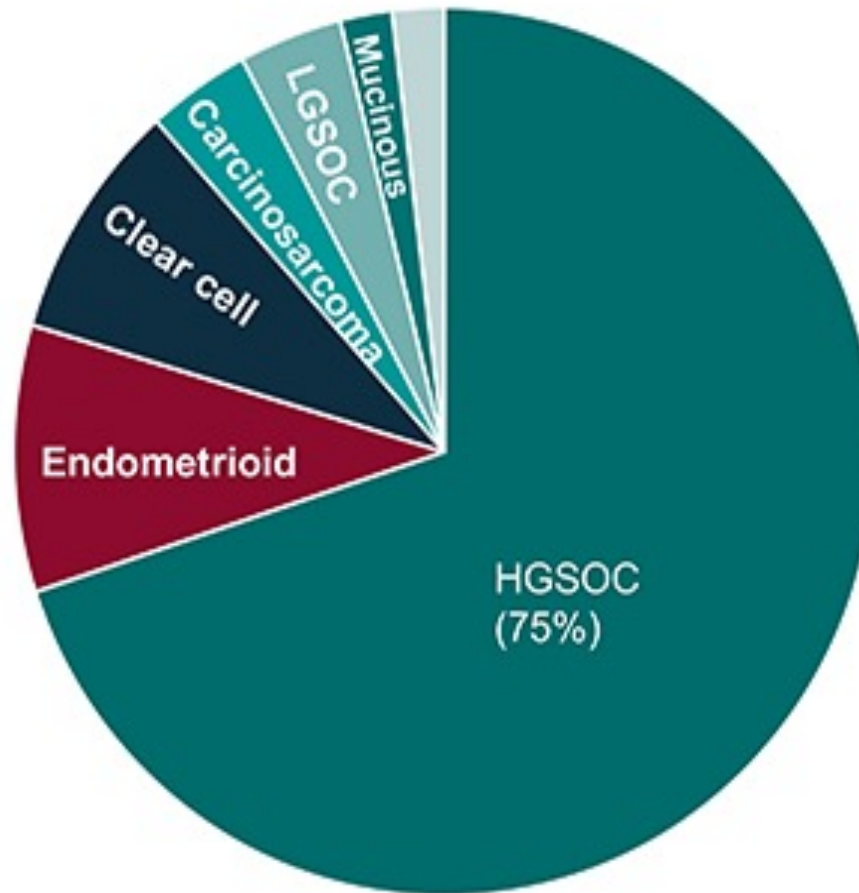
Treatment for platinum-resistant ovarian cancer



Rare ovarian cancers

Rare ovarian cancers:
Low grade serous, Clear cell, Endometrioid, Mucinous,

Ovarian cancers



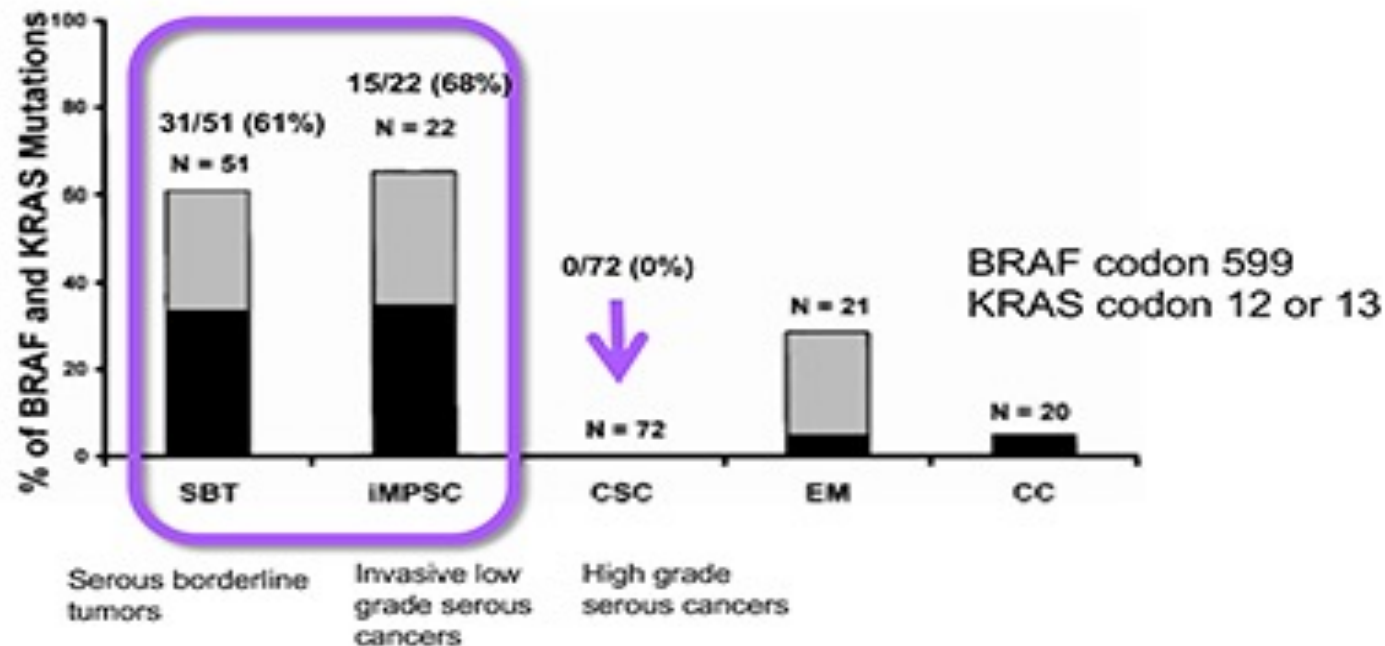
Serous ovarian cancer

Low grade serous ovarian cancer
(LGSOC)

Low grade cancer

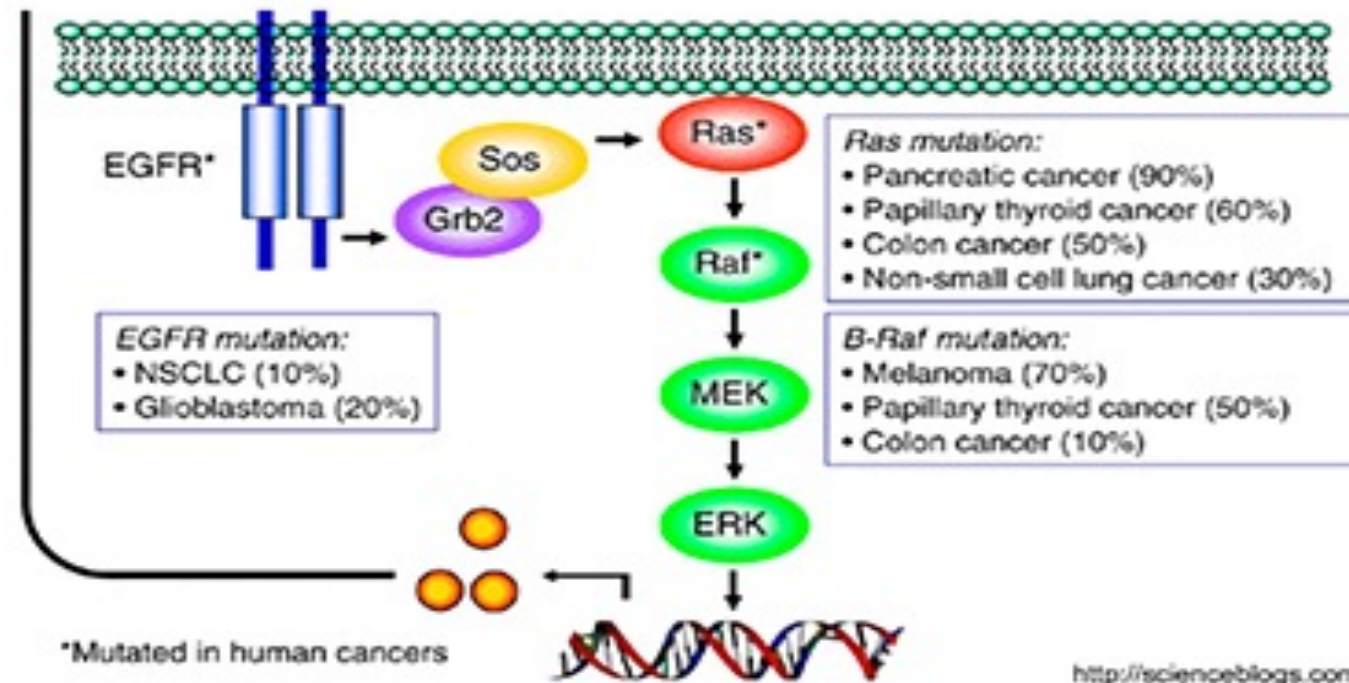
Low grade serous ovarian cancer

- Younger women, indolent, less responsive to chemotherapy
- High ER/PR expression, abbreviations in RAS/RAF/KRAS pathway



RAS signaling

RAS signaling pathway - a therapeutic target

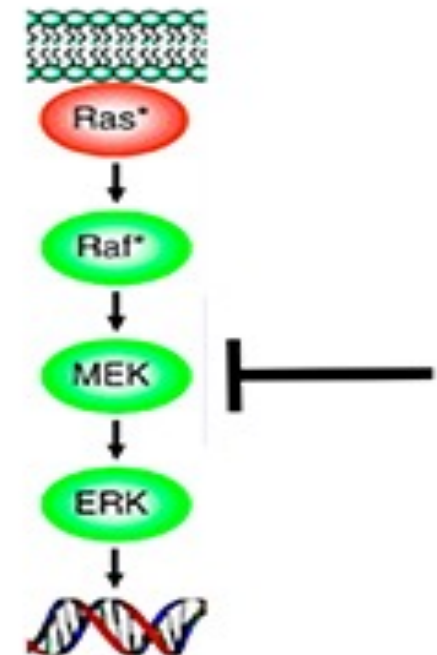


<http://scienceblogs.com/pharyngula/2013/09/21/16271/>

MEK inhibitors

MEK inhibitors in recurrent LGSOC

- Selumetinib: 15% RR
- Trametinib vs chemo: 26.2% vs 6.2% ORR (RP2/3 GOG-281)
- Binimetinib vs chemo:
 - Subgroup analysis: median PFS of 17.7 months (KRAS mut) vs 10.8 months (KRAS wt) (RP3 MILO/ENGOT-ov11)
- Avutometinib +/- defactinib (FAK inhibitor) :
 - Preliminary ORR data (n=59): 28% (8/29) for combo vs 7% (2/30) for monotherapy (RP2 ENGOT-ov60/GOG-3052/RAMP201)



Clear cell

Clear cell ovarian cancer

- 5-10% of all cases in western countries, more frequent in Japan (20-30%)
- Associated with endometriosis (up to 40%)
- Worse response to standard chemotherapy
- ARID1A (epigenetic tumor suppressor) mutated or lost in
 - 50% clear cell
 - Less than 1% serous
 - Unclear therapeutic utility

Adenocarcinoma

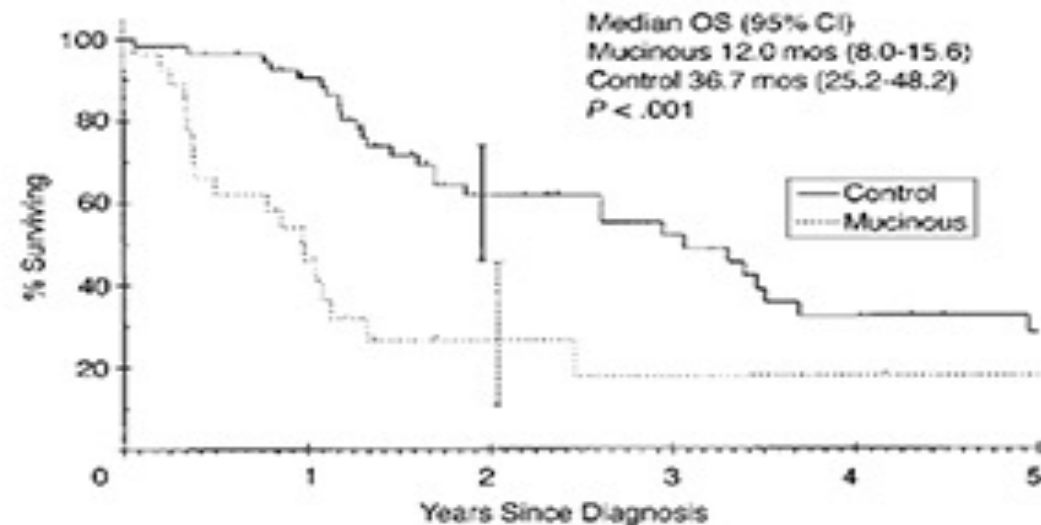
Endometrioid adenocarcinoma

- Strong expression of ER/PR (>80%)
- Associated with endometriosis
- Mean age: 50 years old
- 84% Stage I/II and better prognosis than serous tumors
- May not be as chemo-sensitive as serous tumors
- ARID1A mutated or lost in
 - 40% endometrioid
 - Need therapies targeting these mutations

Mucinous ovarian cancer

Mucinous ovarian cancer

- 83% Stage I, vast majority unilateral
- KRAS mutation/HER2 overexpression
- A routine chemotherapy approach doesn't work
- Clinical trials !

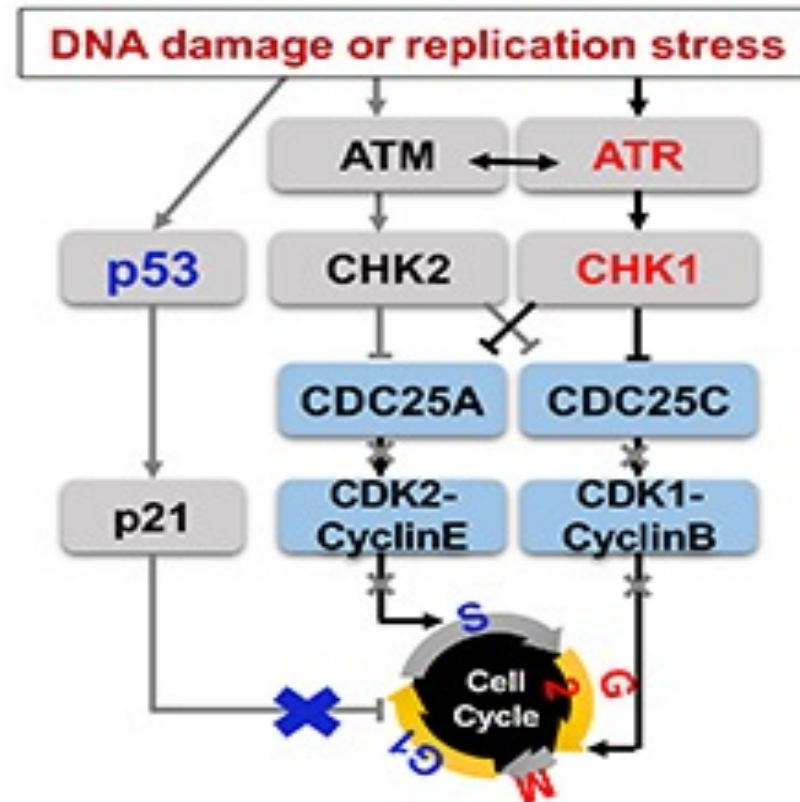


New targets

Exploration of new targets

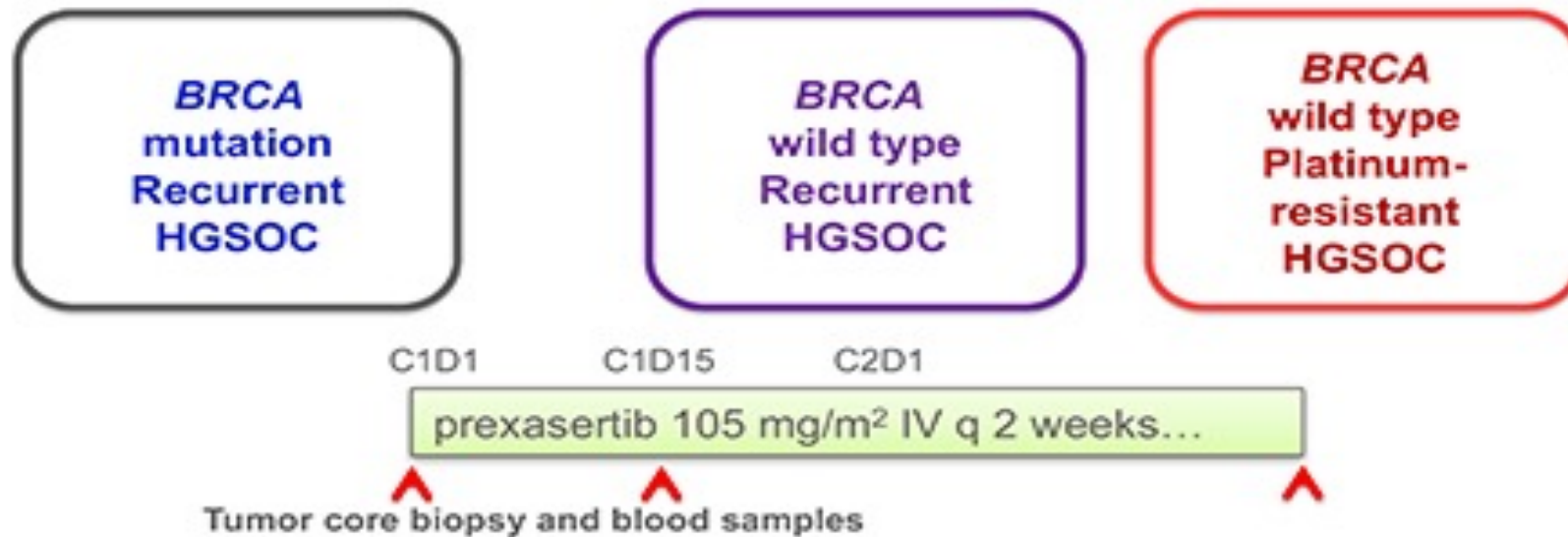
Cell cycle checkpoint

The rationale of targeting cell cycle checkpoint pathways in high grade serous ovarian cancer



Phase II study

NCI Phase II study of CHK1 inhibitor prexasertib (ACR-368)



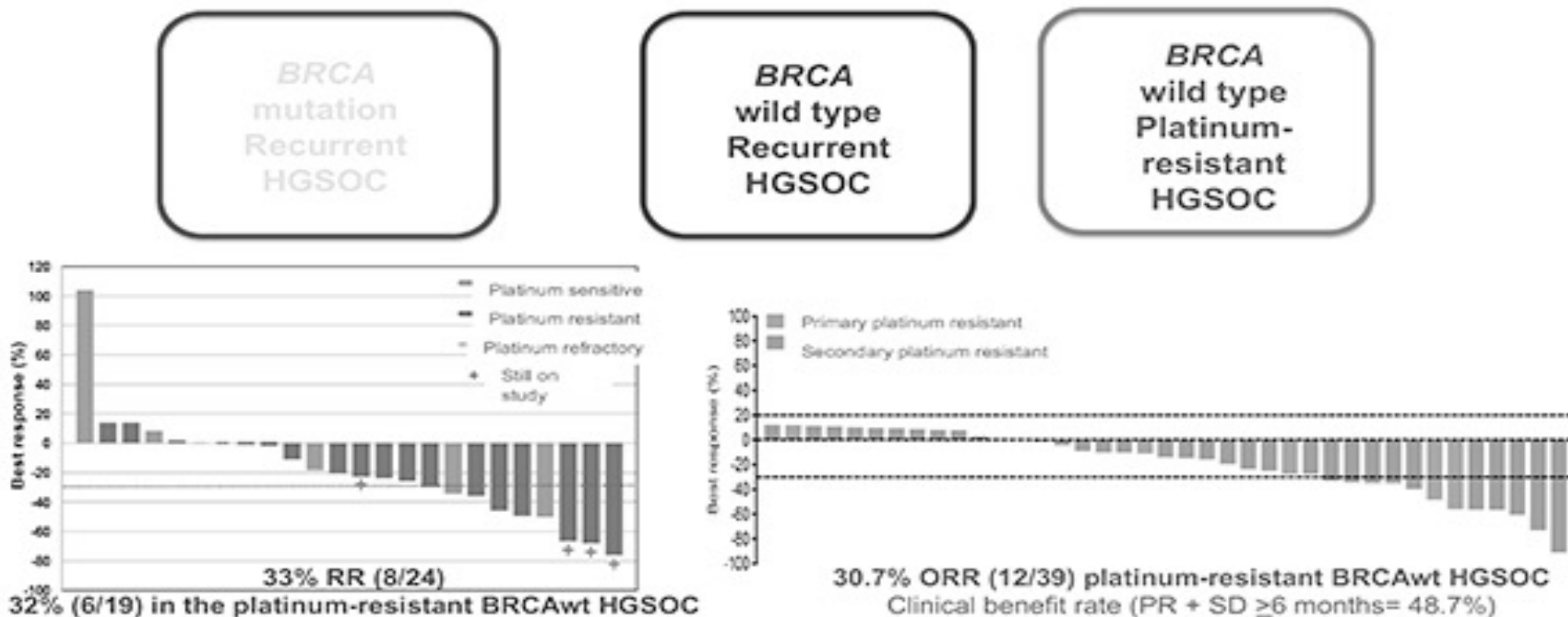
Study objectives

Primary: Response rate by RECISTv1.1

Exploratory: Mechanisms of action and potential predictive biomarkers

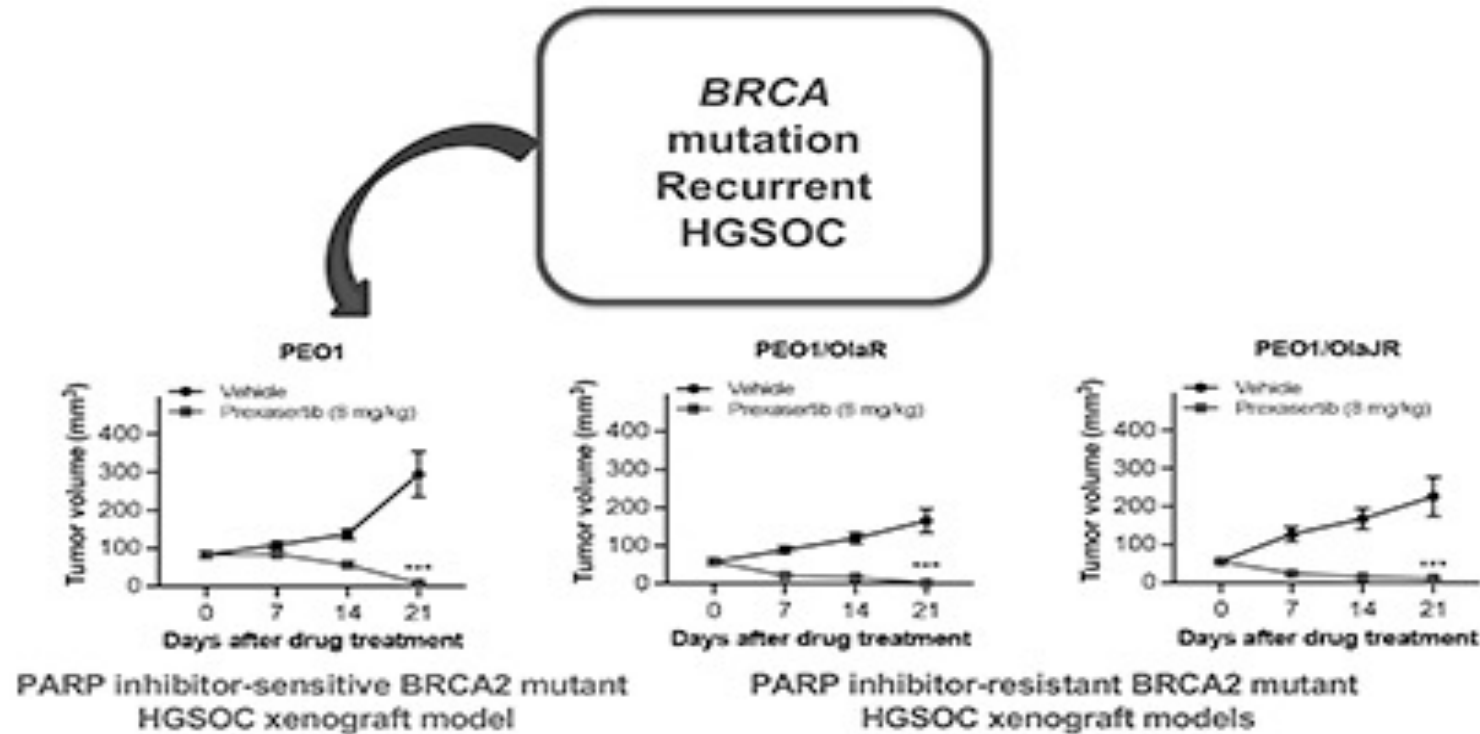
CHK1 inhibitor

CHK1 inhibitor prexasertib in BRCA wild type HGSOC



BRCA mutant

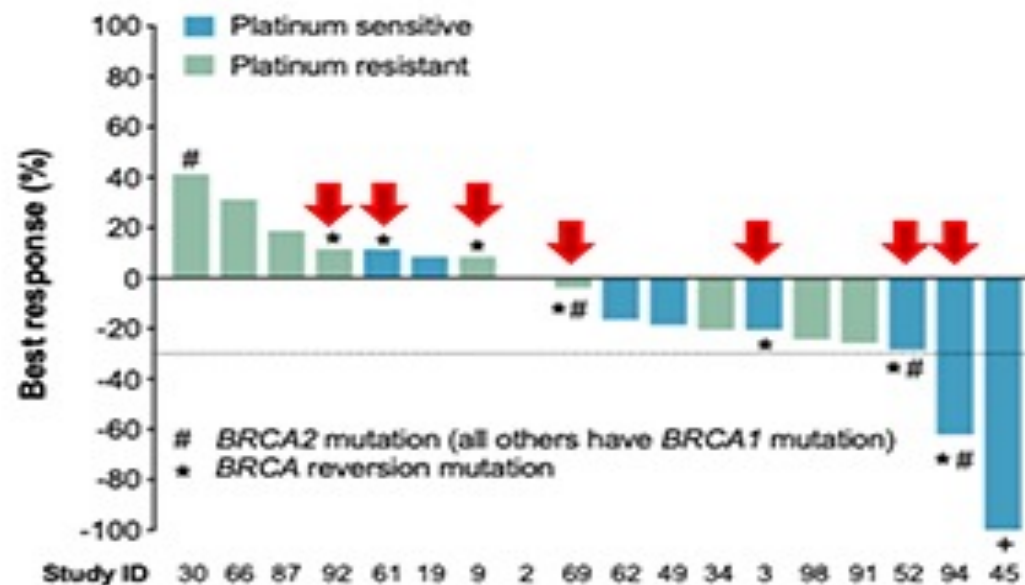
BRCA mutant HGSOC with prior PARP inhibitor exposure



CHK1 inhibitor

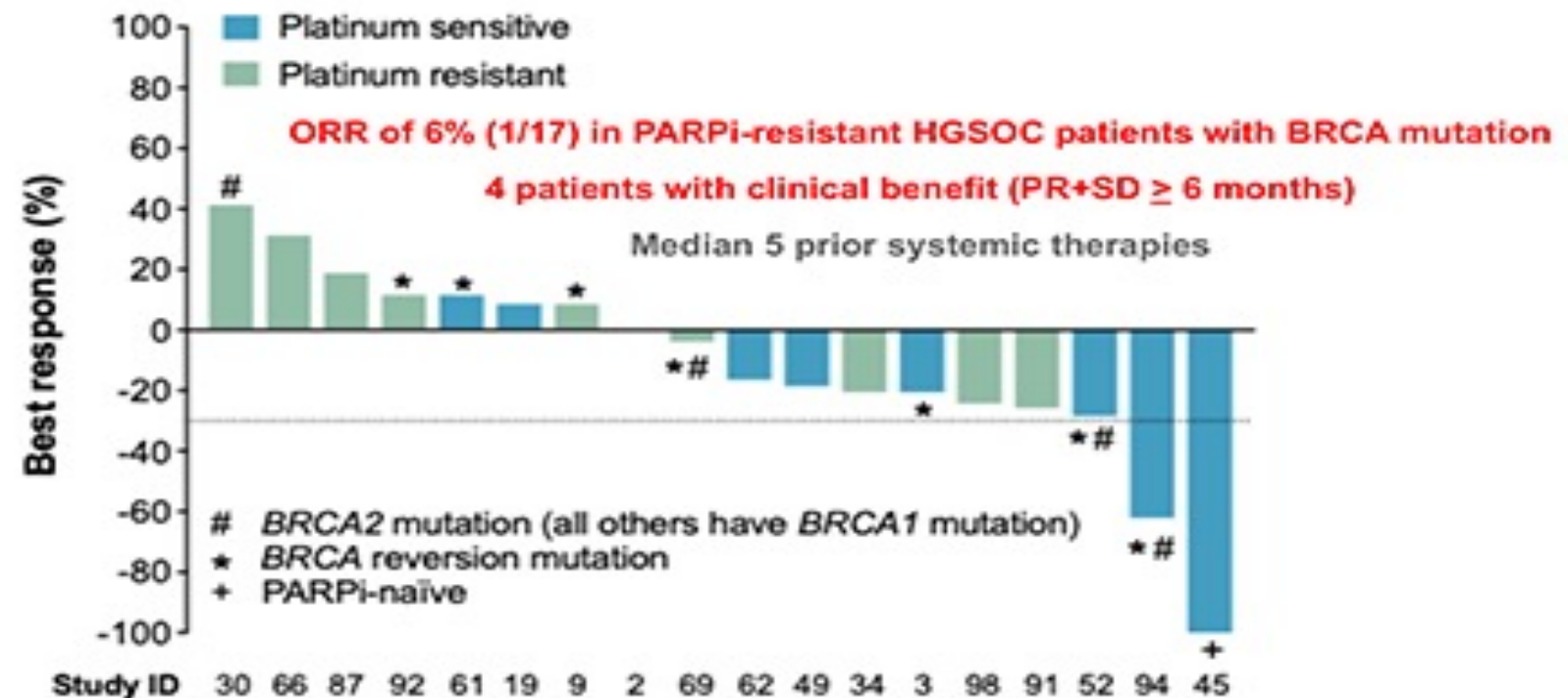
Investigation of molecular characteristics of CHK1 inhibitor response

BRCA reversion mutations and other genes related to DNA damage repair were not associated with response or resistance to CHK1 inhibitor in *BRCA* mutant HGSOC patients with PARPi resistance



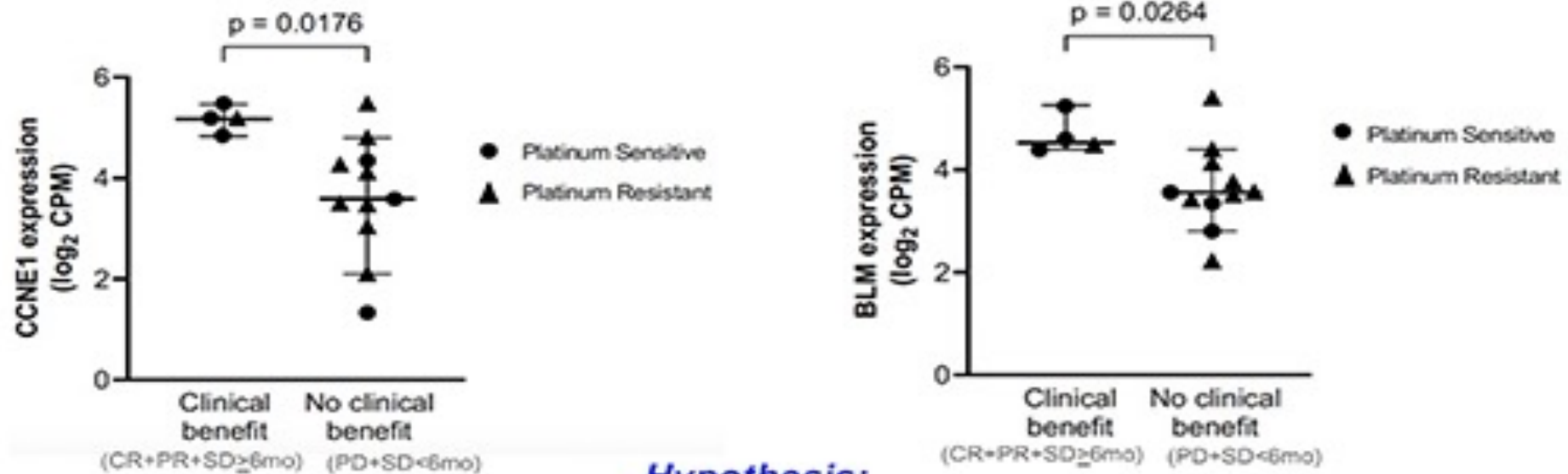
CHK1 inhibitor

CHK1 inhibitor monotherapy in *BRCA* mutant HGSOC with PARP inhibitor resistance



mRNA expression

High mRNA expressions of *BLM* and *CCNE1* are associated with CHK1 inhibitor clinical benefit



Hypothesis:

Increased replication fork stabilization along with replication stress (high levels of *BLM* and *CCNE1*) may better predict the sensitivity to CHK1 inhibitor in BRCA mutant HGSOC.

*All 4 patients with clinical benefit also had CCNE1 copy number gain/amplification
CPM: counts per million

GOG-3082

GOG-3082: Phase Ib/II basket study of CHK1 inhibitor ACR-368

- 3 cohorts: platinum-resistant ovarian, endometrial and bladder cancers
- Fresh core biopsy required for OncoSignature® biomarker test
- Primary endpoint: ORR per RECISTv1.1 (target 30% ORR (one-sided alpha level of 0.025 and 80% power)
- Total 333 patients



Conclusions

Conclusions

- Ovarian cancer is not a single disease, it consists of multiple entities that require an individualized approach to treatment
- Precision medicine allows for individualization of treatment strategies for women with ovarian cancer based on differences in histological and molecular/genetic characteristics
- Not all mutations or proteins are “actionable” and have a treatment
- Significant progress in the last few decades with treatment and understanding of molecular biology

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