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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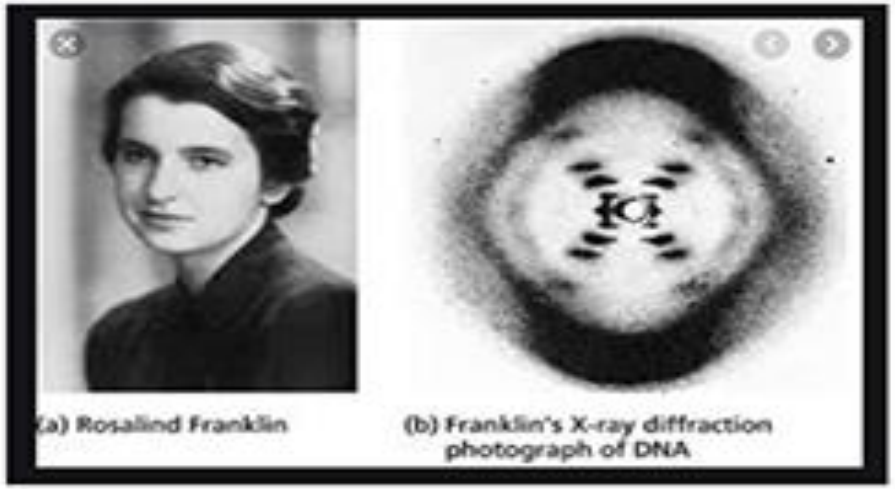
Rosalind Franklin

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

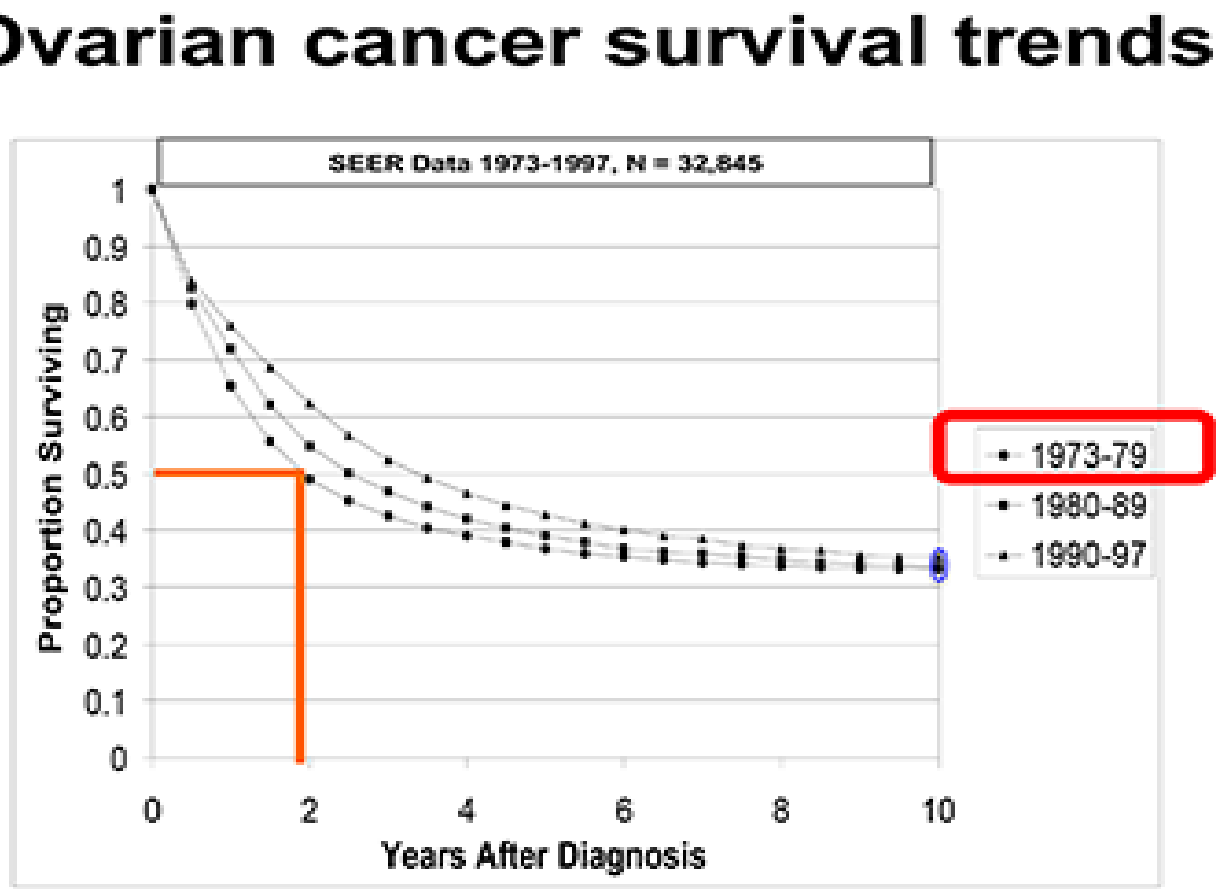
(b) Franklin's X-ray diffraction photograph of DNA

Ovarian cancer

Ovarian cancer

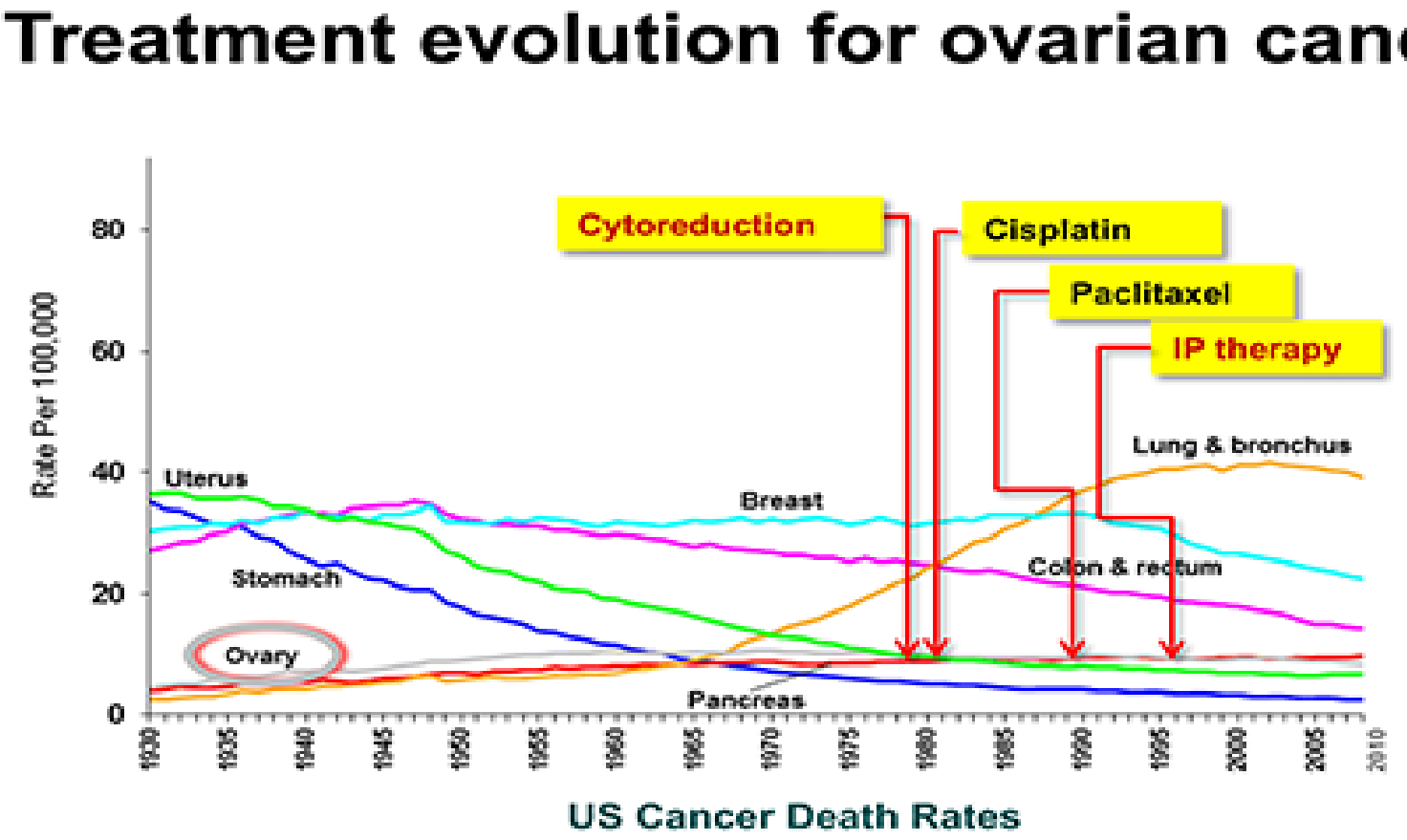
- Most lethal gynecologic malignancy in the US
  - >16,000 deaths/year
  - 5th most common cancer death for women
- 70% diagnosed with advanced disease

Cancer survival

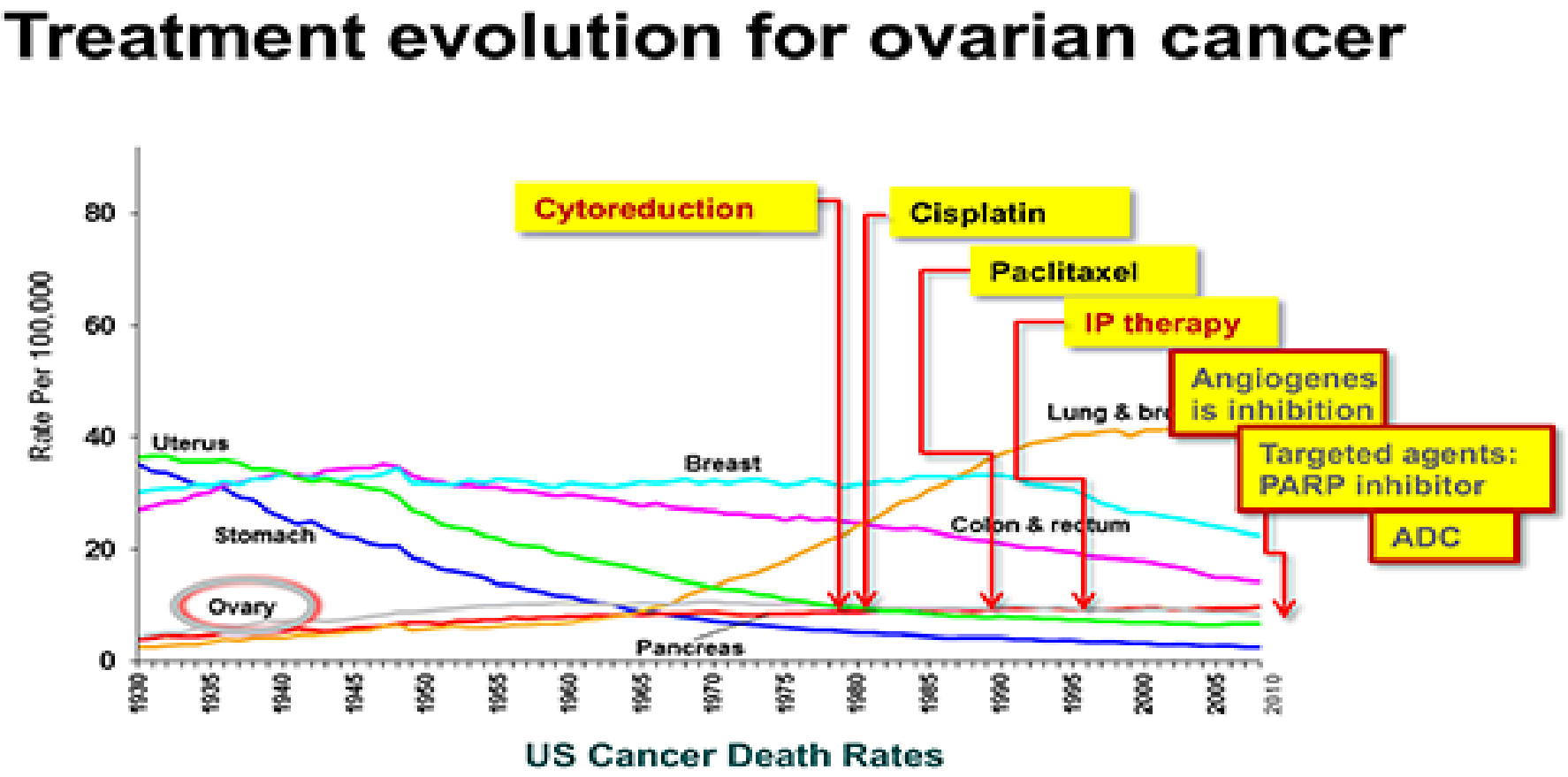


SEER: The Surveillance, Epidemiology, and End Results

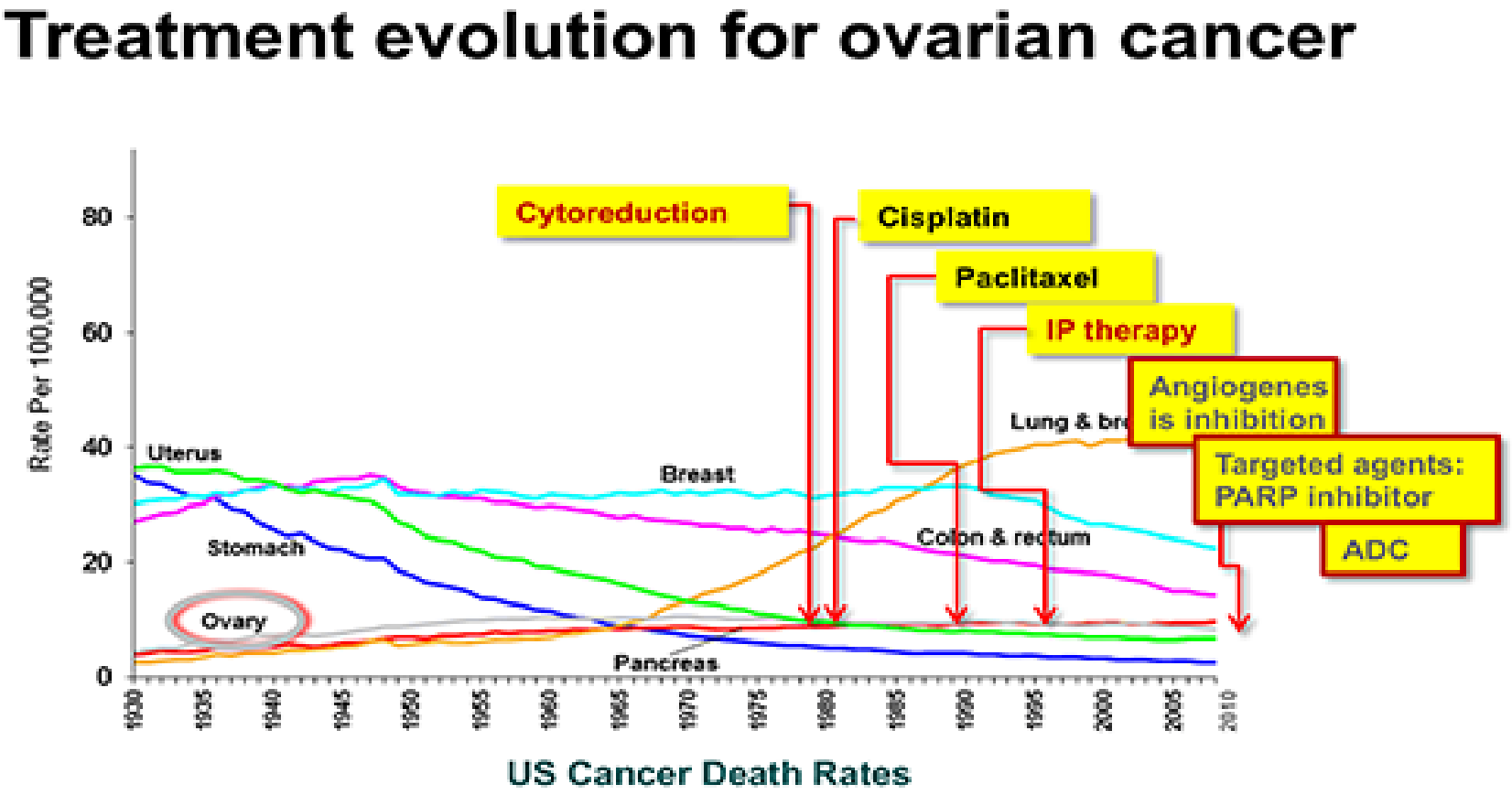
Cancer treatment



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

Treatment evolution

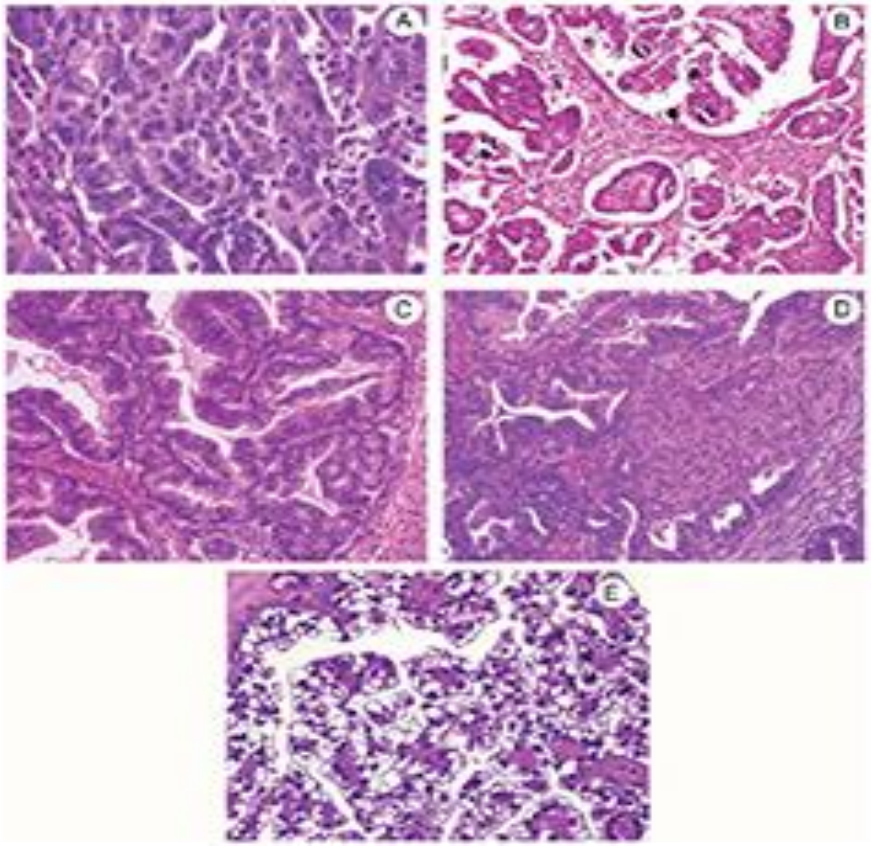


Ovarian cancer types

Ovarian cancer

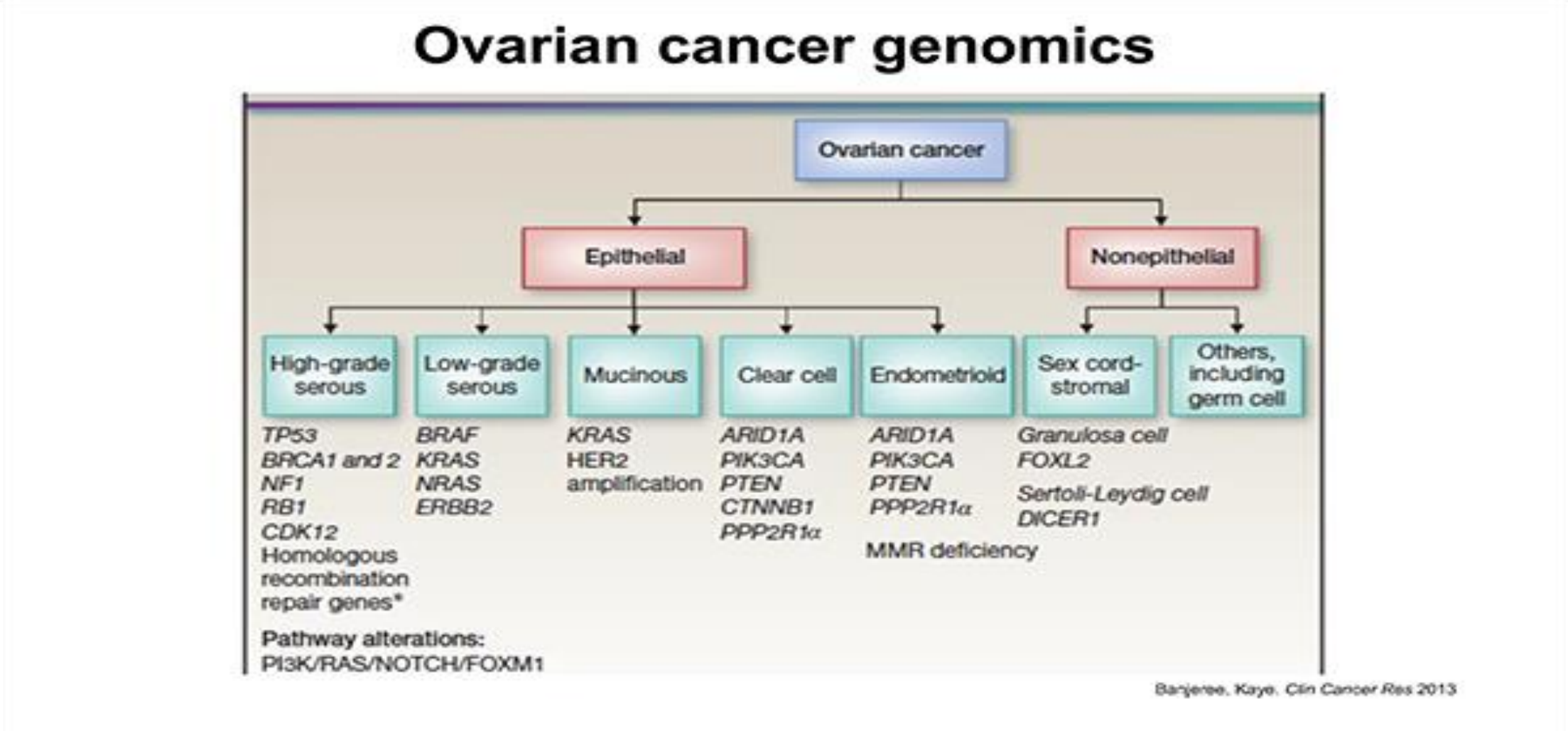
Prevalence

- 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*

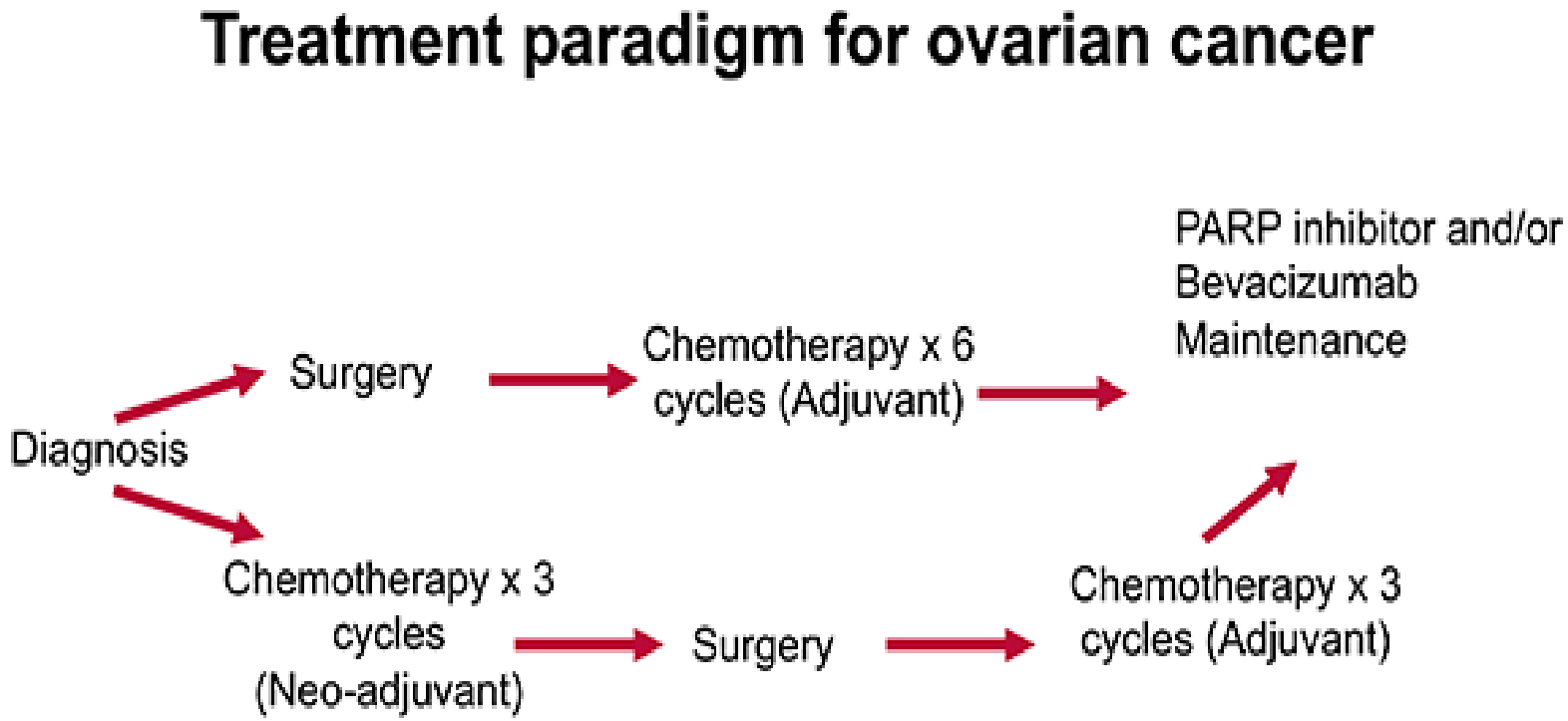
Treatment

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

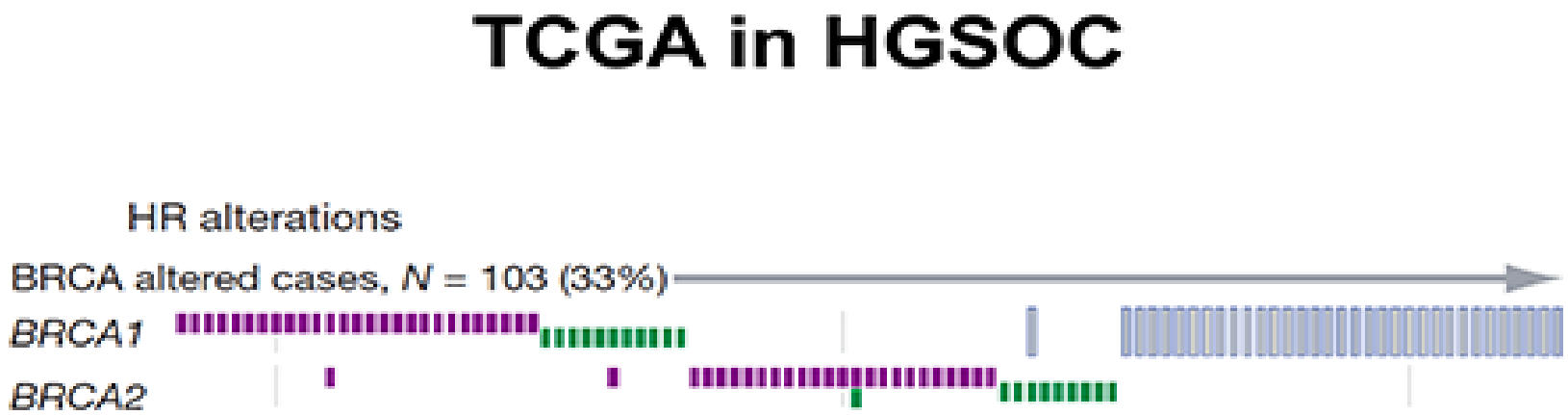


Slide courtesy of Dr. Annunziata

Serous ovarian cancer

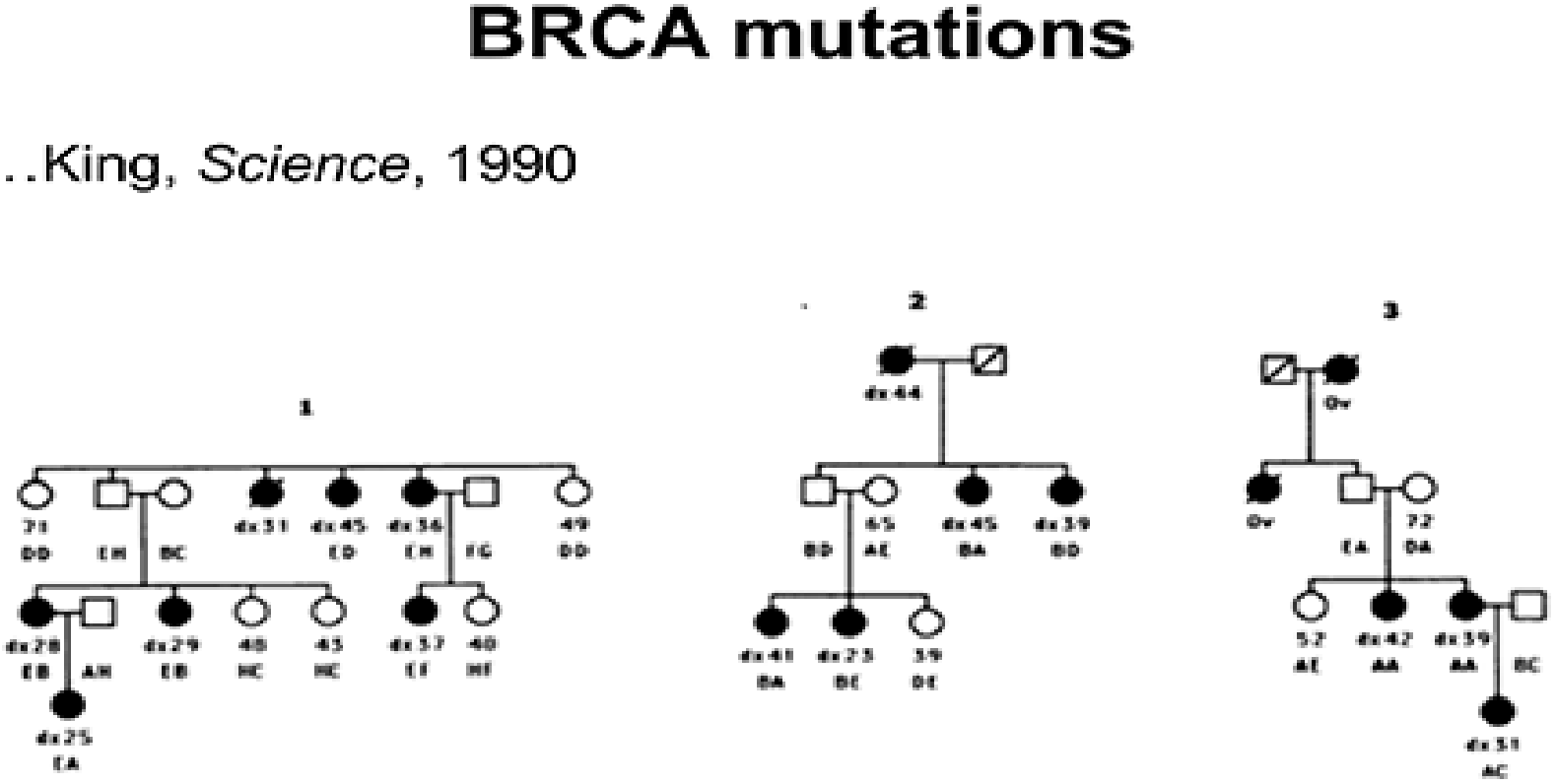
High grade serous ovarian carcinoma (HGSOC)

TCGA



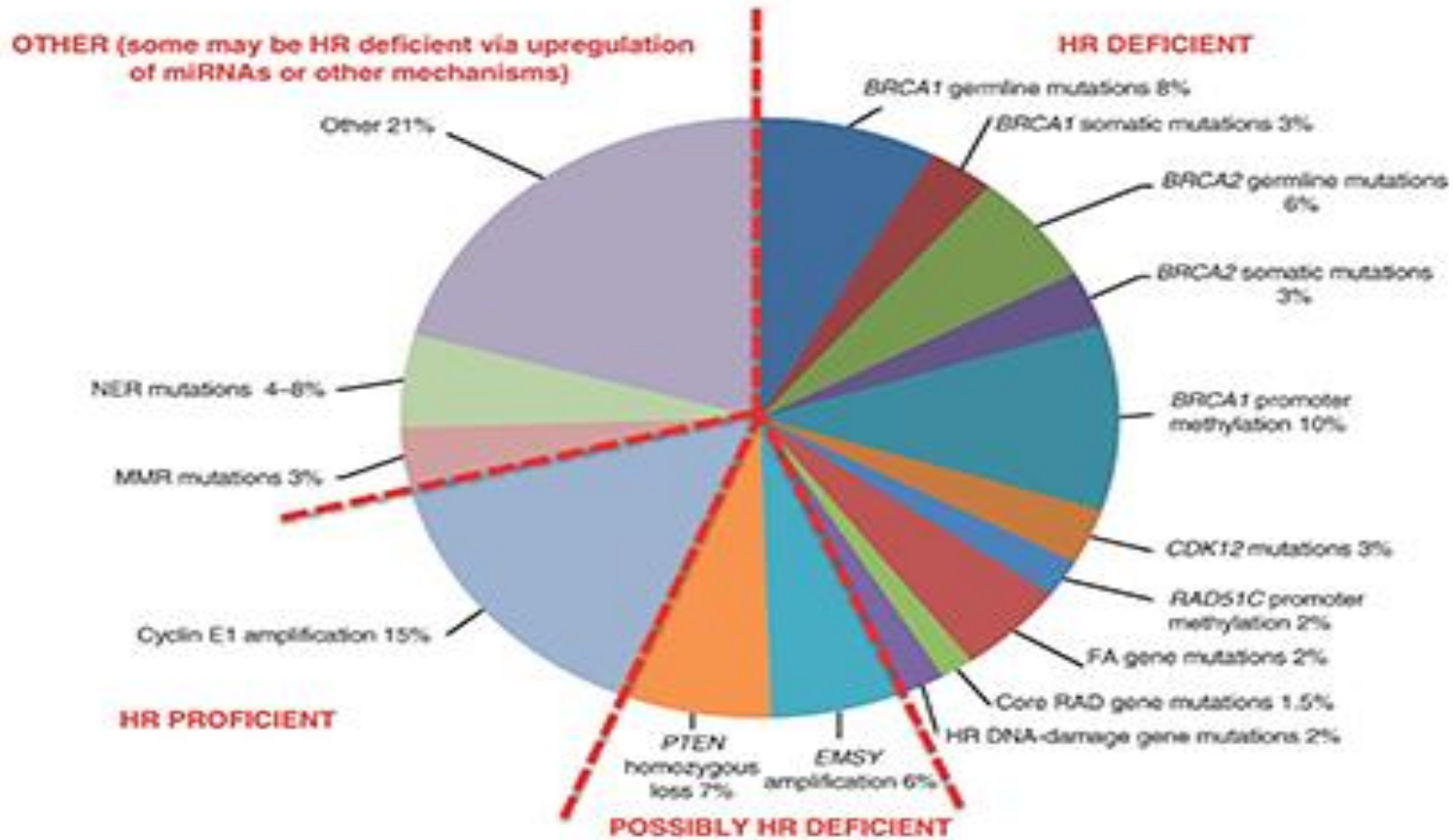
The Cancer Genome Atlas, *Nature* 2011

BRCA mutations



Slide courtesy of Dr. Annunziata

Genetic mutations



Konstantinopoulous *et al. Cancer Discov.* 2015

PARP inhibitors

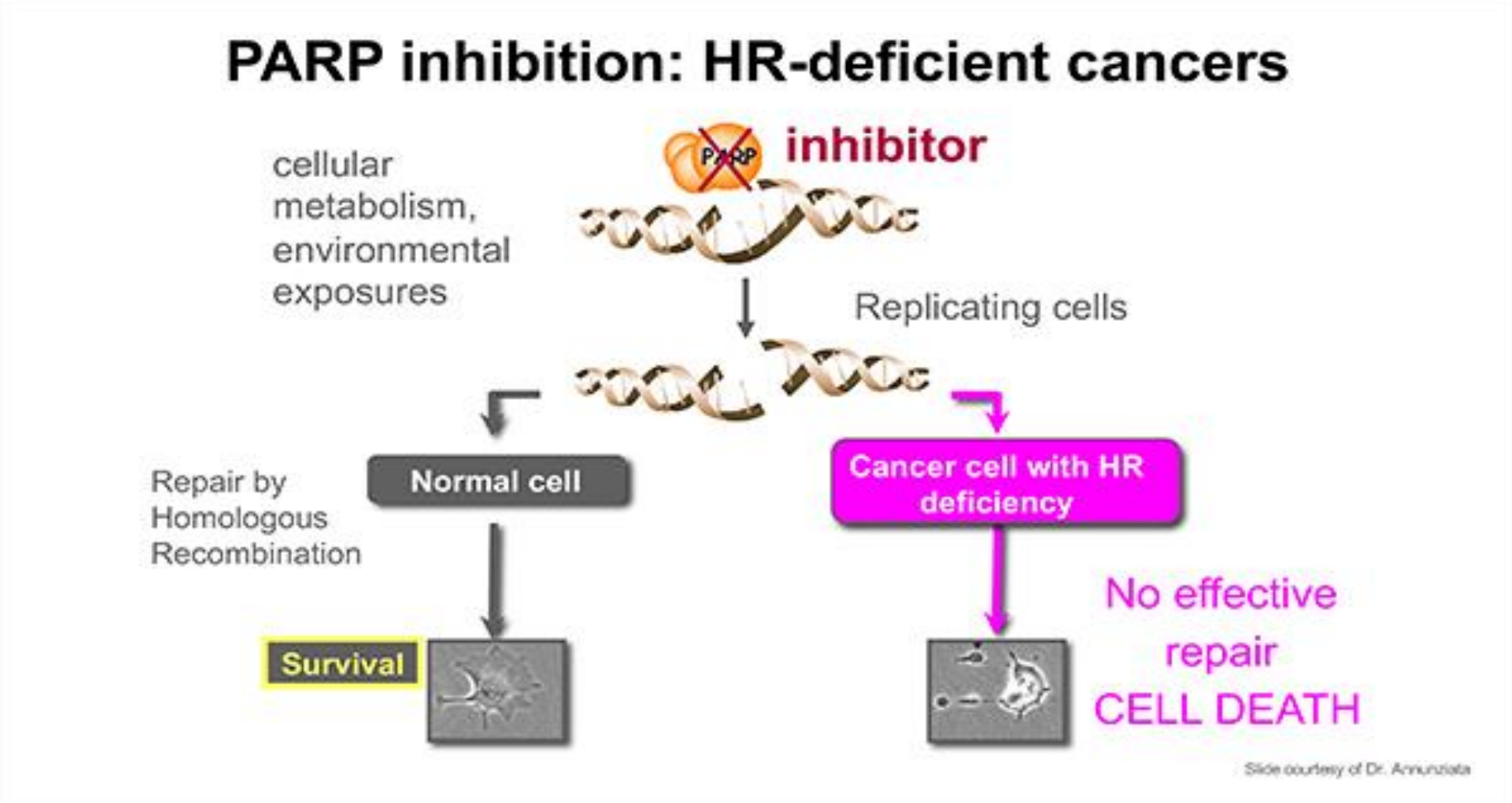
DNA repair

How is DNA repaired?

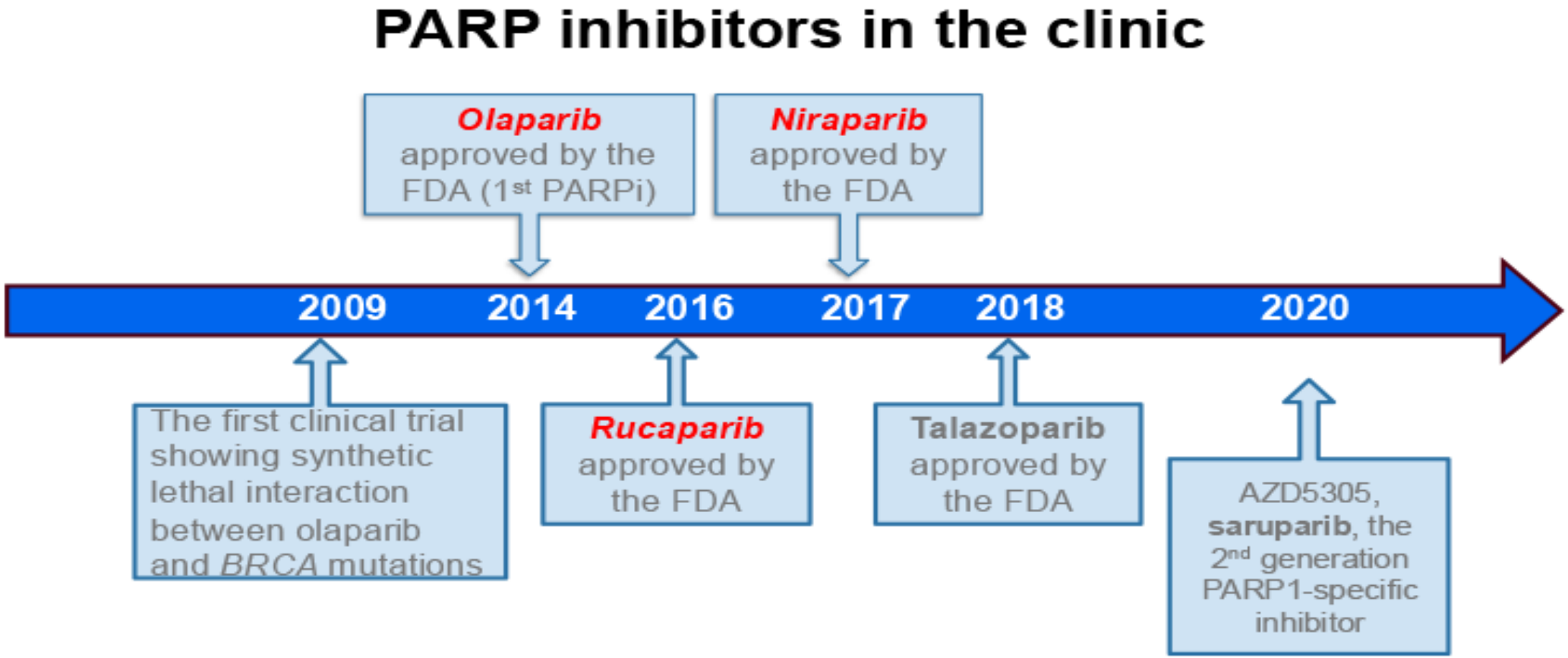
- Homologous recombination **(HR)**
- Undamaged DNA is the guide
- Replaces damaged part with the “correct” code
- **Uses BRCA**

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

PARP inhibition

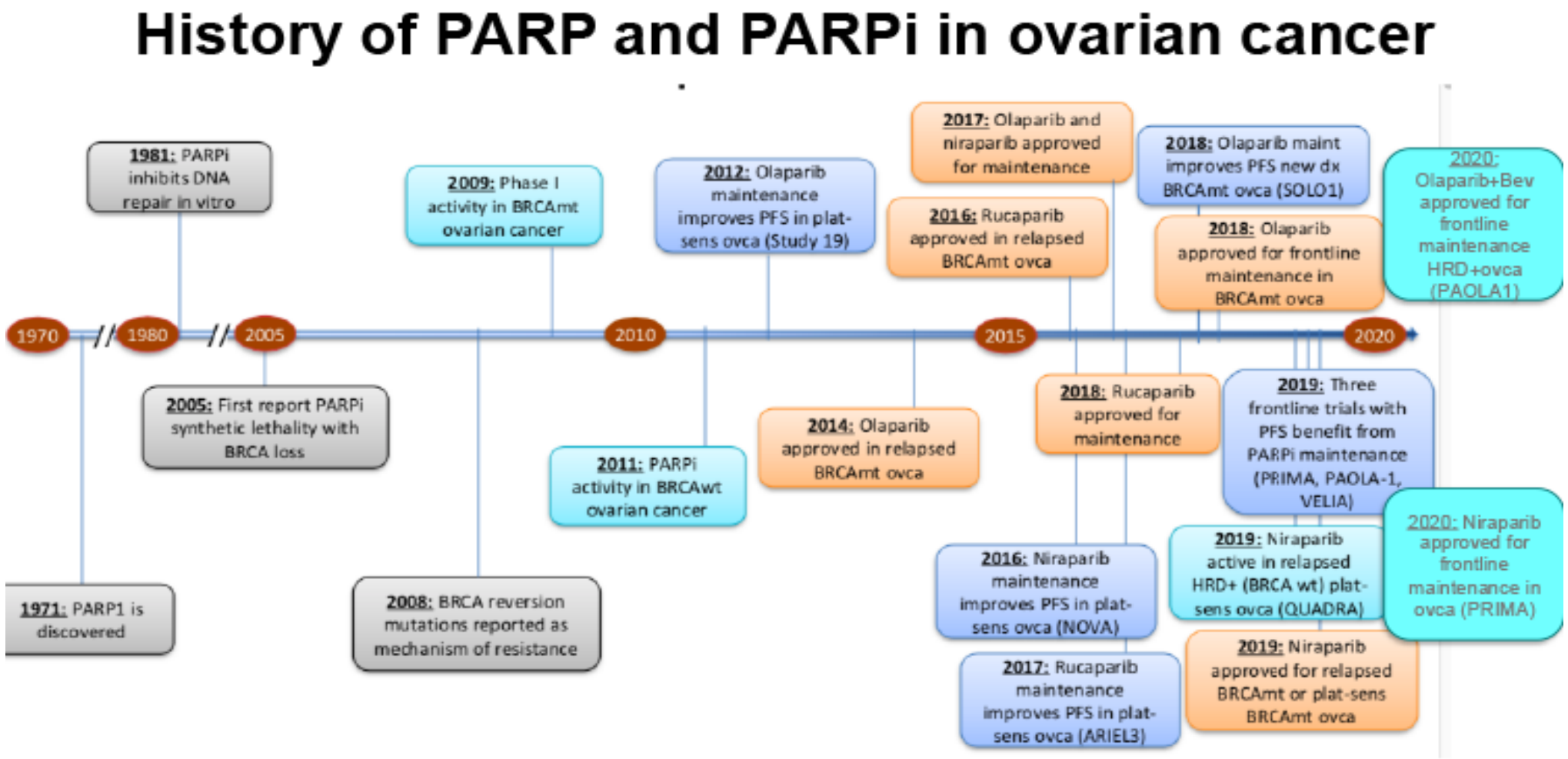


Clinical inhibitors



Slide courtesy of Dr. Shih

PARP and ovarian cancer



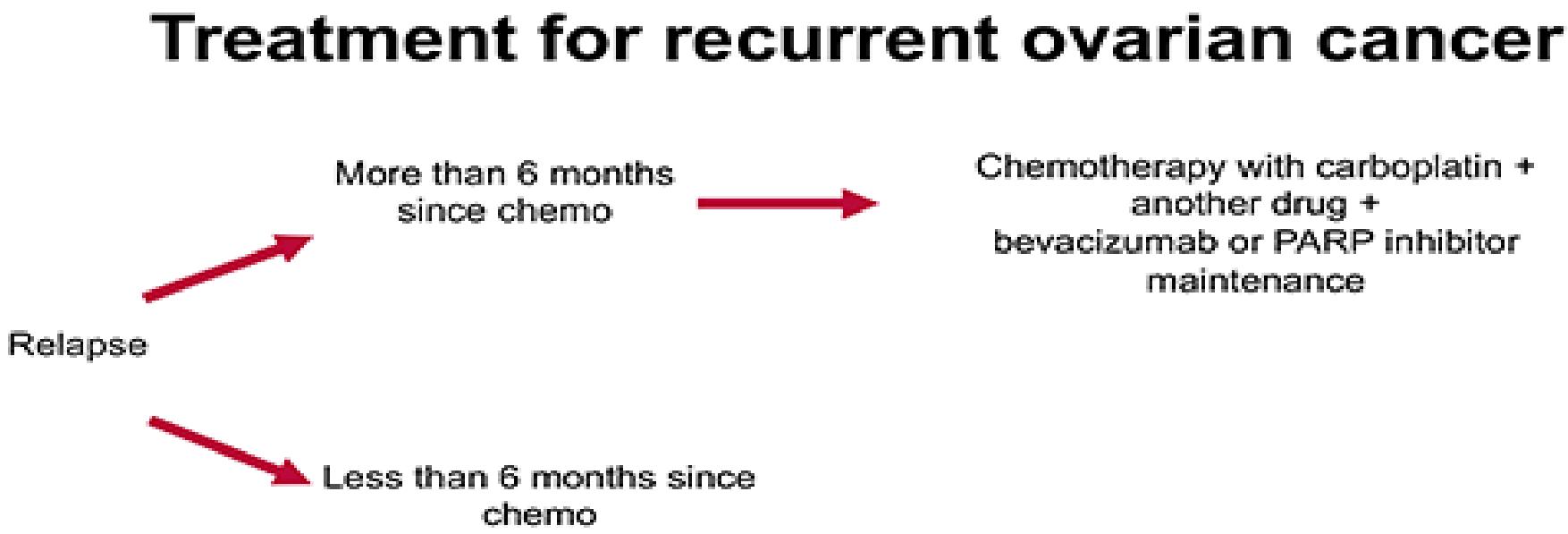
PARP inhibitor use

PARP inhibitors – when to use

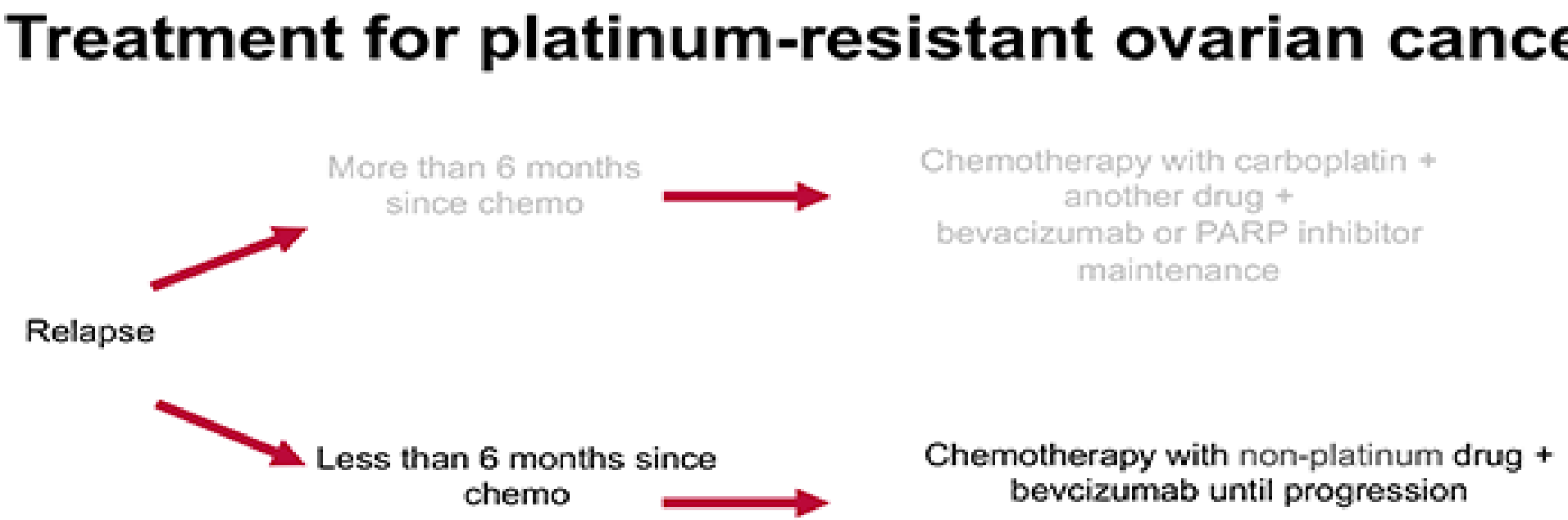
- First-line maintenance therapy
  - BRCA mutation - germline (hereditary) or somatic (tumor only)
  - BRCA wild type with HRD – mutations in particular genes or changes in DNA
  - As monotherapy or in combination with bevacizumab for BRCAm and BRCA wild type with HRD only
  - Not used for BRCA wild type without HRD
- Second-line maintenance therapy
  - Response to second round of carboplatin/cisplatin if no prior PARPi
- Treatment
  - Not currently recommended

Relapsed ovarian cancer

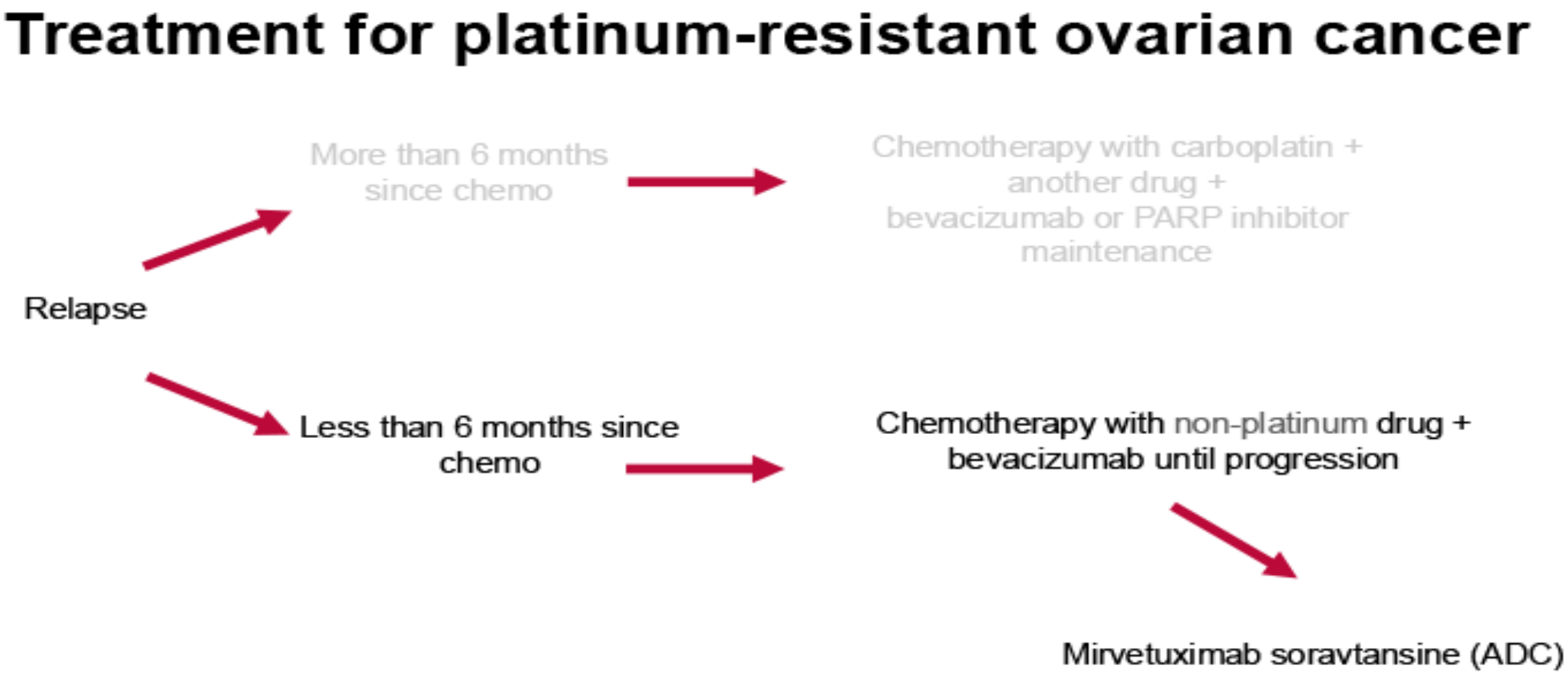
Recurrent ovarian cancer



Platinum resistant cancer

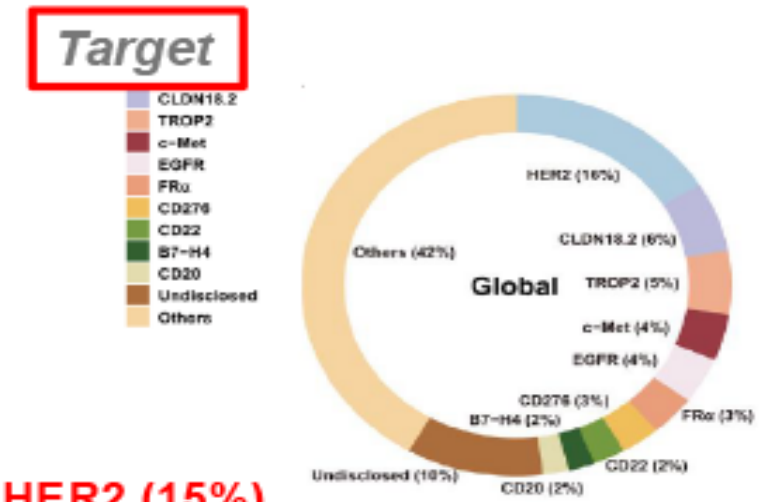


Platinum resistant cancer

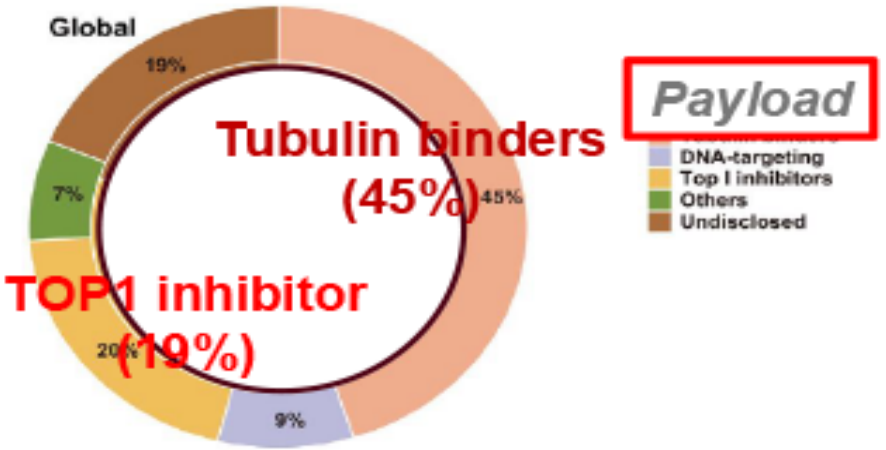


ADCs in clinical trial

More than 200 ADCs are now being tested in clinical trials

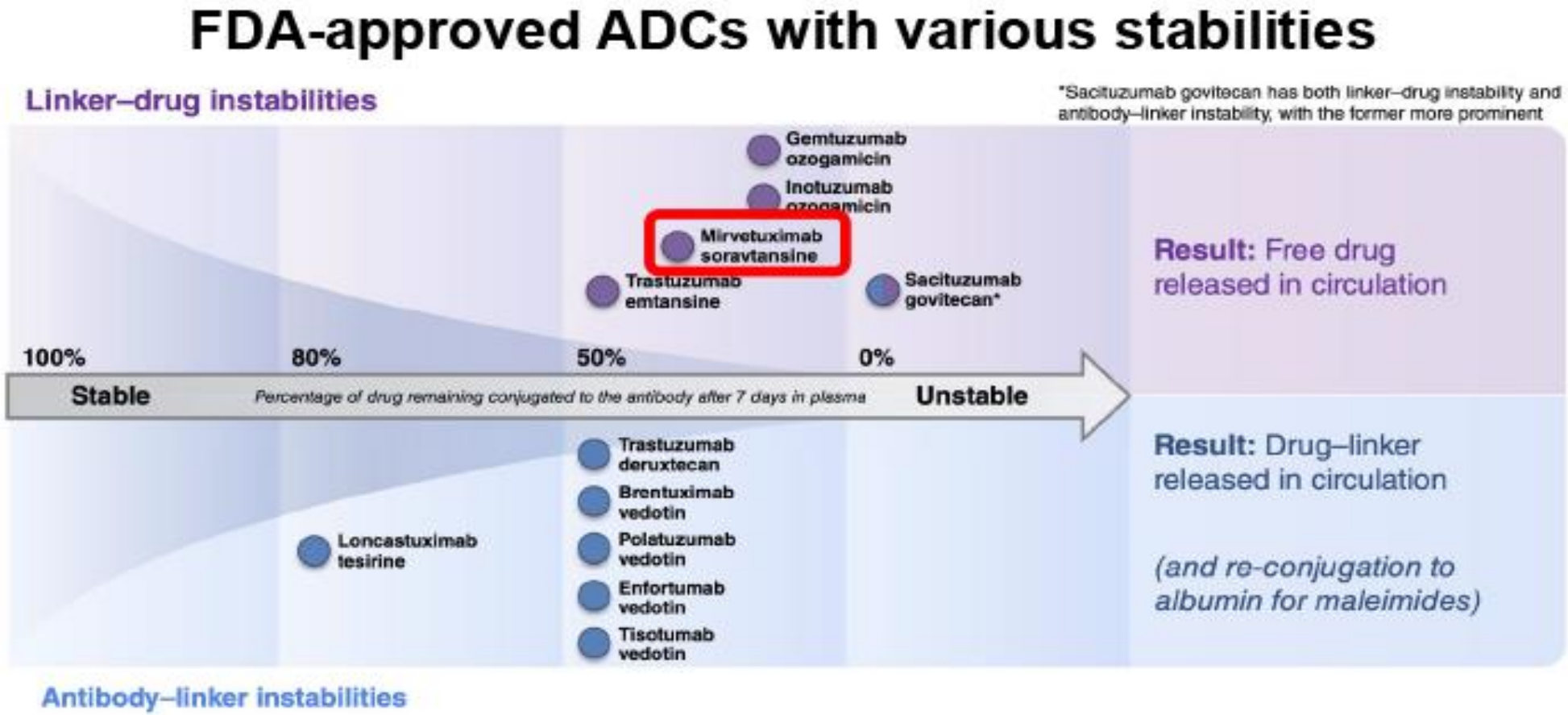


HER2 (15%)
CLDN18.2 (6%)
TROP2 (5%)
FR alpha, B7-H4, etc



Modified from Ruan *et al. Cancer Commun.* 2024

ADC stability



Mirvetuximab soravtansine

Mirvetuximab soravtansine

- FRα is expressed in a majority of ovarian carcinomas and at high levels (≥75% positive with ≥2+ intensity) in ~35%-40% of PROC cases
- Mirvetuximab soravtansine is an anti-FRα ADC with a maytansinoid DM4 payload
- Ph II SORAYA trial: FRα-high PROC treated with 1-3 prior therapies: an ORR of 32.4% and a median DoR of 6.9 mo, leading to accelerated FDA approval.
- Ph III confirmatory study (MIRASOL) in patients with high FRα-expressing, PROC
  - Median PFS was 5.62 mo vs 3.98 mo with investigator's choice of CT (P <.0001)
  - Median OS was 16.46 mo vs 12.75 mo with investigator's choice of CT (P <.0046)

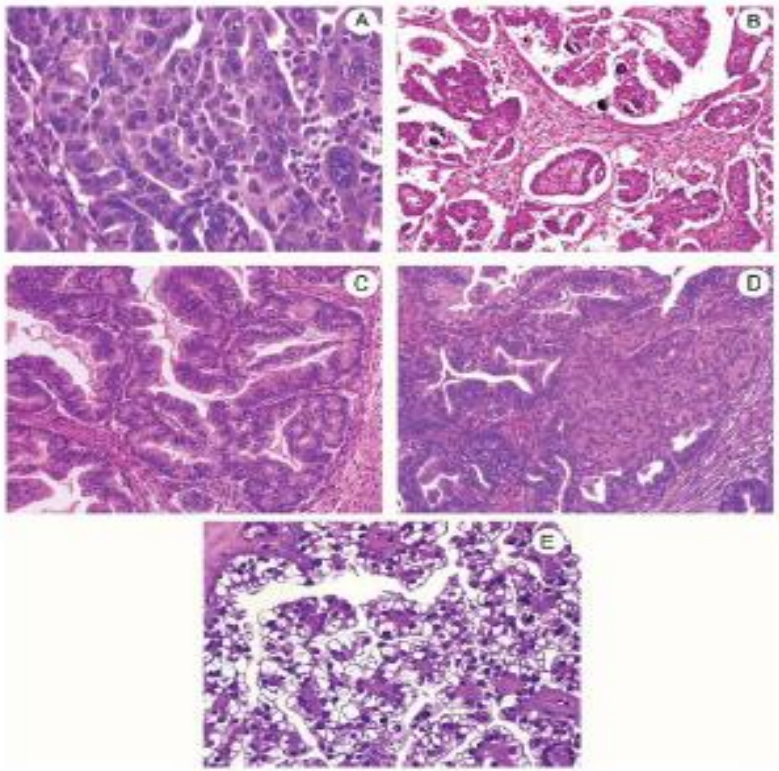
Rare ovarian cancers

Ovarian cancer subtypes

Subtypes of ovarian carcinoma

Prevalence

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

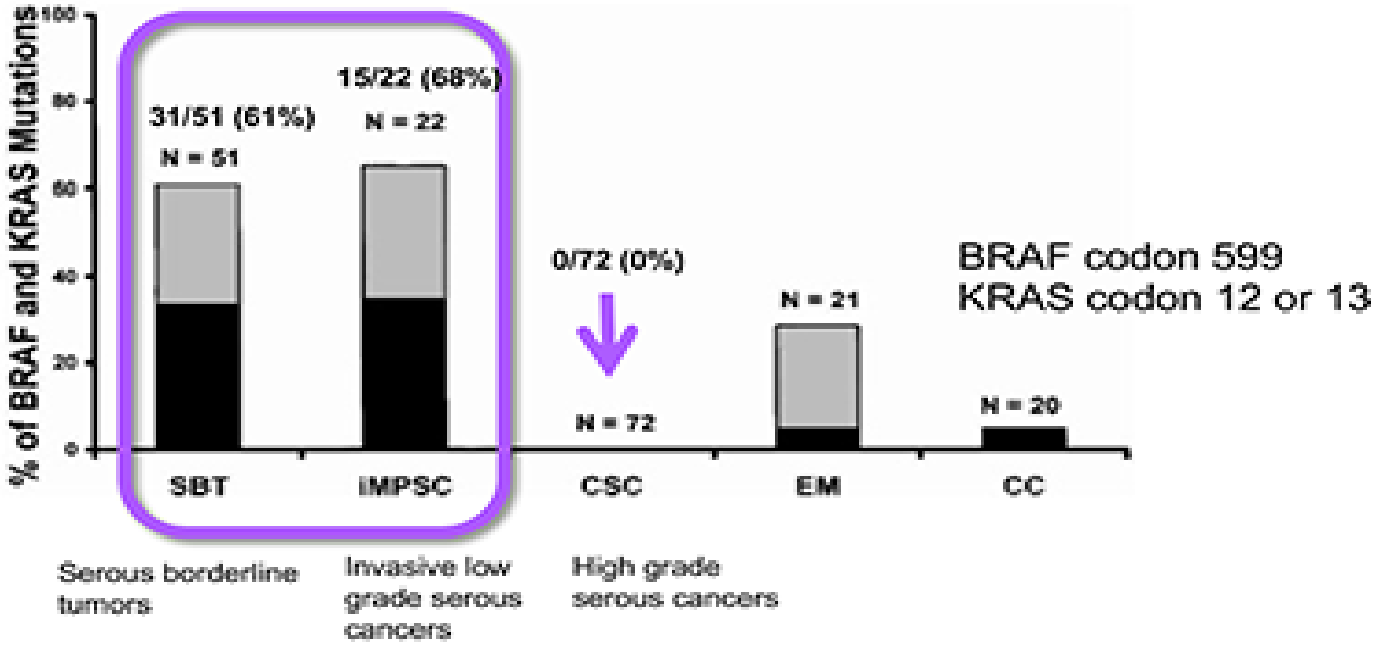


Soslow R. *Int J Gyneol Pathol*, 2008

Low grade cancer

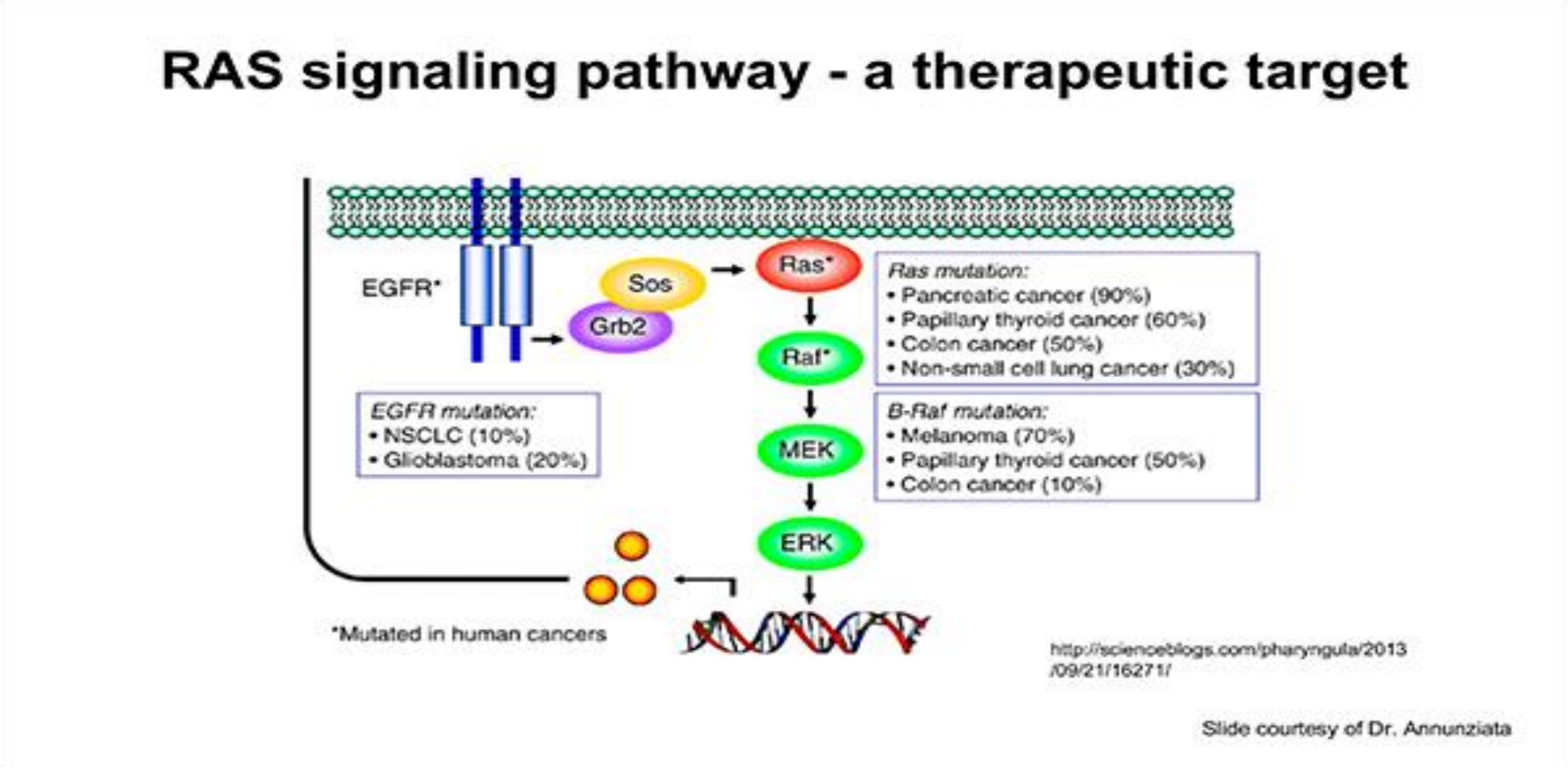
Low grade serous ovarian cancer

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



Singer, JNCI 2003

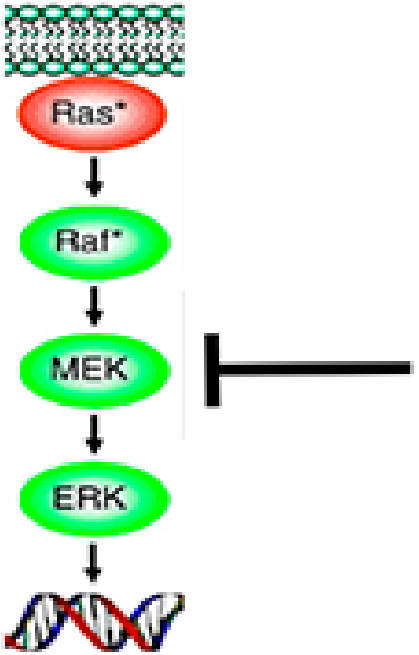
RAS signaling



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

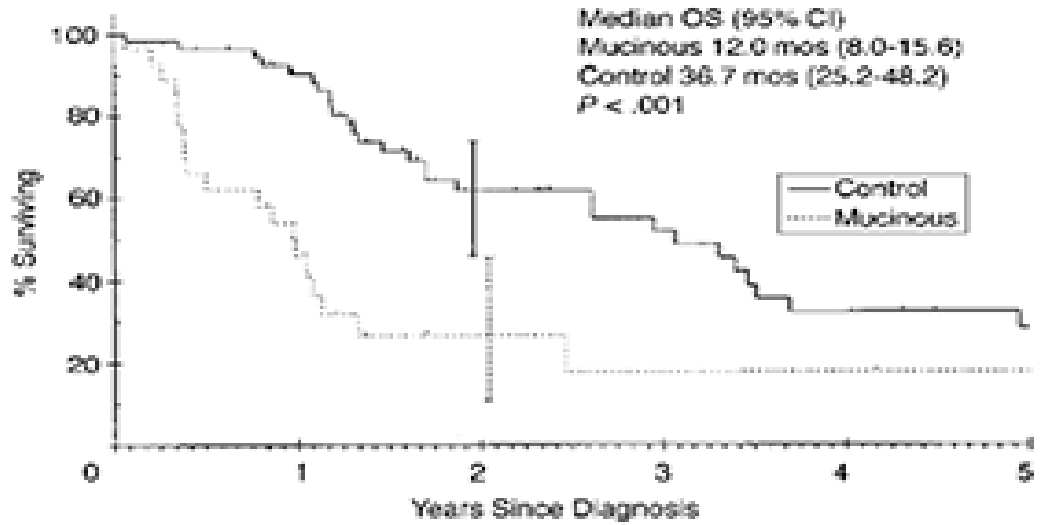
- Strong expression of ER/PR (>80%)
- Associated with endometriosis
- Mean age: 50 years old
- 84% Stage I/II and better prognosis than serous tumors
- May not be as chemo-sensitive as serous tumors
- ARID1A mutated or lost in
  - 40% endometrioid
  - Need therapies targeting these mutations

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

Summary

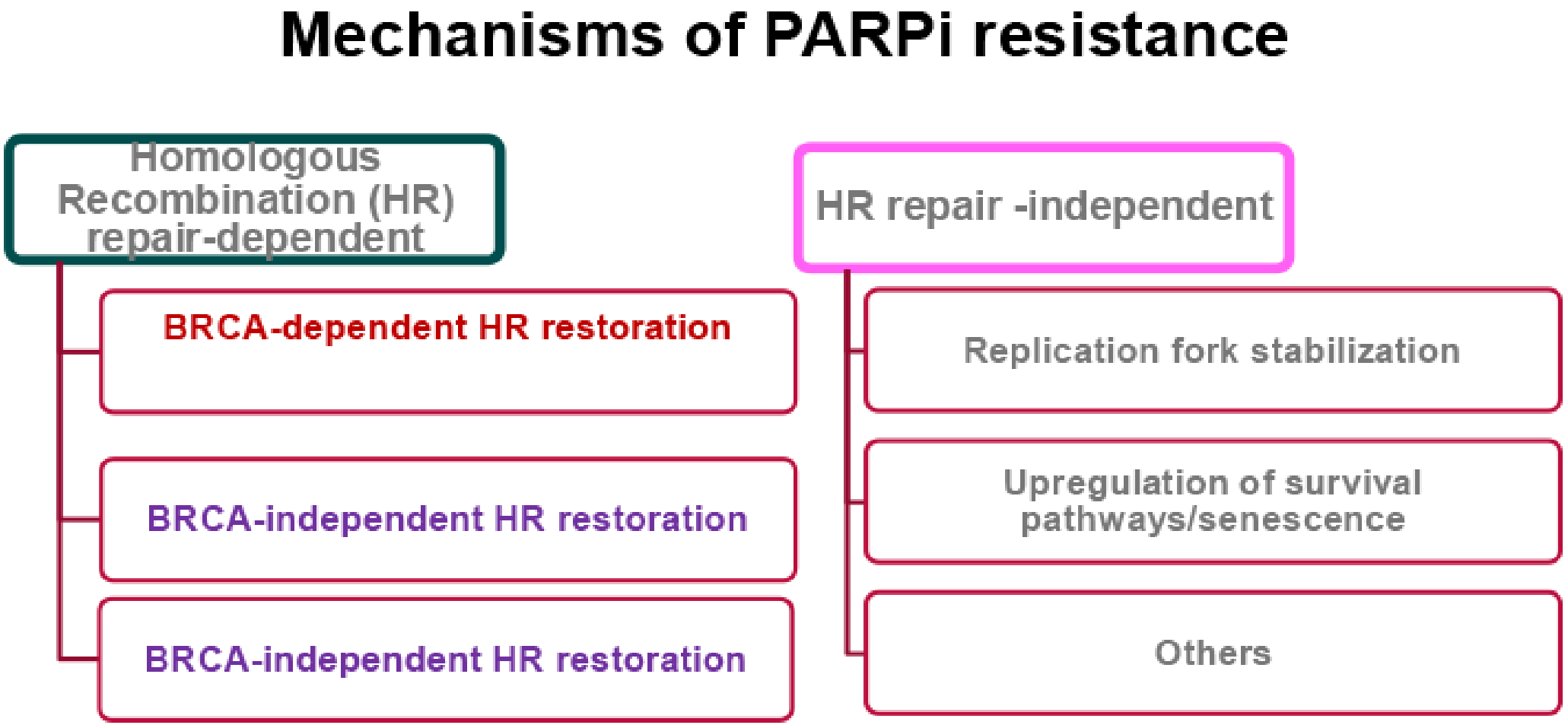
Summary

- Ovarian cancer is not a single disease and has many characteristics that may contribute to treatment susceptibility *e.g.*, germline mutations.
- Platinum-based chemotherapy is the standard of care for newly diagnosed ovarian cancer along with PARP inhibitor and/or bevacizumab maintenance therapy.
- The ”right” targeted therapies or “right” combination to create clinical synthetic lethality may be disease-specific, subtype-specific, or patient-specific.

New targets

Exploration of new targets

PARPi resistance



Gupta…Lee. *Pharmacol Res*, 2022

Ovarian cancer subtypes

Subtypes of ovarian carcinoma

Prevalence

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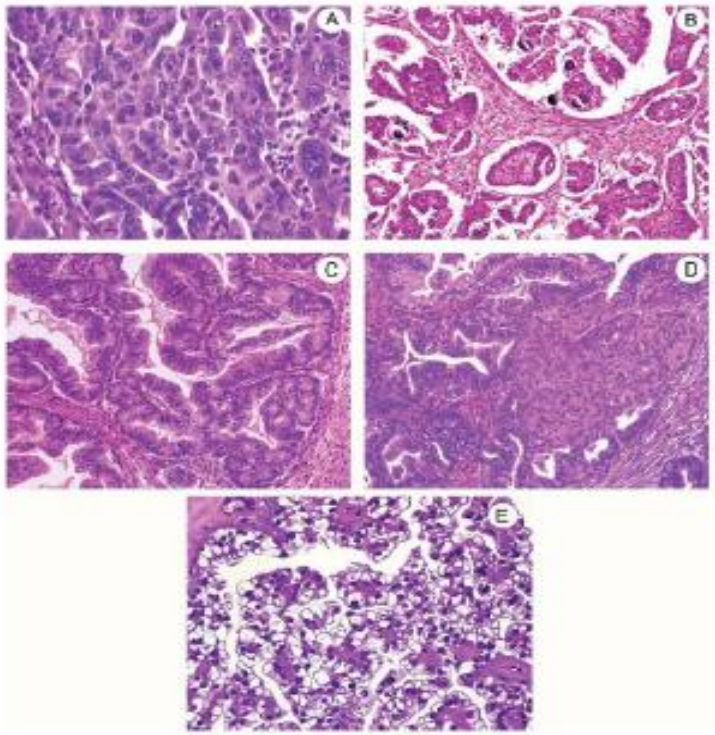
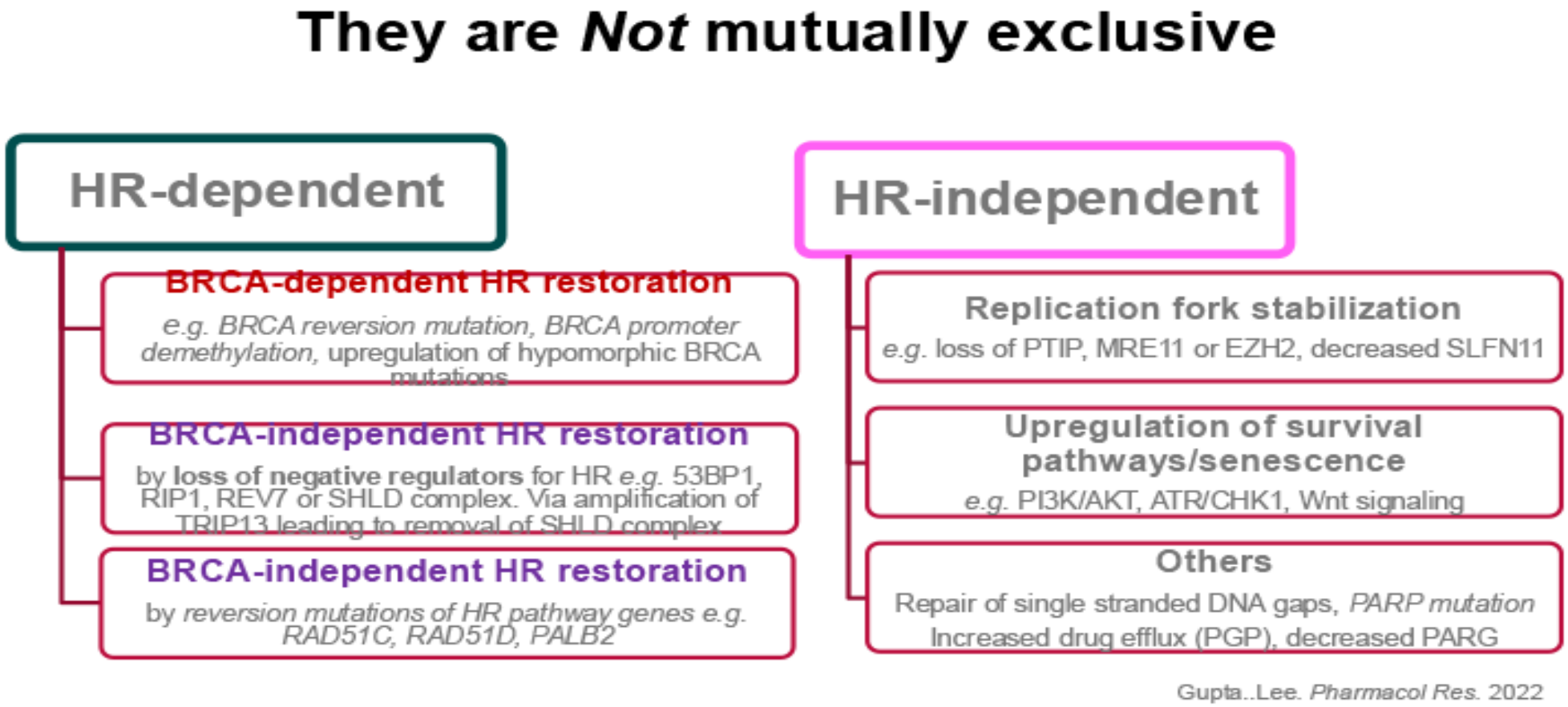
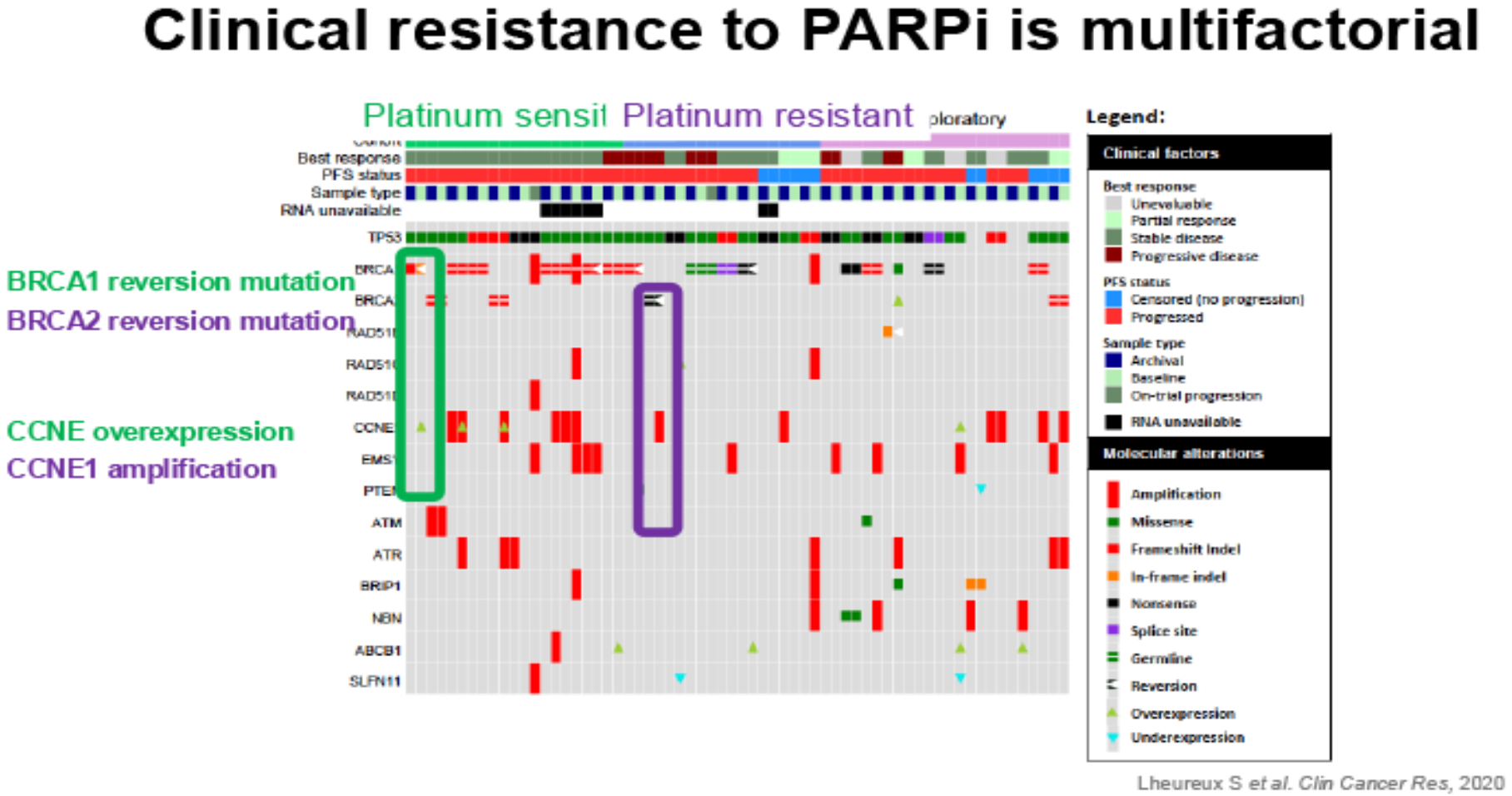


Soslow R. *Int J Gyneol Pathol*, 2008

Hormone dependent cancer



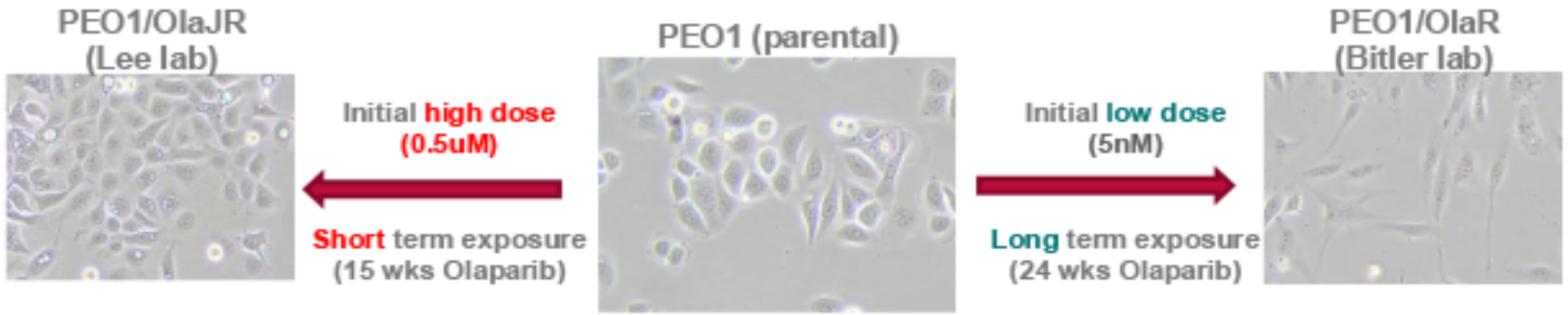
Clinical resistance



Lheureux S *et al. Clin Cancer Res*, 2020

Distinct characteristics

Distinct characteristics of PARPi-resistant cells



PARPi resistance mechanisms

- Epithelial-like phenotype (less aggressive)
- ↑ Heterozygous *BRCA2* reversion mutation

-> HR restoration & fork stabilization

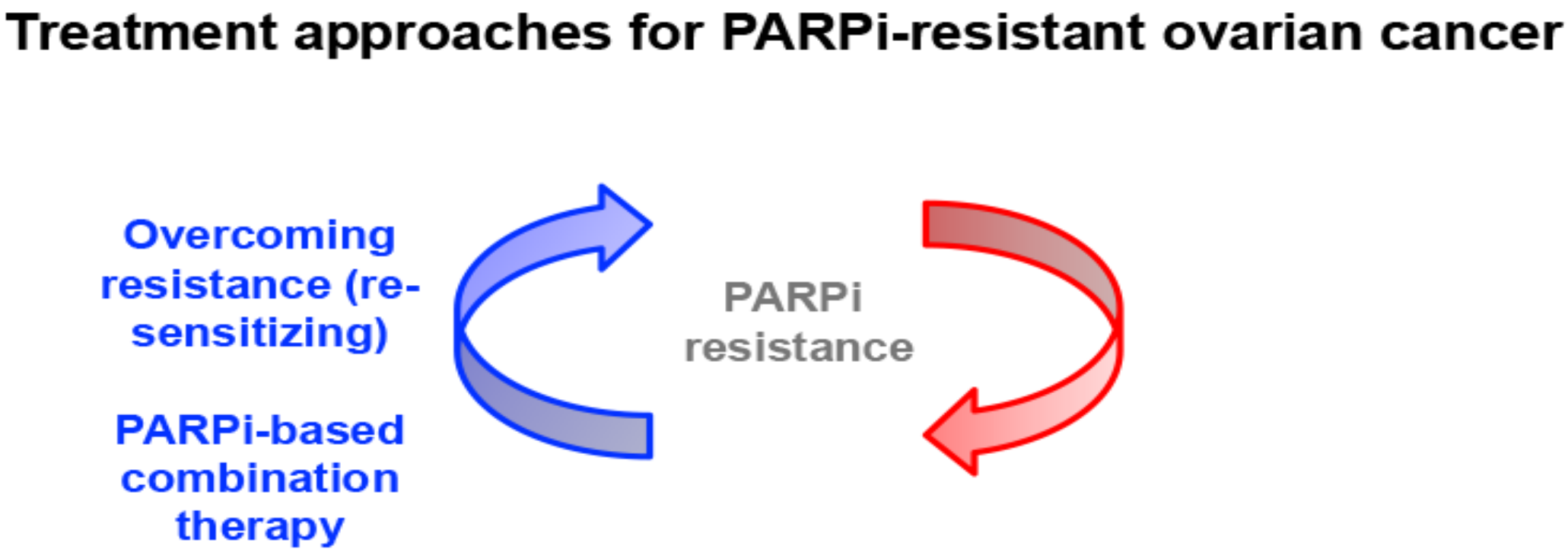
- ↑ drug efflux ABCB1 activity

Huang…Lee, Nair. *Oncogene*, 2022

PARPi resistance mechanisms

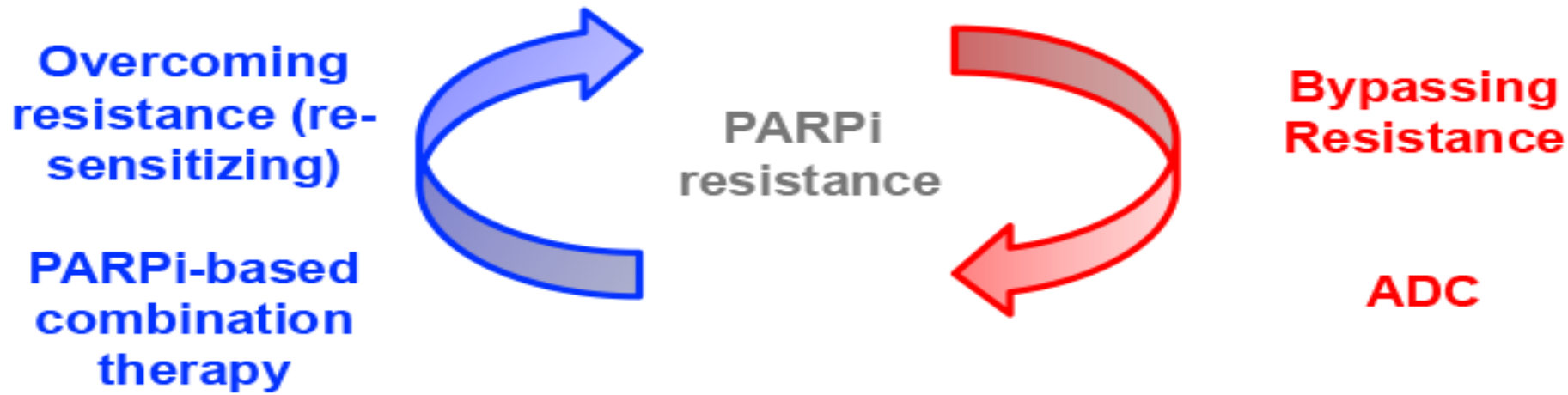
- Mesenchymal-like phenotype (more aggressive)
- BRCA2-independent HR
- Fork stabilization (probably via ↓ EZH2 & ↓ MUS81)
- More dependence on ATR/CHK1 pathway to origin firing, stabilize replication forks and ↑ HR
- TCF/LEF transcription factors, Wnt signaling pathways (WNT3A) and H3K9me2, EHMT1/2

Treatment approaches

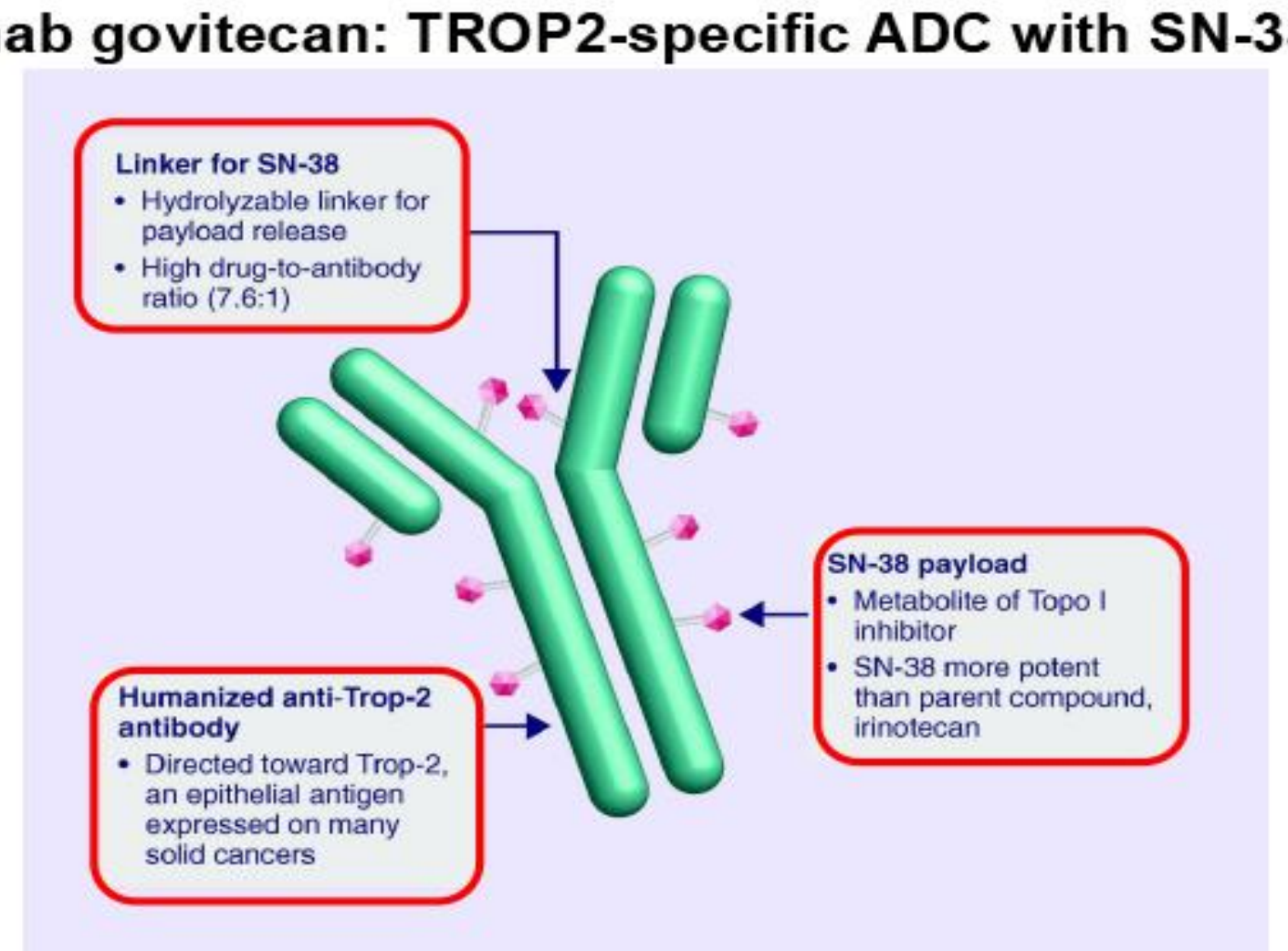


Bypassing resistance

Treatment approaches for PARPi-resistant ovarian cancer

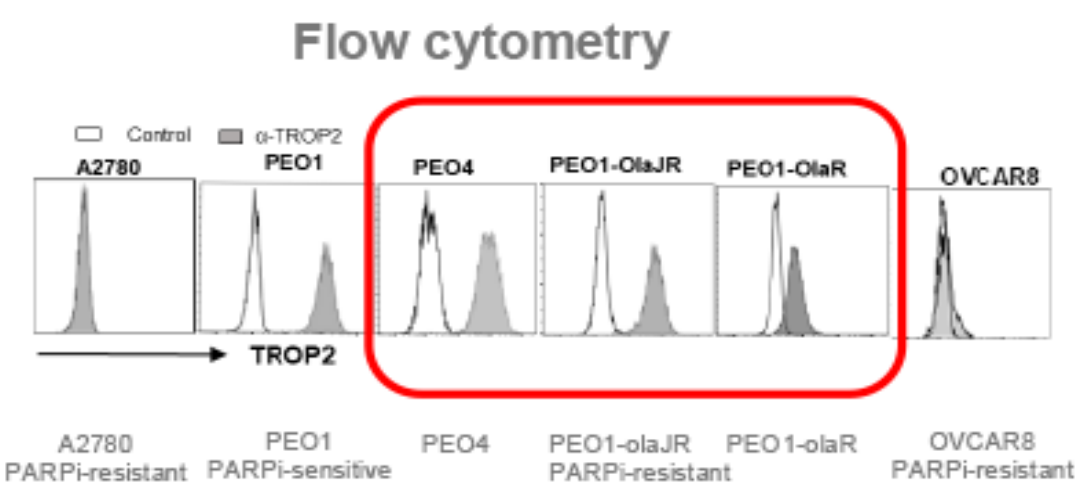


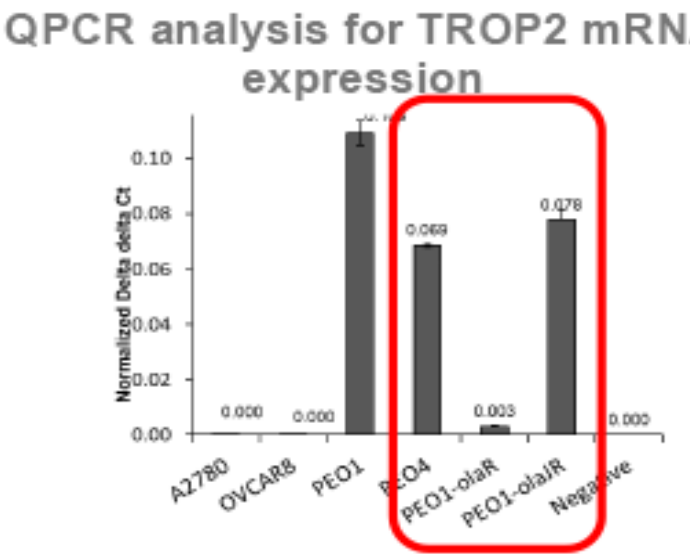
Sacituzumab govitecan



Expression levels

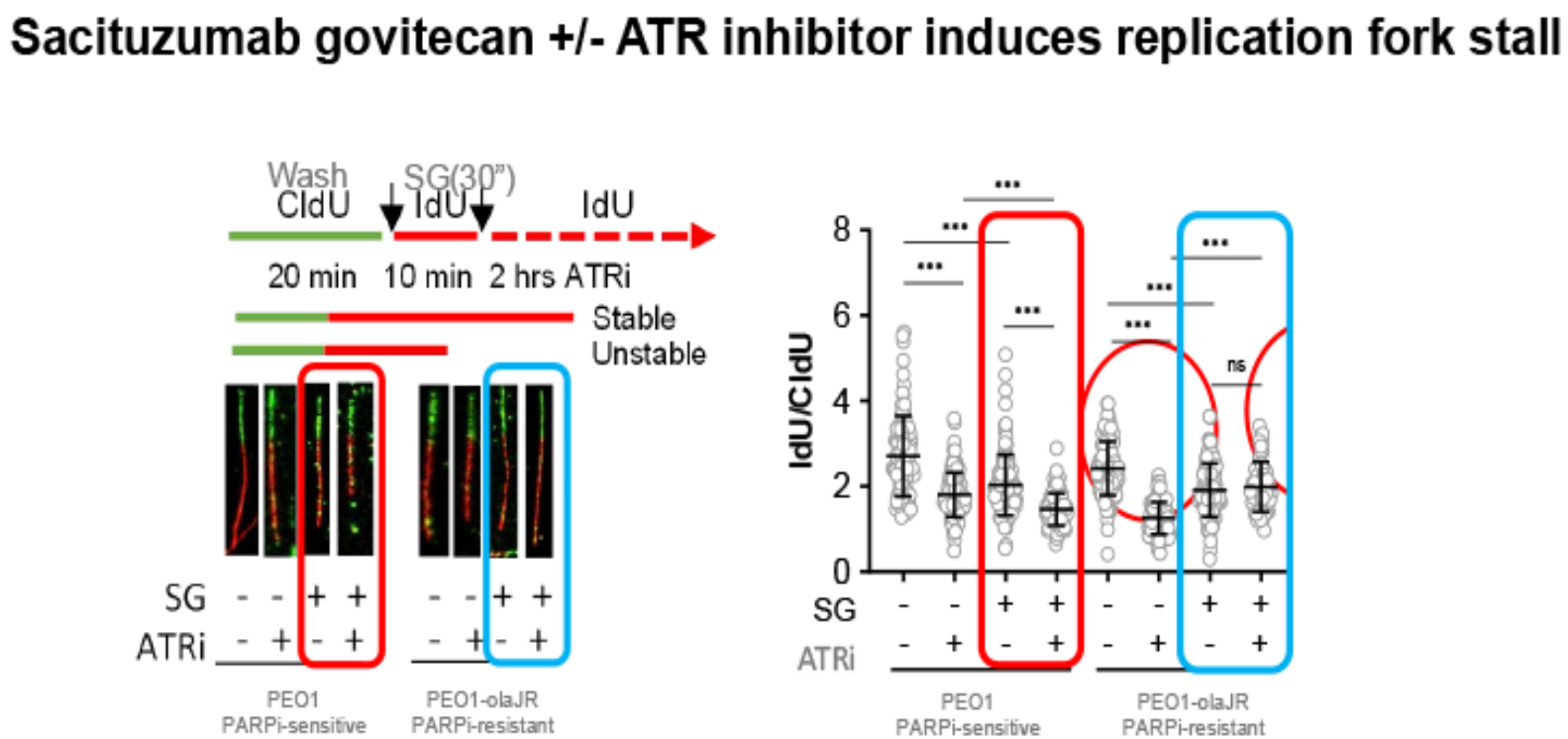
Expression levels of TROP2 on PARP inhibitor-resistant HGSOC





Nair, ...Lee. *iScience* 2024

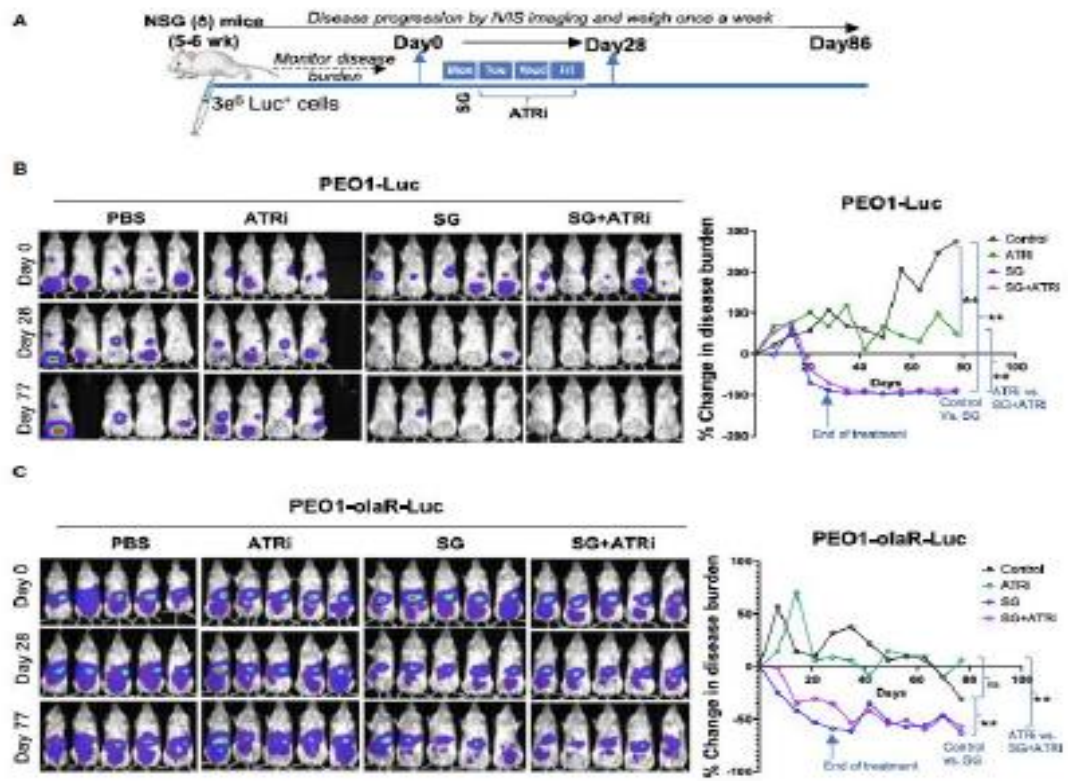
Replication fork stall



Nair, ...Lee. *iScience* 2024

Drug combination

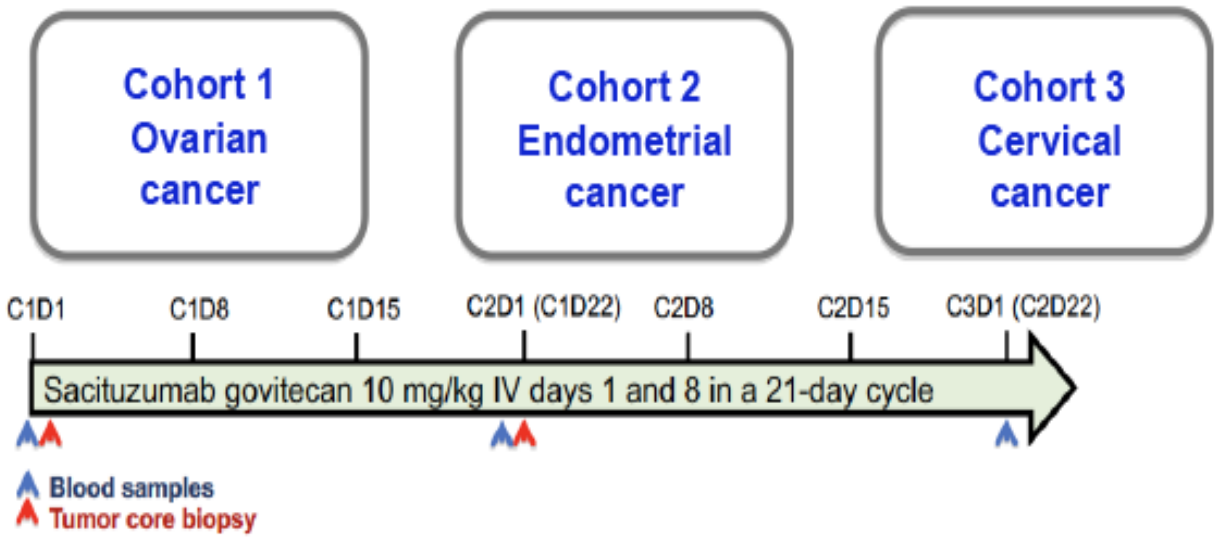
Sacituzumab govitecan +/- ATR inhibitor induces tumor shrinkage



Nair, ...Lee. *iScience* 2024

Phase II trial

NCI phase II pilot study of SG in gynecological cancers



- **Primary:** Objective response rate
- **Secondary:** Progression free survival and safety
- **Exploratory:** TROP2 expression in tumors and blood samples, mutations of TROP2 genes, ctDNA, RNAseq to investigate their associations with clinical response or resistance

NCT06865677

Summary

Summary

- DNA replication targeting drugs either as monotherapy or in combination may overcome drug resistance in HGSOC.
- Identifying the novel therapeutic targets and potential predictive biomarkers are important.
- Understanding of the clinical and molecular characteristics and stratification of patients are necessary in the future trials.
- Both bench to bedside and back to bench approaches are critical for the development of next generation clinical trials.

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