Ovarian Cancer

Ovarian cancer

Advances in clinical and translational research

TRACO lecture

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NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

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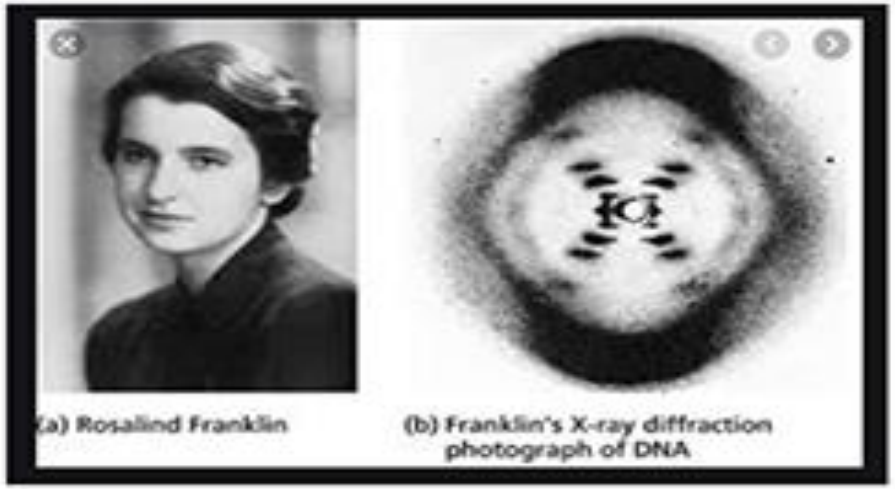
Rosalind Franklin

Rosalind Franklin

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



(a) Rosalind Franklin

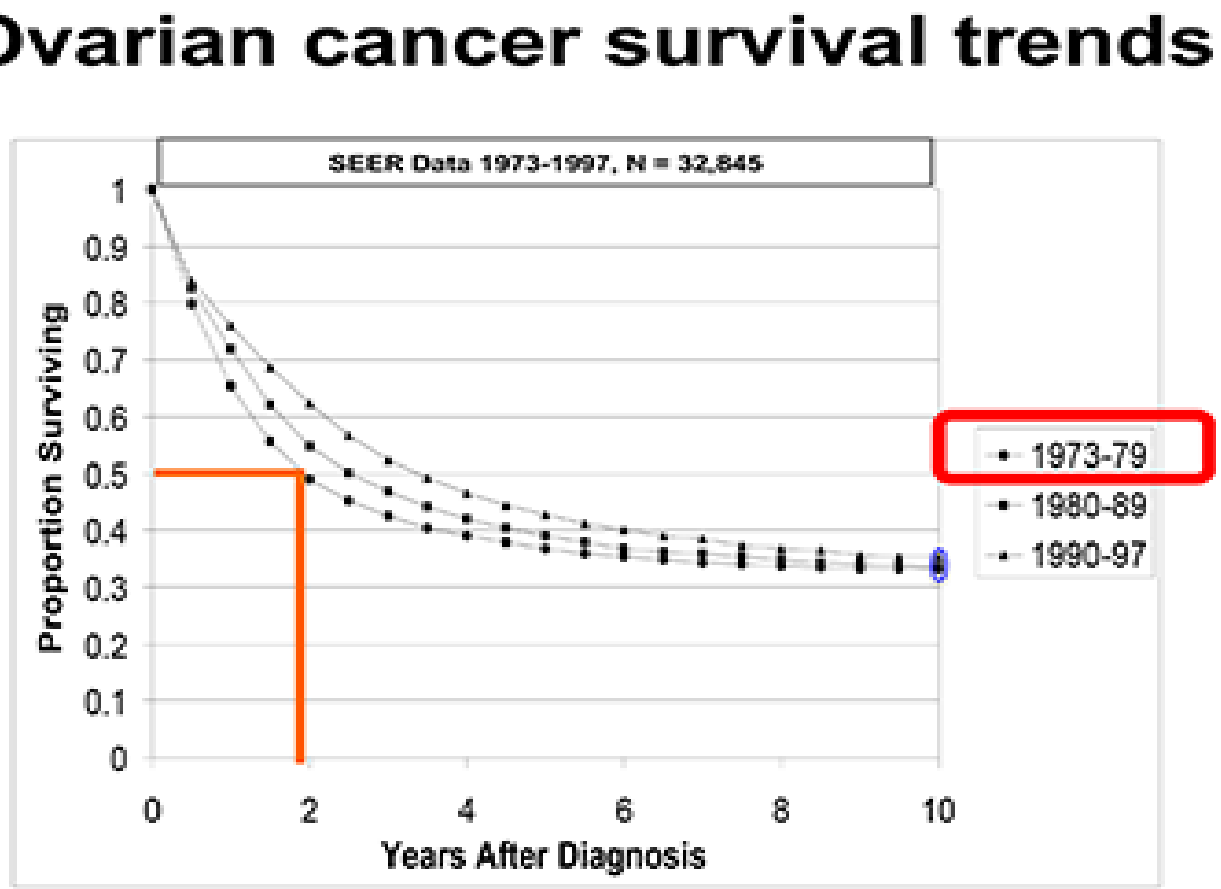
(b) Franklin's X-ray diffraction photograph of DNA

Ovarian cancer

Ovarian cancer

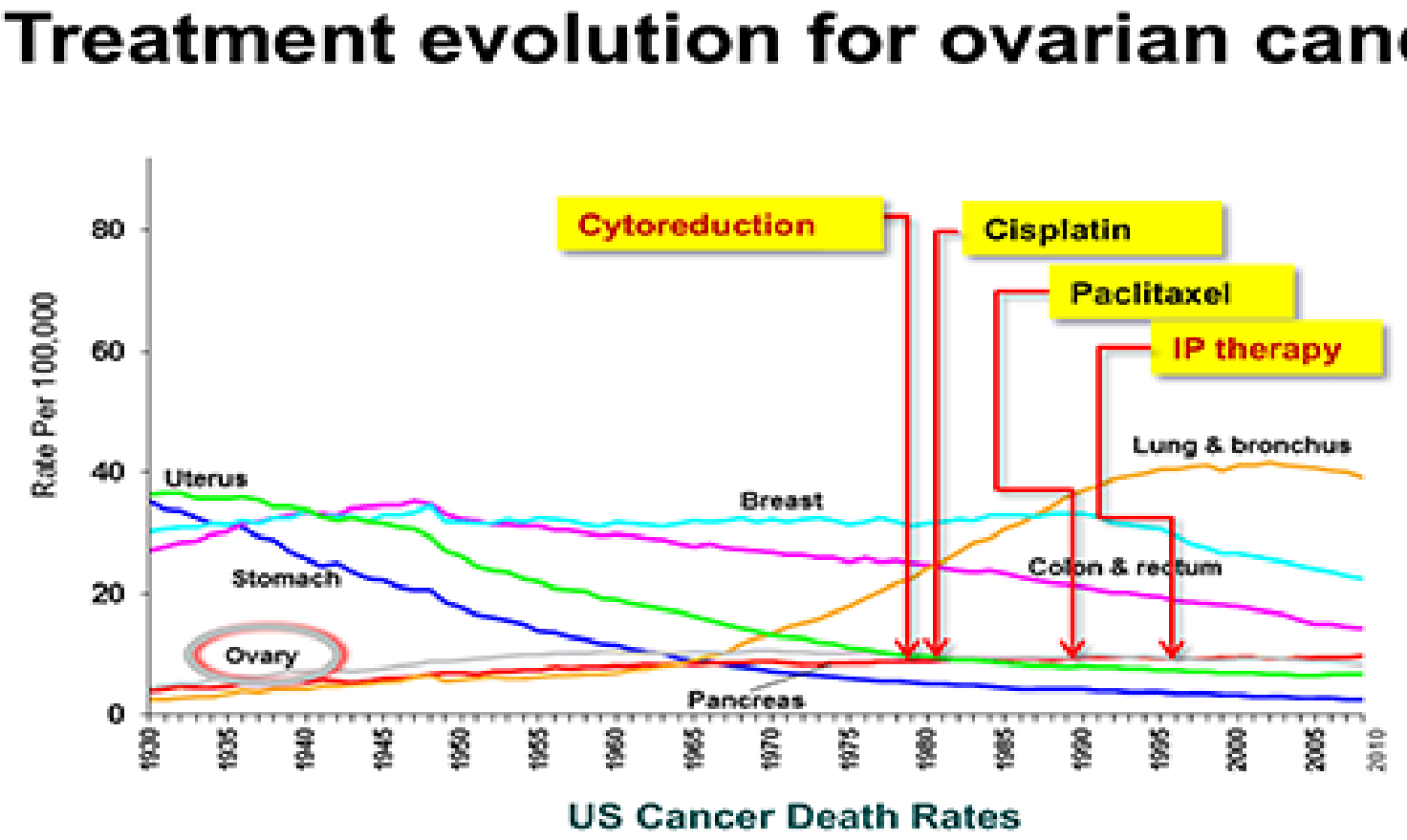
- Most lethal gynecologic malignancy in the US
  - >16,000 deaths/year
  - 5th most common cancer death for women
- 70% diagnosed with advanced disease

Cancer survival

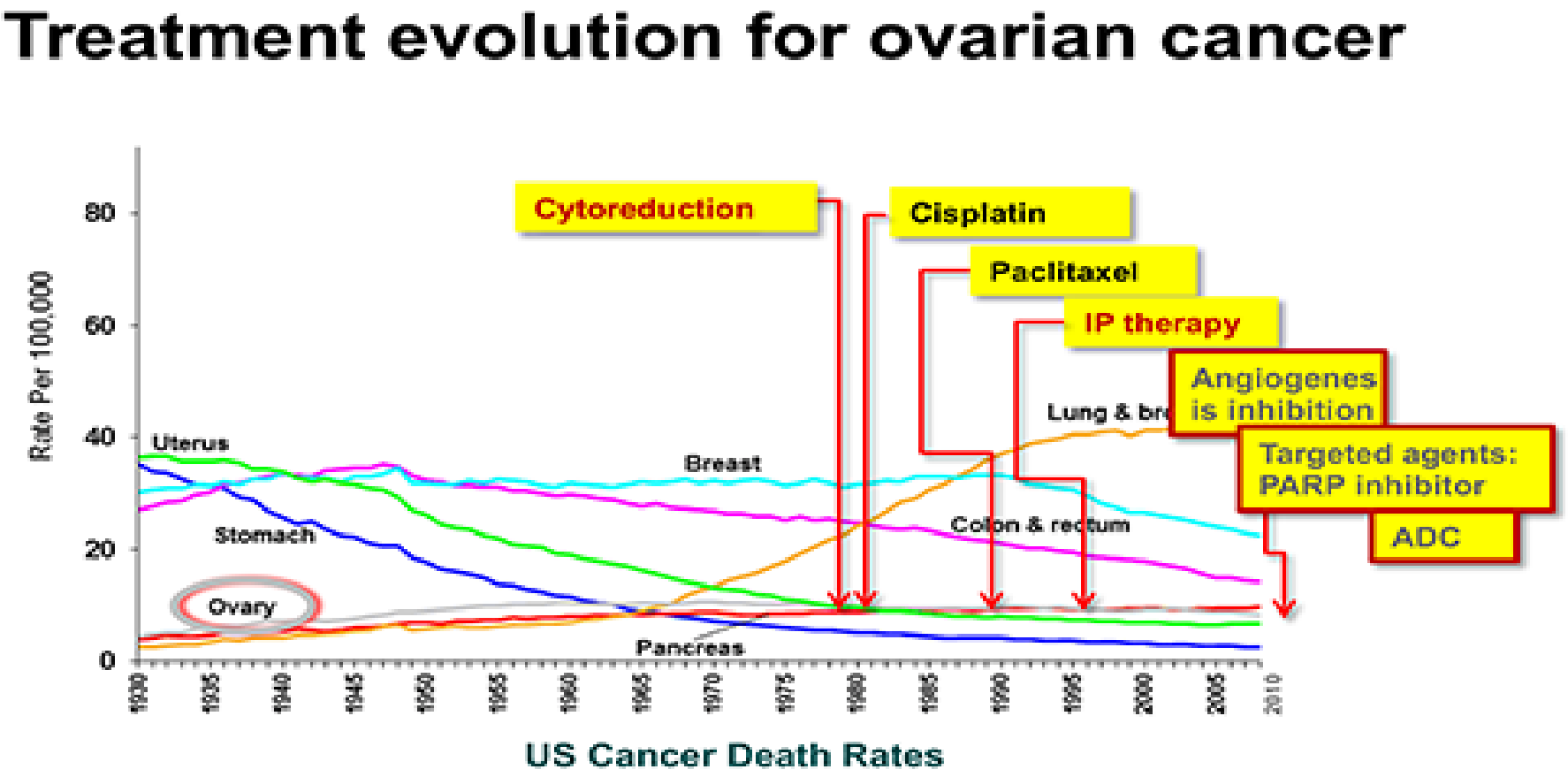


SEER: The Surveillance, Epidemiology, and End Results

Cancer treatment



Evolution

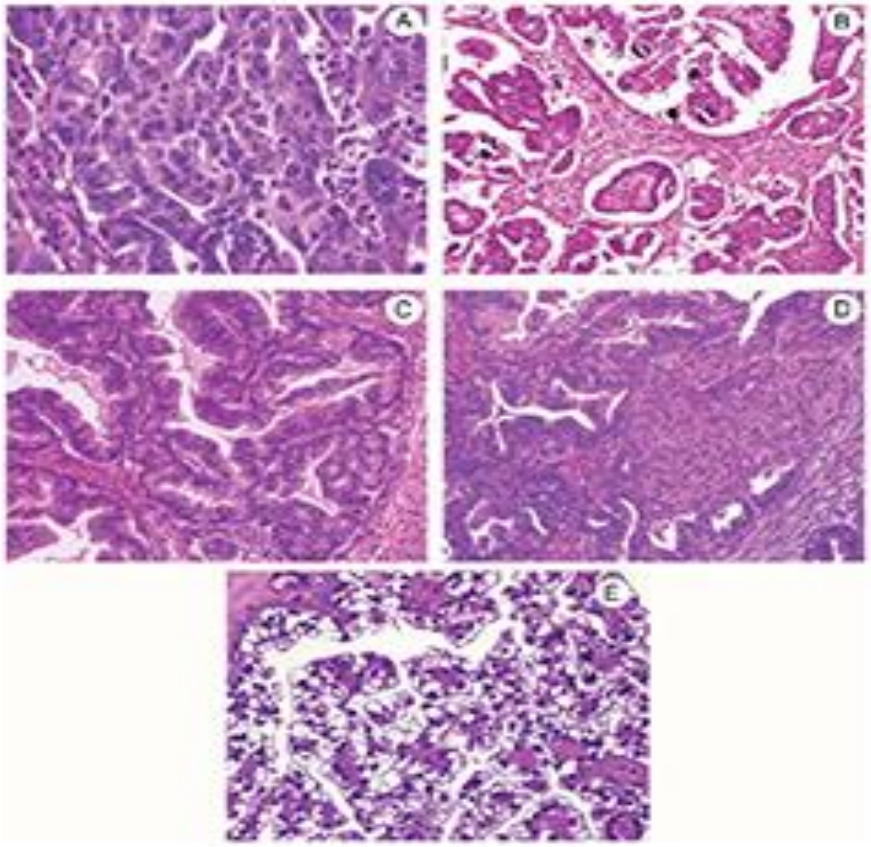

Treatment evolution for ovarian cancer
Cytoreduction
Cisplatin
Paclitaxel
IP therapy
Angiogenes is inhibition
Targeted agents: PARP inhibitor
ADC
Lung & br
Colon & rectum
Breast
Uterus
Stomach
Ovary
Pancreas
Rate Per 100,000
0
20
40
60
80
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
US Cancer Death Rates

Ovarian cancer types

Ovarian cancer

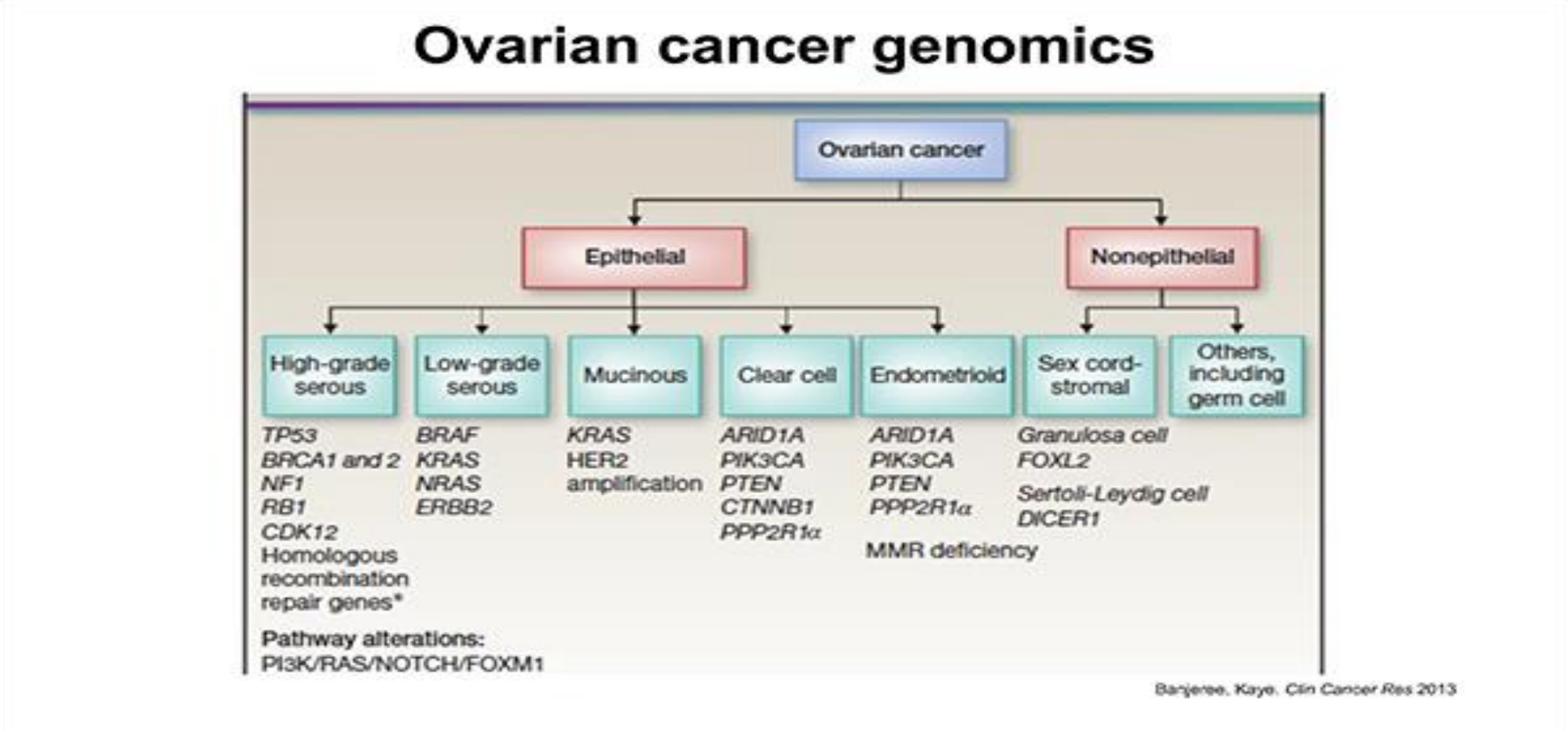
Prevalence

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



Soslow R. *Int J Gynecol Pathol*, 2008

Genomics


Ovarian cancer genomics
Ovarian cancer
Epithelial
Nonepithelial
High-grade serous
Low-grade serous
Mucinous
Clear cell
Endometrioid
Sex cord-stromal
Others, including germ cell
TP53
BRCA1 and 2
NF1
RB1
CDK12
Homologous recombination repair genes*
BRAF
KRAS
NRAS
ERBB2
KRAS
HER2 amplification
ARID1A
PIK3CA
PTEN
CTNNB1
PPP2R1α
ARID1A
PIK3CA
PTEN
PPP2R1α
MMR deficiency
Granulosa cell
FOXL2
Sertoli-Leydig cell
DICER1
Pathway alterations:
PI3K/RAS/NOTCH/FOXM1
Banjeree, Kaye. Clin Cancer Res 2013

Treatment

Treatment for newly diagnosed ovarian cancer

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

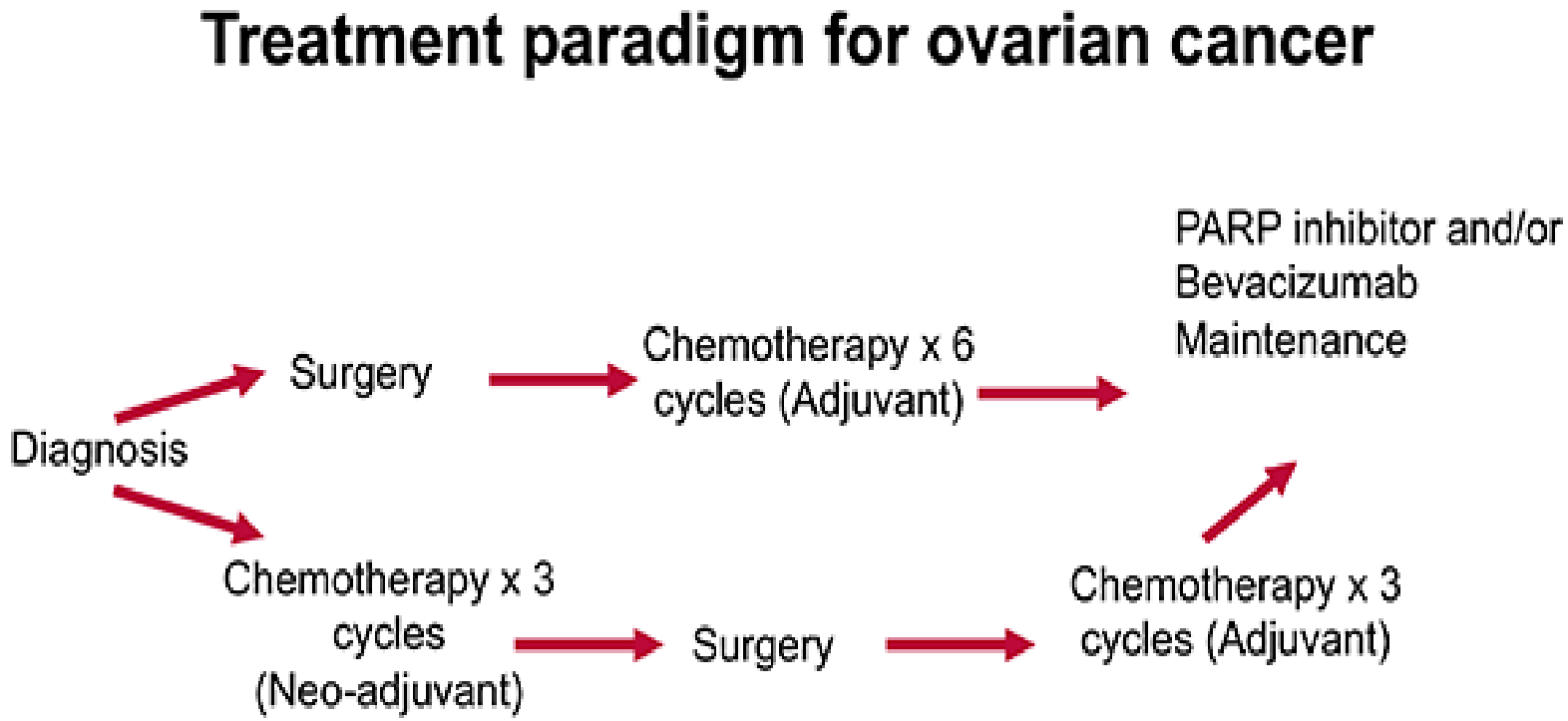
Treatment

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

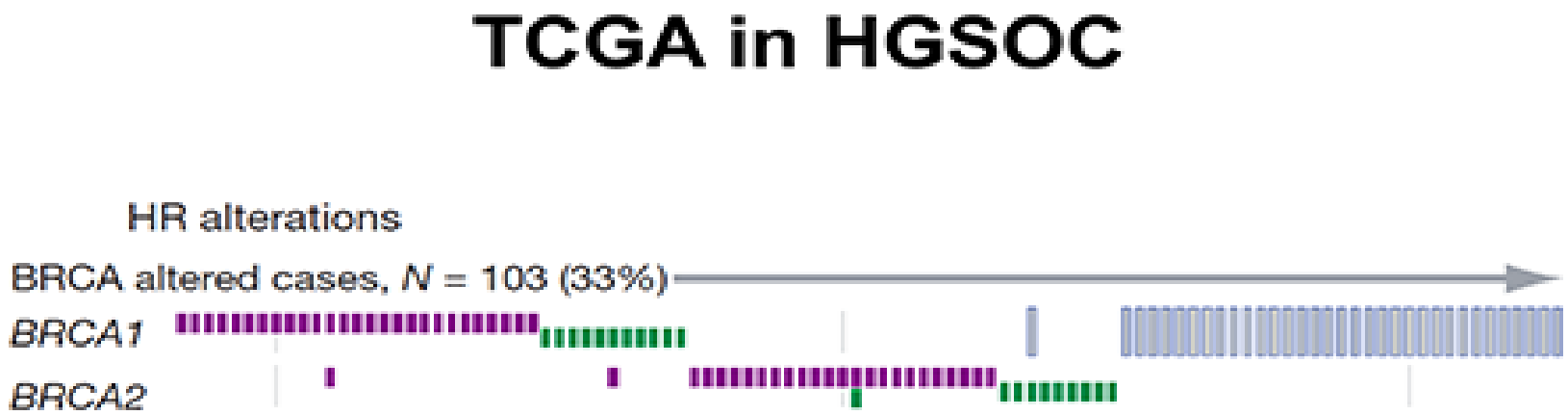


Slide courtesy of Dr. Annunziata

Serous ovarian cancer

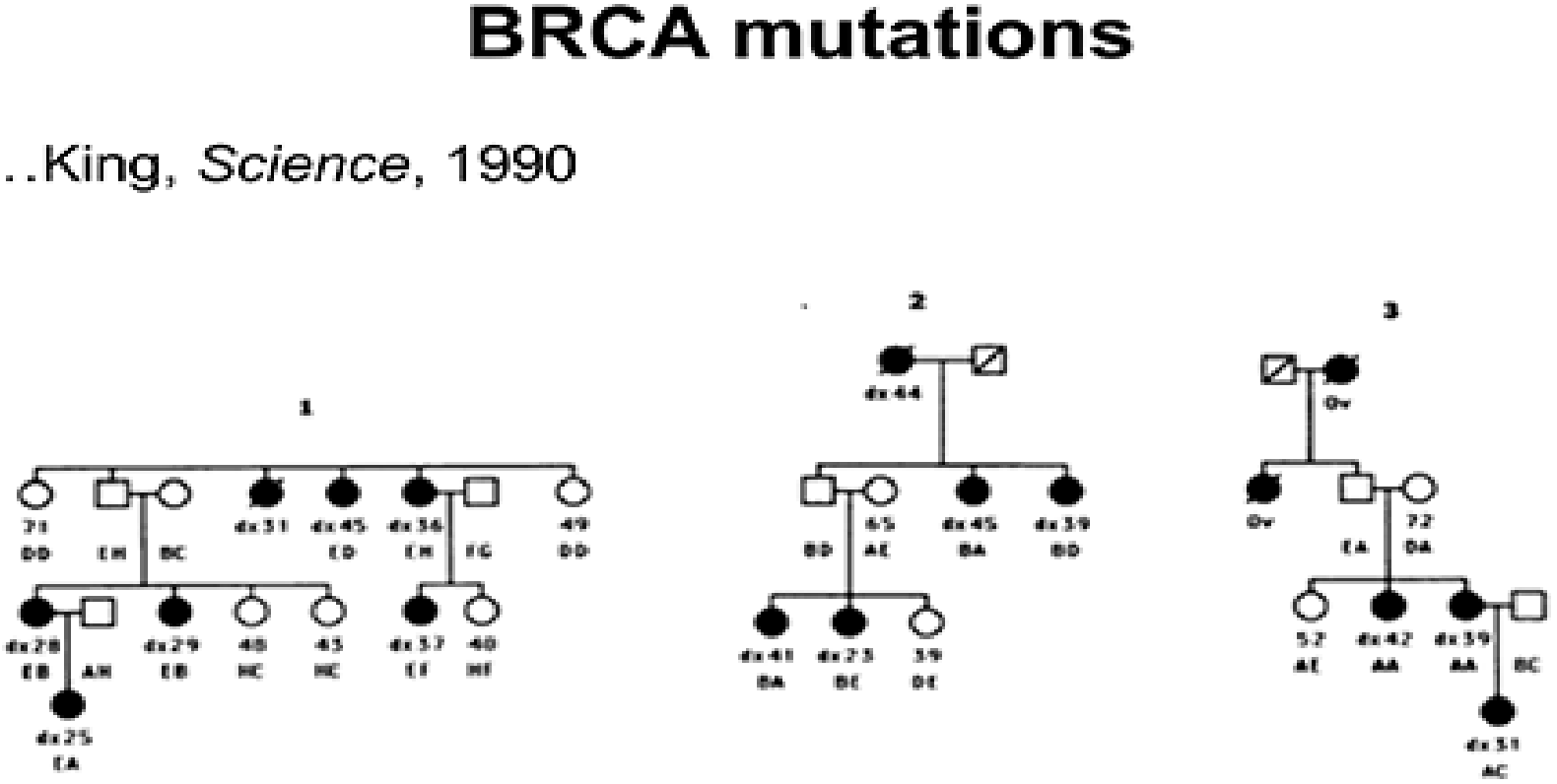
High grade serous ovarian carcinoma (HGSOC)

TCGA



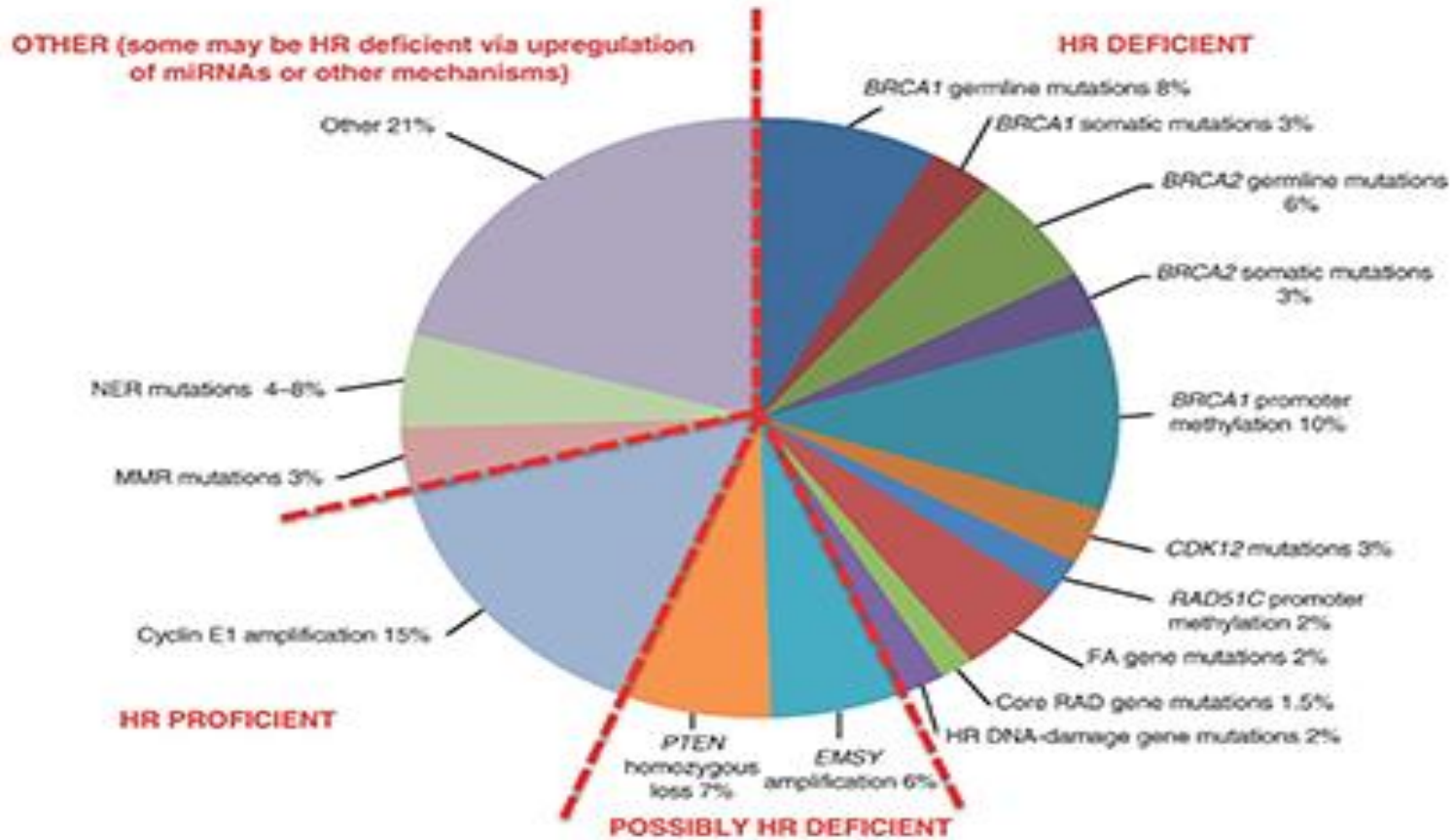
The Cancer Genome Atlas, *Nature* 2011

BRCA mutations



Slide courtesy of Dr. Annunziata

Genetic mutations



Konstantinopoulous *et al. Cancer Discov.* 2015

PARP inhibitors

DNA repair

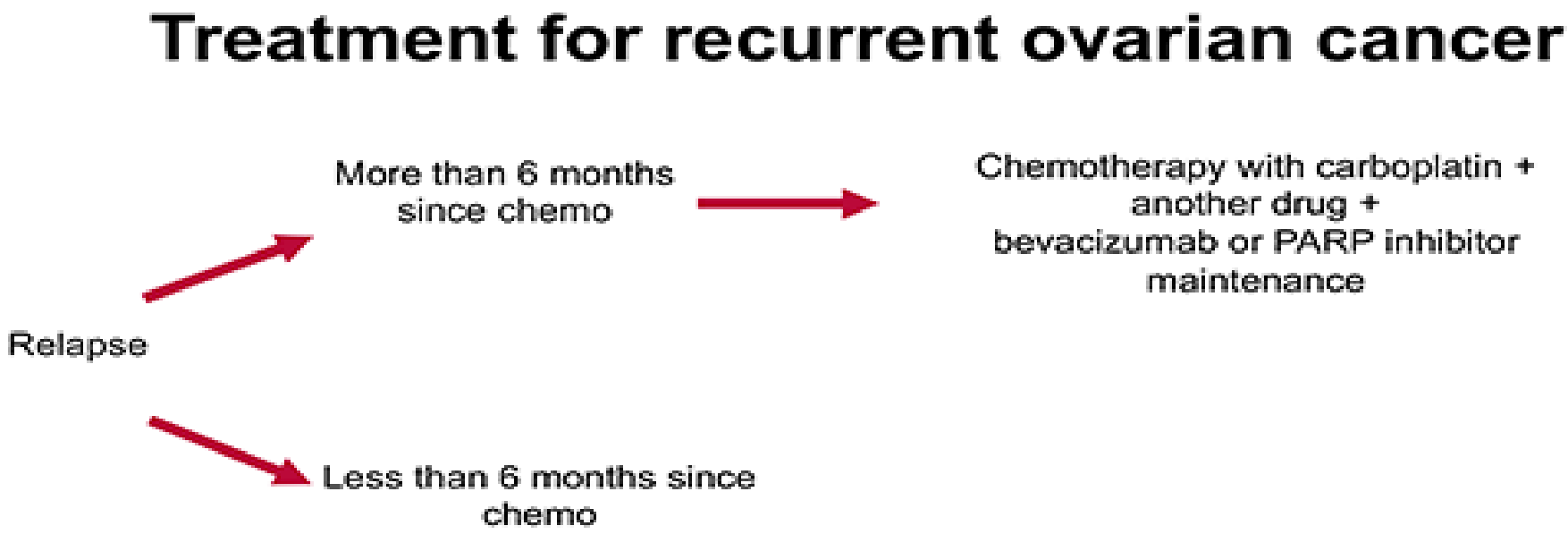
How is DNA repaired?

- Homologous recombination **(HR)**
- Undamaged DNA is the guide
- Replaces damaged part with the “correct” code
- **Uses BRCA**

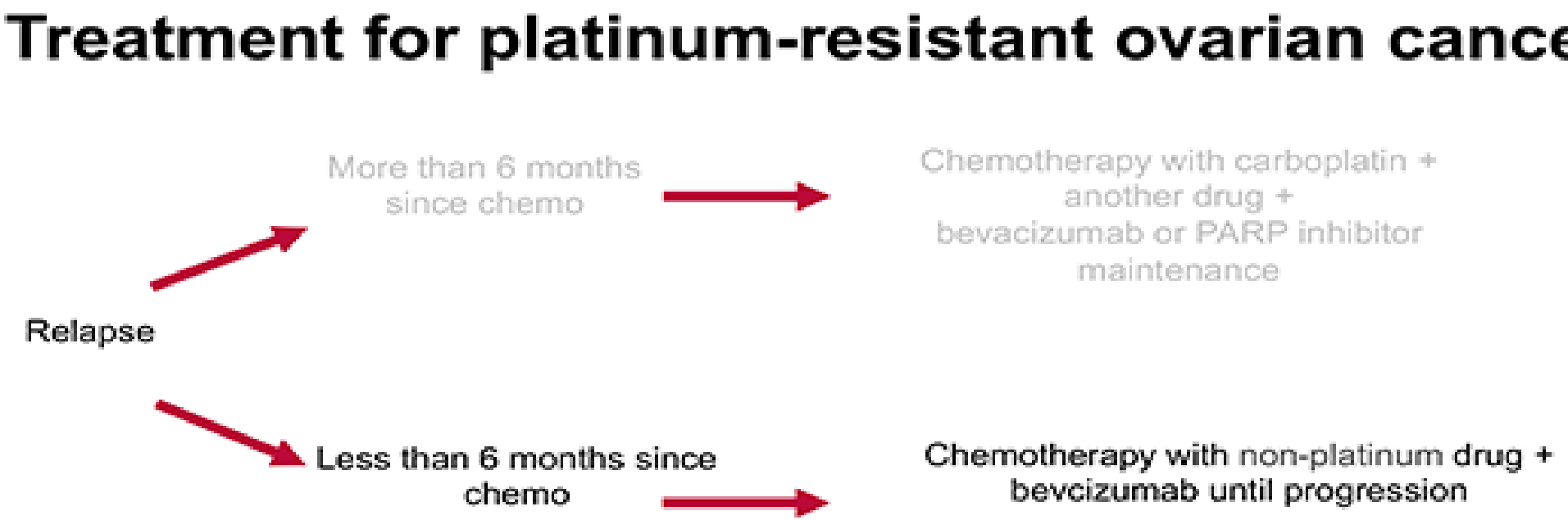
- Base excision repair **(BER)**
- Cuts out damaged DNA
- Joins cut end with another piece
- **Uses PARP**

Relapsed ovarian cancer

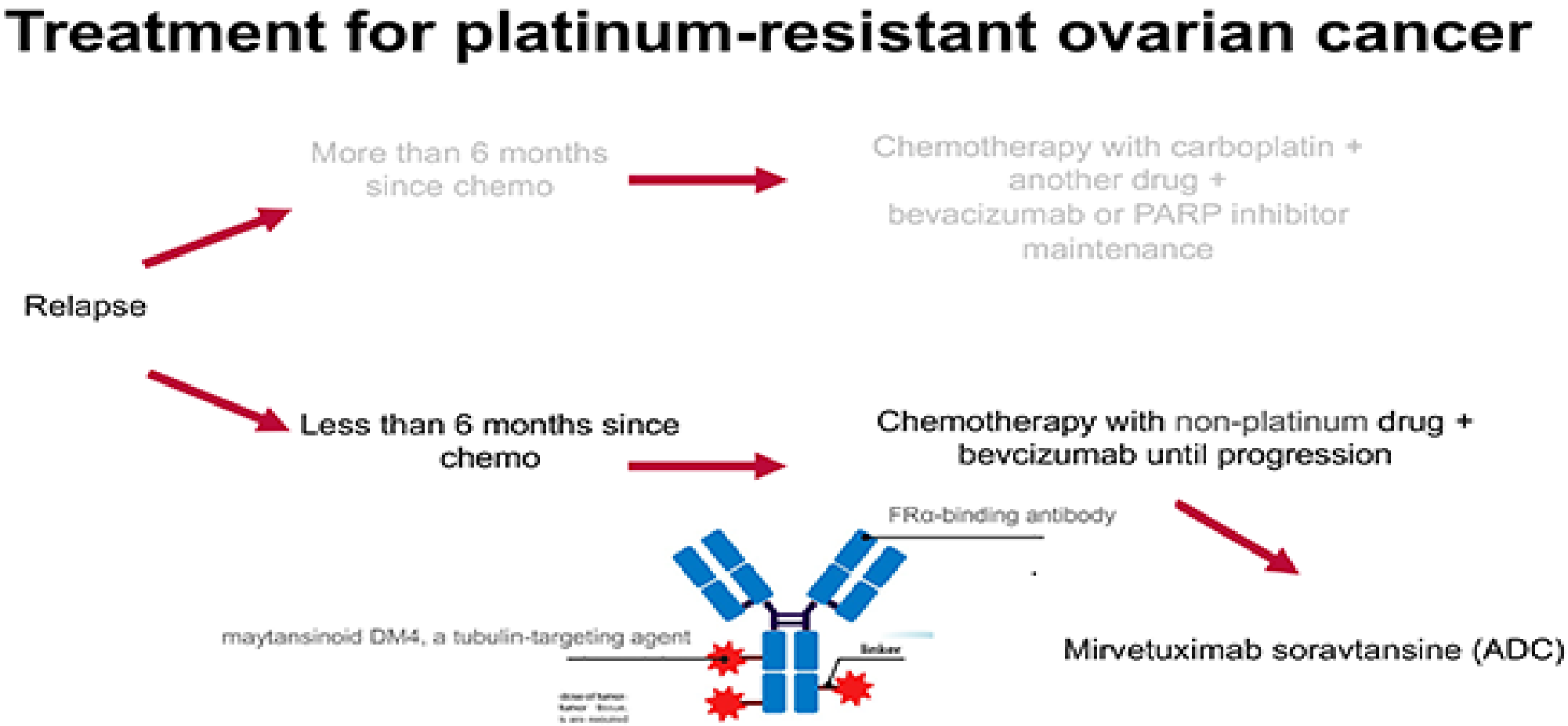
Recurrent ovarian cancer



Platinum resistant cancer



Platinum resistant cancer

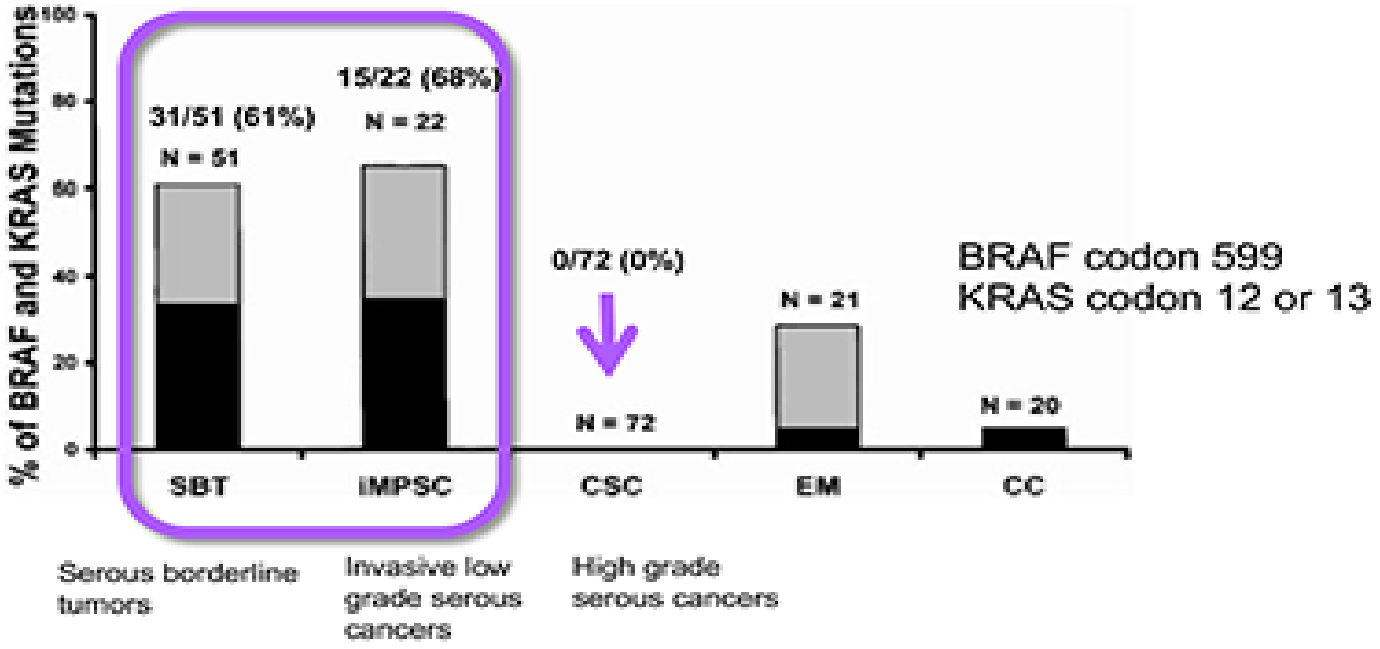


Rare ovarian cancers

Low grade cancer

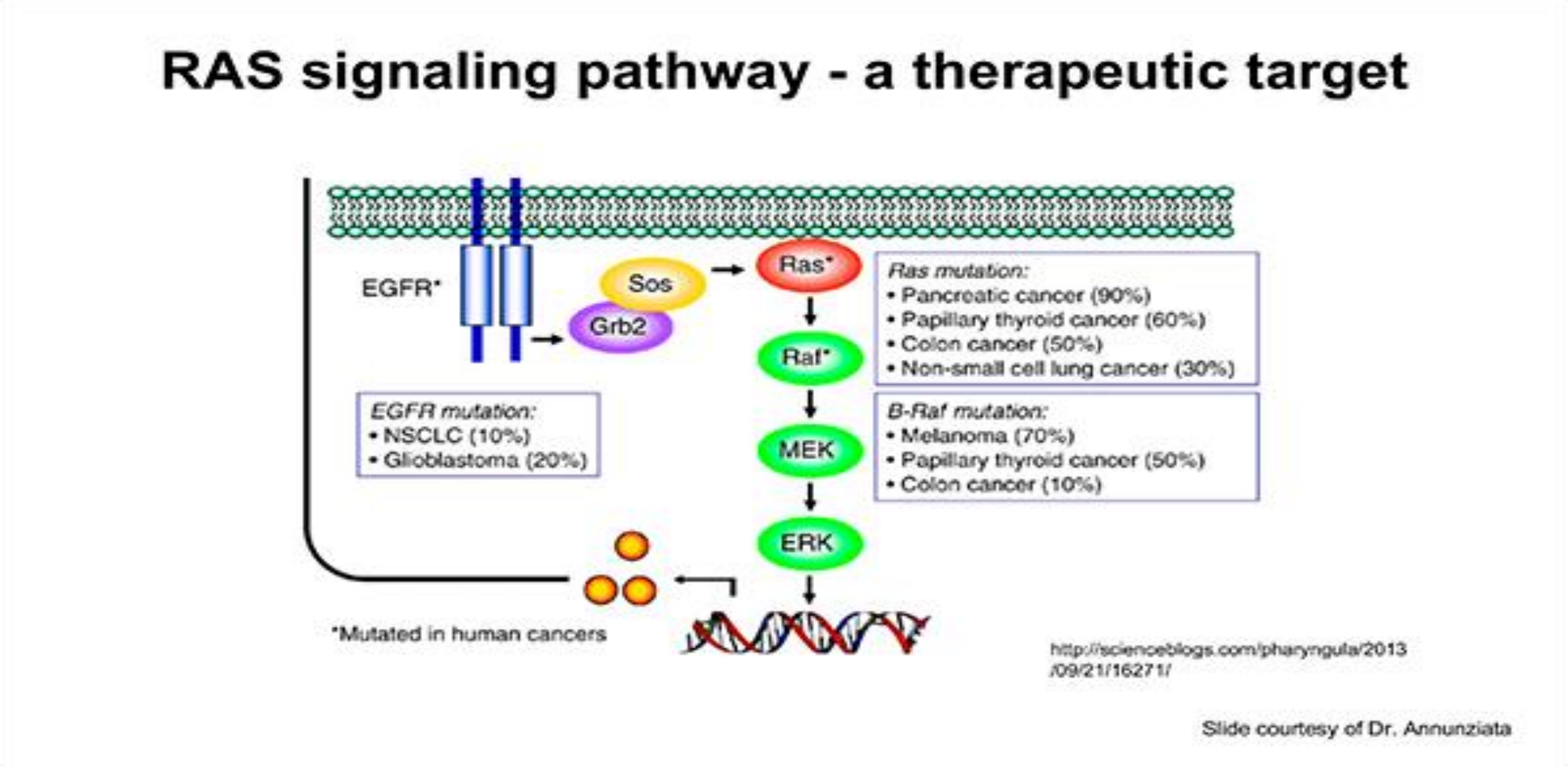
Low grade serous ovarian cancer

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



Singer, JNCI 2003

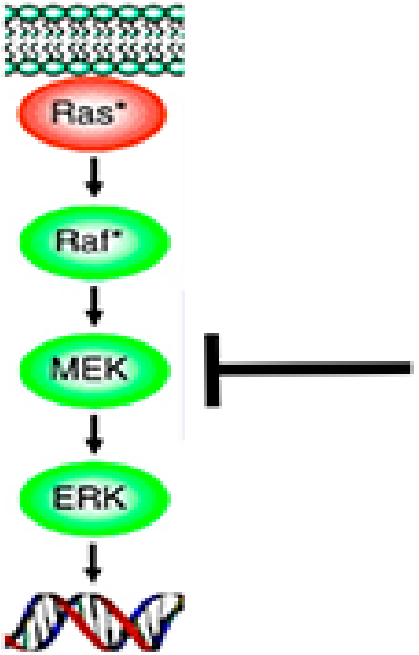
RAS signaling



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 of17.7 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

Wiegand *et al, NEJM* 2010

Adenocarcinoma

Endometrioid adenocarcinoma

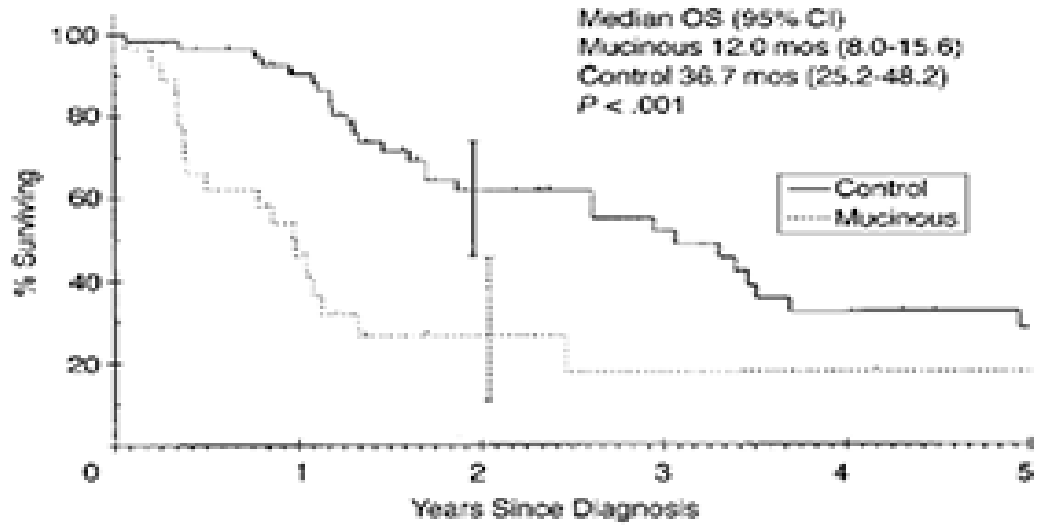
- Strong expression of ER/PR (>80%)
- Associated with endometriosis
- Mean age: 50 years old
- 84% Stage I/II and better prognosis than serous tumors
- May not be as chemo-sensitive as serous tumors
- ARID1A mutated or lost in
  - 40% endometrioid
  - Need therapies targeting these mutations

Weigand *et al*, *NEJM* 2010

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 !

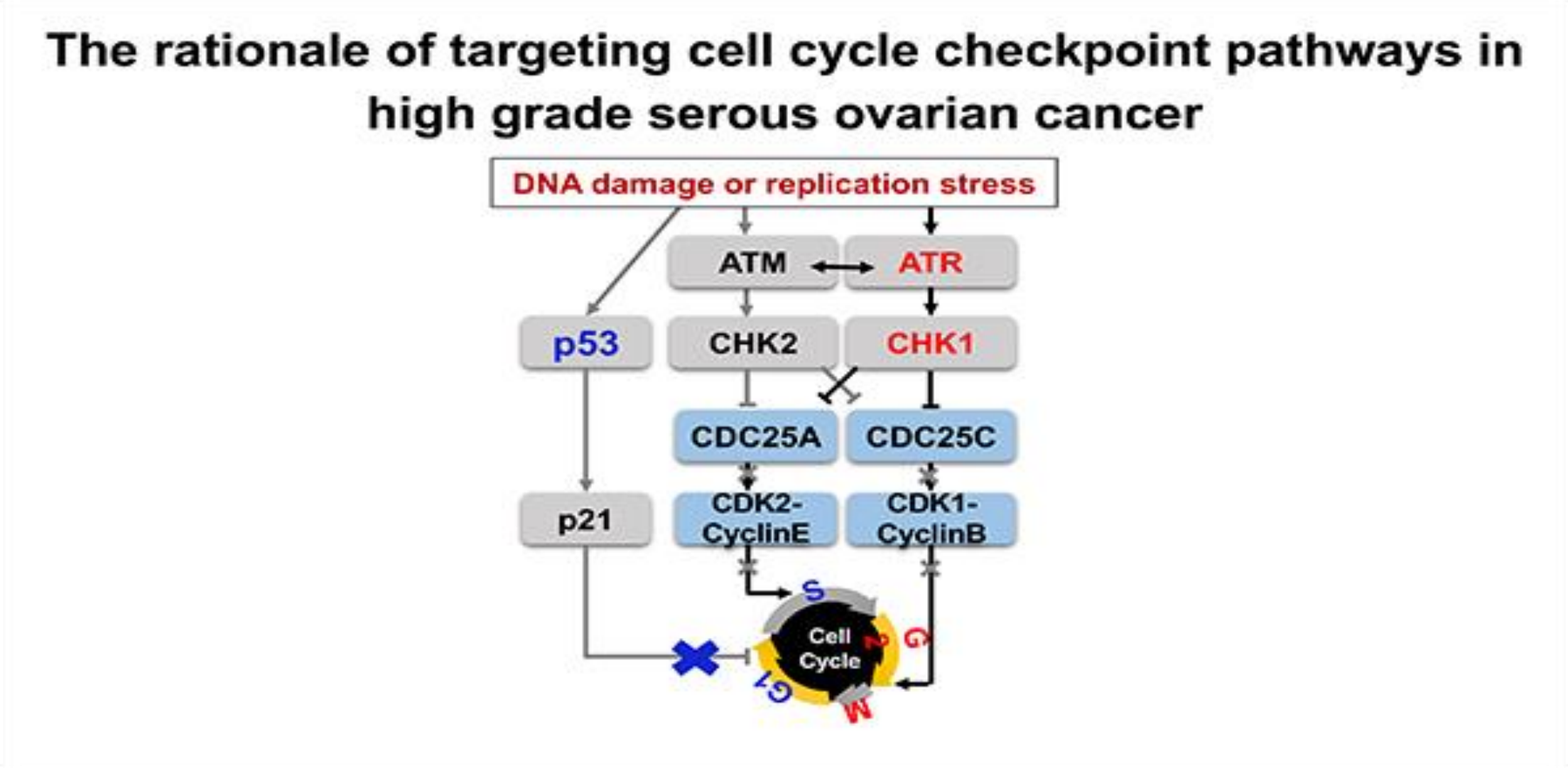


Hess, *et al, J Clin Oncol*, 2004

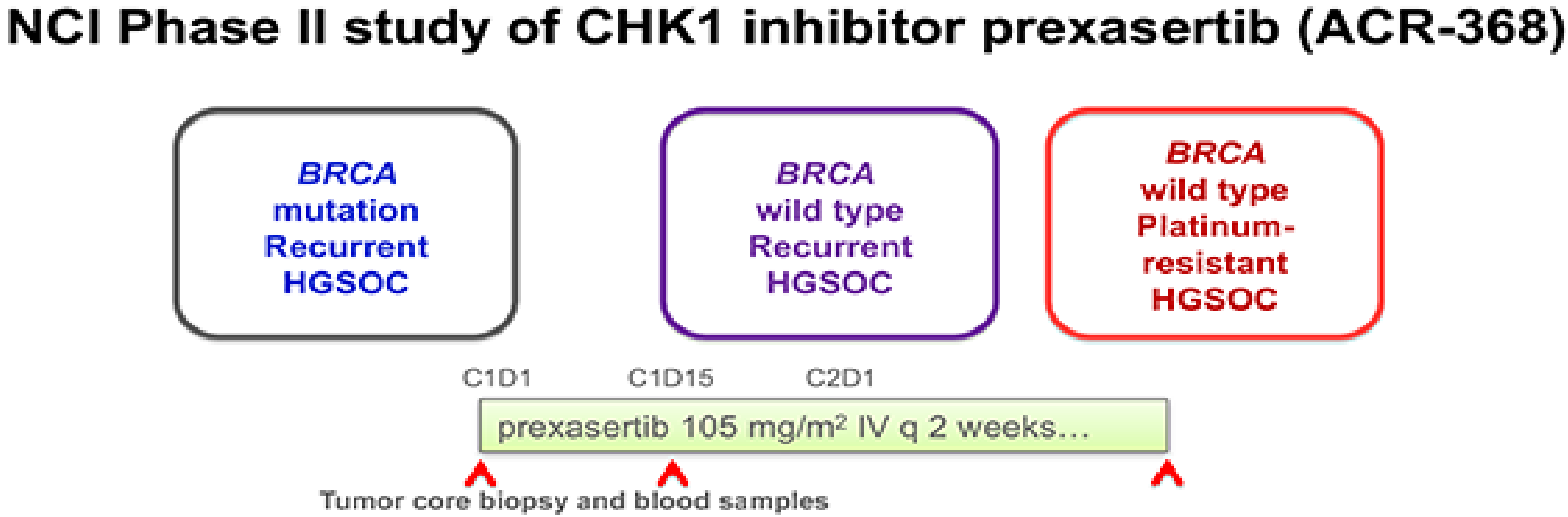
New targets

Exploration of new targets

Cell cycle checkpoint



Phase II study



Study objectives

Primary: Response rate by RECISTv1.1

Exploratory: Mechanisms of action and potential predictive biomarkers

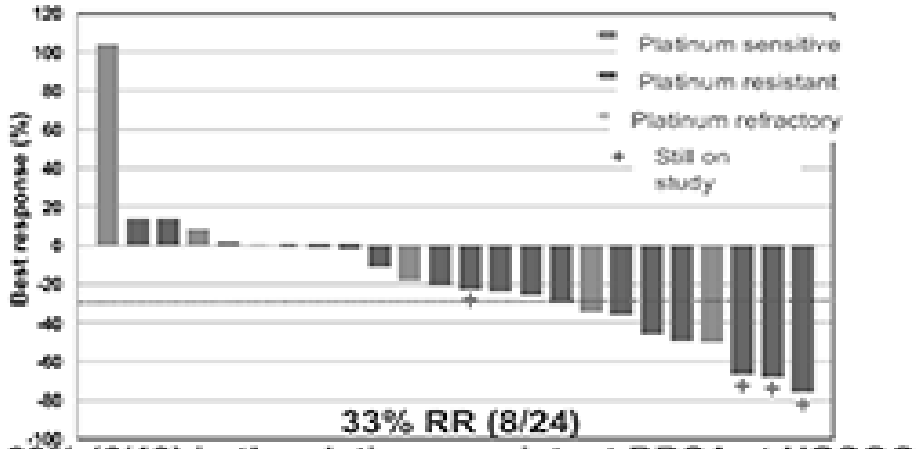
CHK1 inhibitor

CHK1 inhibitor prexasertib in BRCA wild type HGSOC

BRCA mutation Recurrent HGSOC

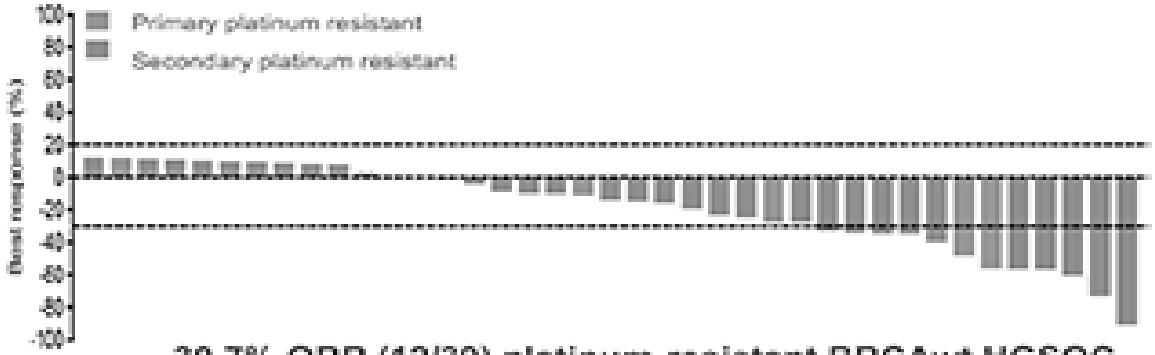
BRCA **wild type Recurrent HGSOC**

BRCA **wild type Platinum-resistant HGSOC**



32% (6/19) in the platinum-resistant BRCAwt HGSOC

Lee *et al. Lancet Oncol.* 2018



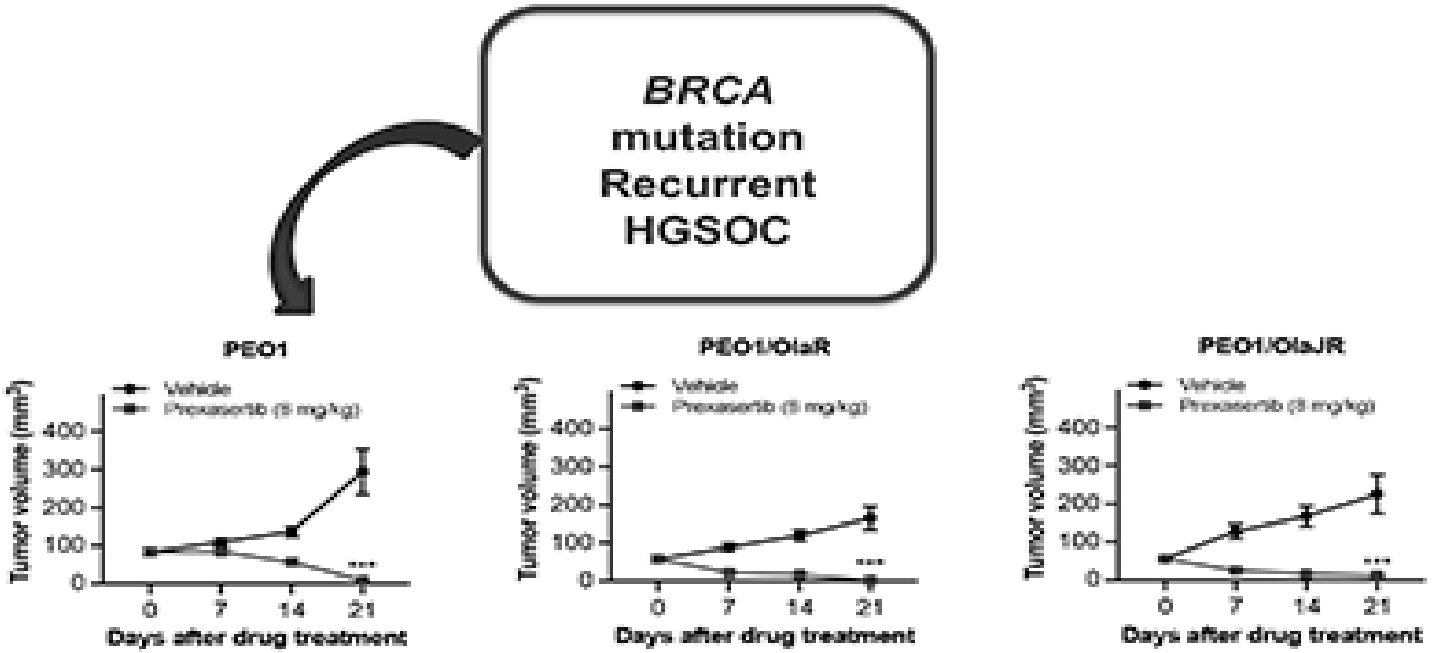
30.7% ORR (12/39) platinum-resistant BRCAwt HGSOC

Clinical benefit rate (PR + SD ≥6 months= 48.7%)

Giudice…Lee. *Submitted*

BRCA mutant

BRCA mutant HGSOC with prior PARP inhibitor exposure



PARP inhibitor-sensitive BRCA2 mutant HGSOC xenograft model

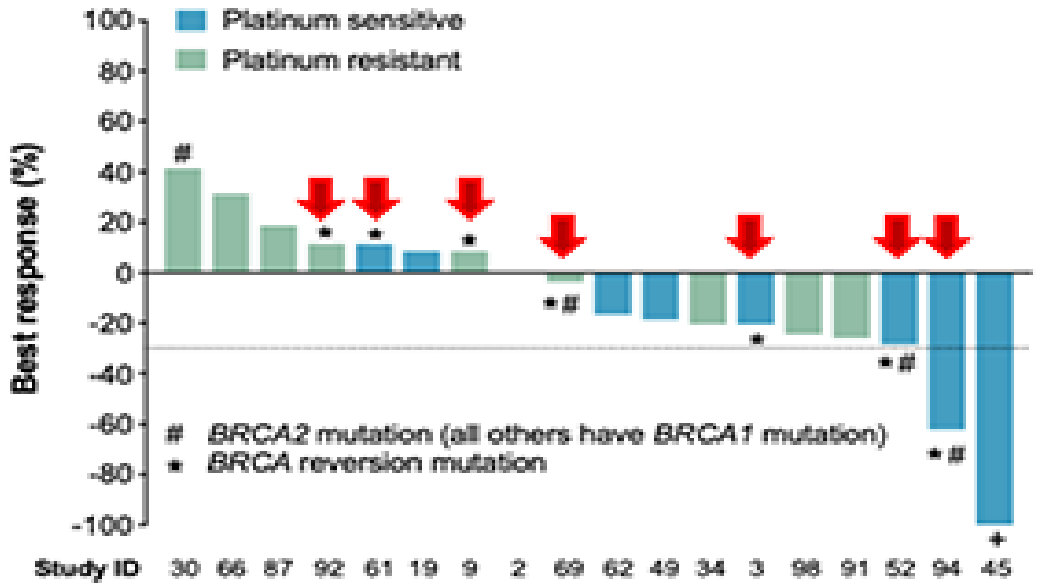
PARP inhibitor-resistant BRCA2 mutant HGSOC xenograft models

Gupta, Huang, Nair…Lee. *Sci Transl Med.* 2023

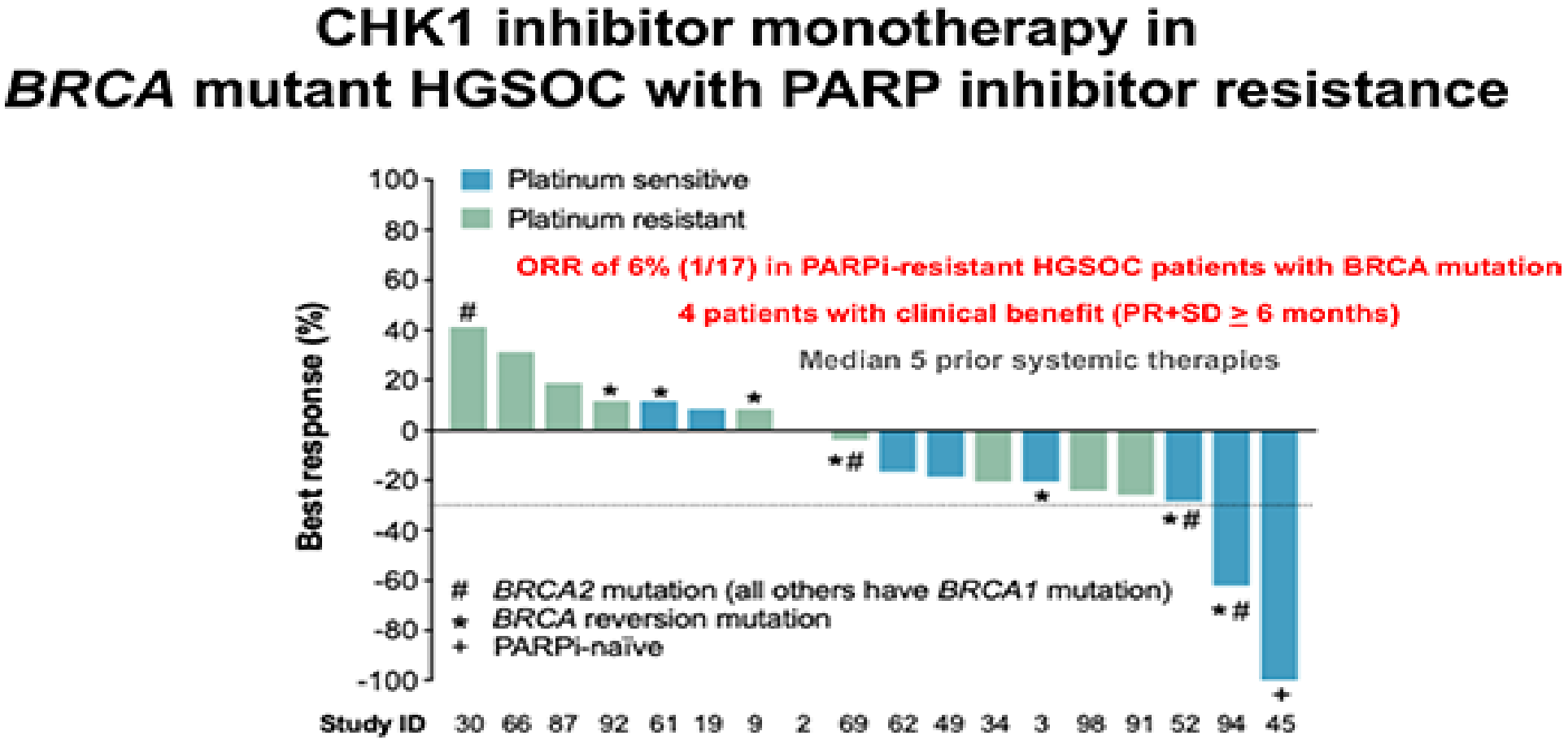
CHK1 inhibitor

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

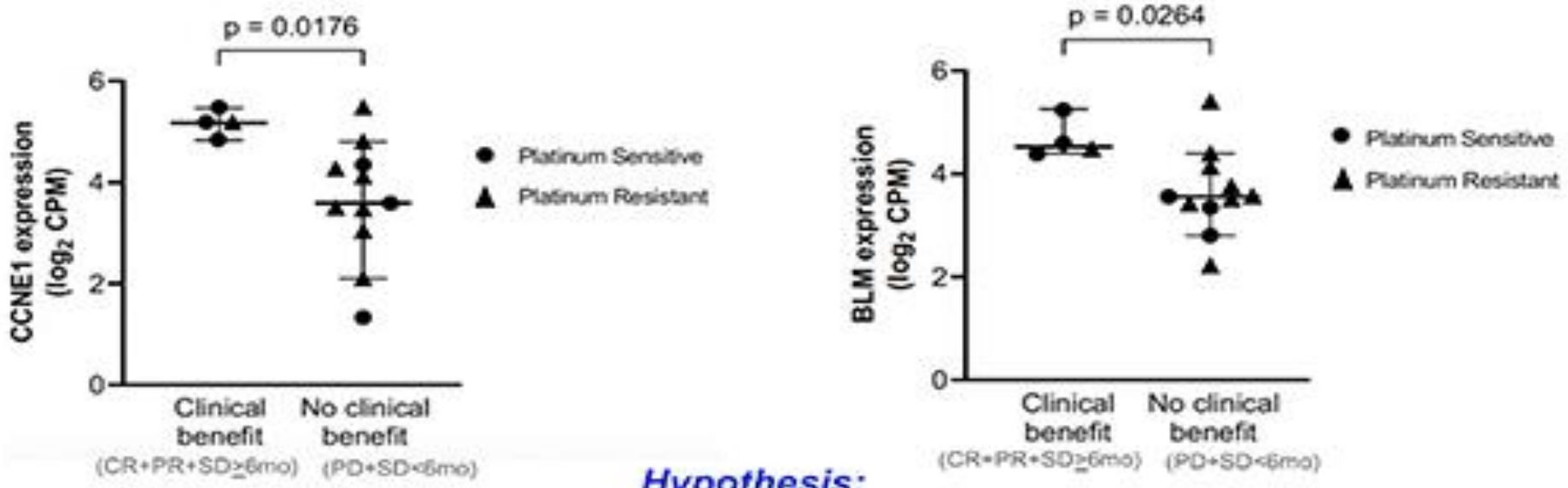


CHK1 inhibitor



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.

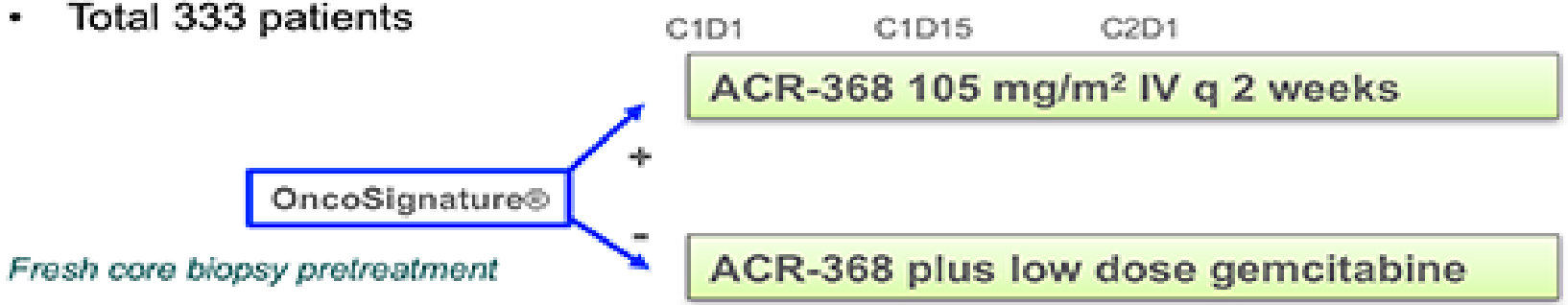
*All 4 patients with clinical benefit also had CCNE1 copy number gain/amplification
CPM: counts per million

Gupta, Huang, Nair…Lee. *Sci Transl Med.* 2023

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



NCT05548296

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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