Flash talk:
Understanding resistance

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Disclosures

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Advisory Boards: Artios Pharma, Eisai, Merck/MSD, Pfizer, VBL Therapeutics, Bristol Myers Squibb, Nuvation, Ellipses, Immagene

Independent Data Monitoring Committee :Regeneron, Mersana

Clinical Research Grants: AstraZeneca, MSD/Merck Research

Institutional Clinical Research: Clovis Oncology, Pfizer, Merck/MSD, Eisai, AstraZeneca, GSK

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Non-financial Leadership: Past Vice-President ESGO, Chair Joint ESGO-IGCS IGJC journal committee

Non-financial Editorial Boards: Cancer, Gynecological Oncology

It means the drugs don’t work- but its not so simple!

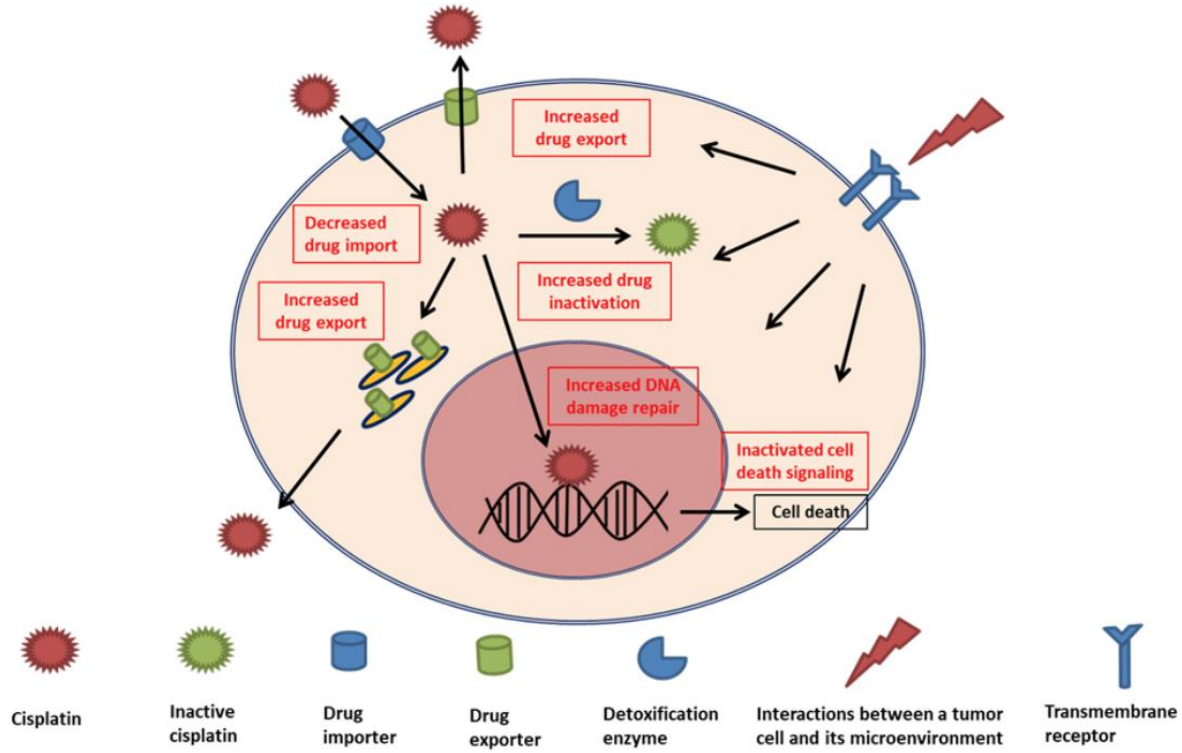
- Platinum resistance
  - Moving from simplicity to reality
- Real-time evaluation of emerging resistance
  - Pathological markers
  - Biochemical evaluation
- PARP inhibitor resistance
  - A challenge and learning opportunity

Platinum Resistance

Platinum-Free Interval (Interval from last date of platinum dose until progression)	Expected platinum sensitivity
Progression while receiving last line of platinum- based therapy or within 1 month of last platinum dose	**Refractory**
1–6 months	**Resistant**
6–12 months	**Partially sensitive**
>12 months	**Fully sensitive**

4th Ovarian Cancer Consensus Conference, 25–27 June 2010, UBC Life Sciences Institute, Vancouver, BC, Canada

Platinum resistance is phenotypic - **no biomarker** to confirm resistance

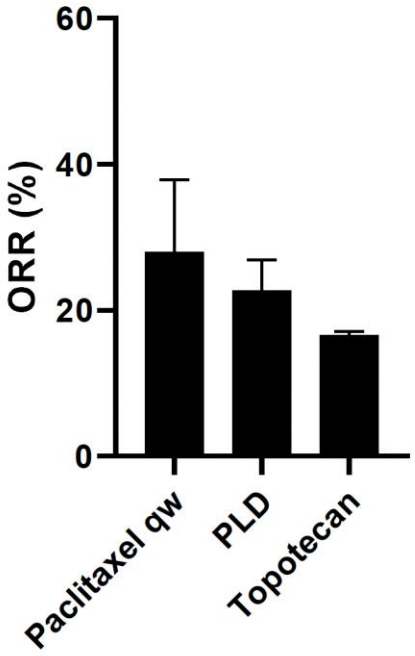


Chen and Chang Int J Mol Sci 2019 20:4136;

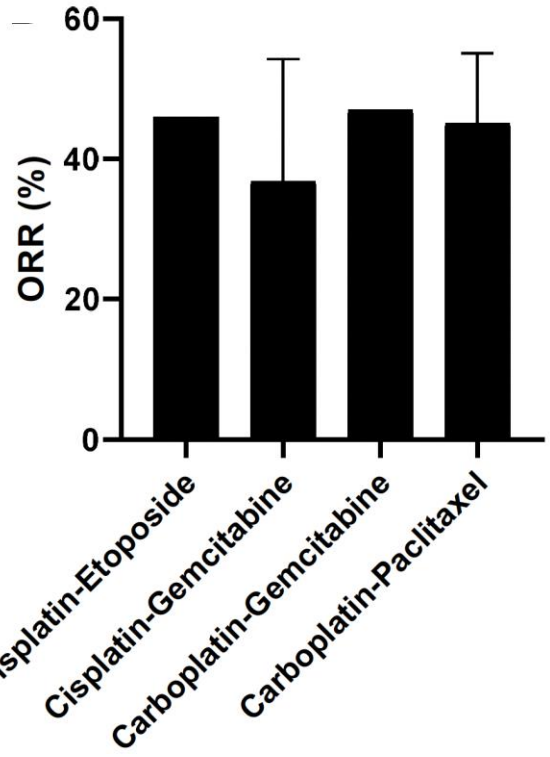
Outcome of patients with recurrent ovarian cancer challenged with or without platinum with **Platinum-Free Interval** < 6 months

Overall Response Rate

Non Platinum

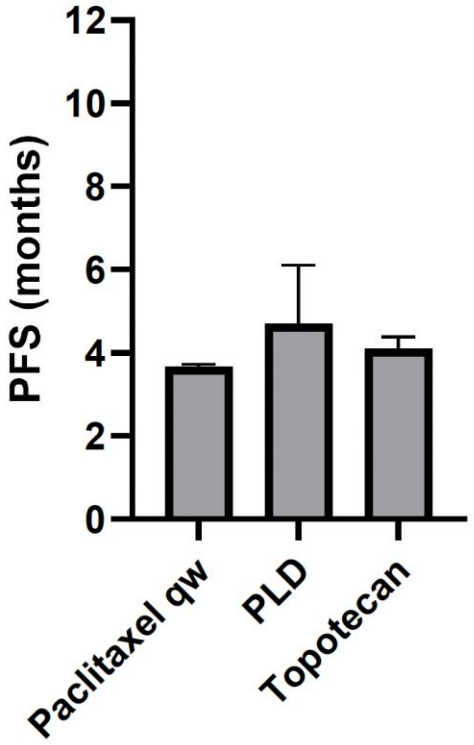


Platinum-based

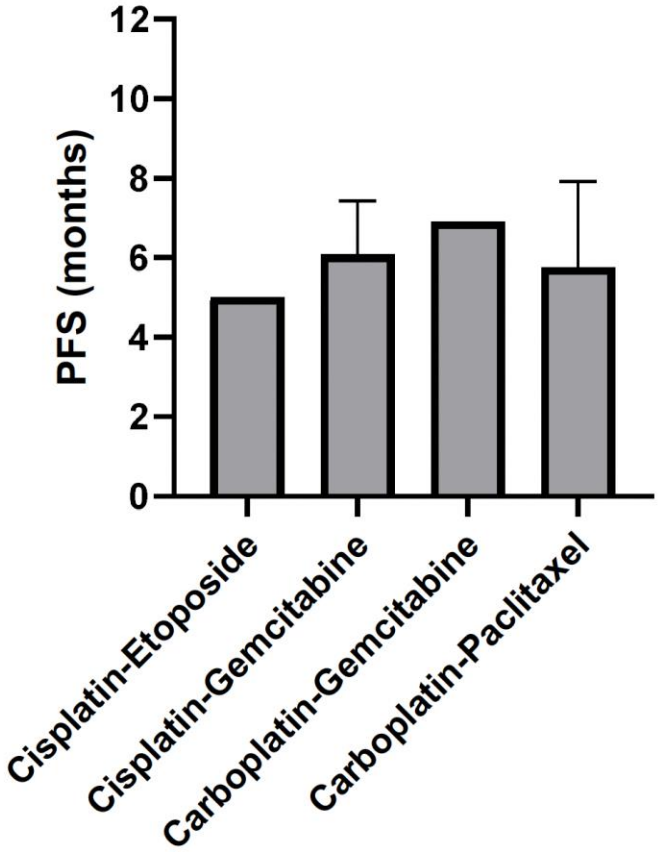


Progression-Free Survival

Non Platinum

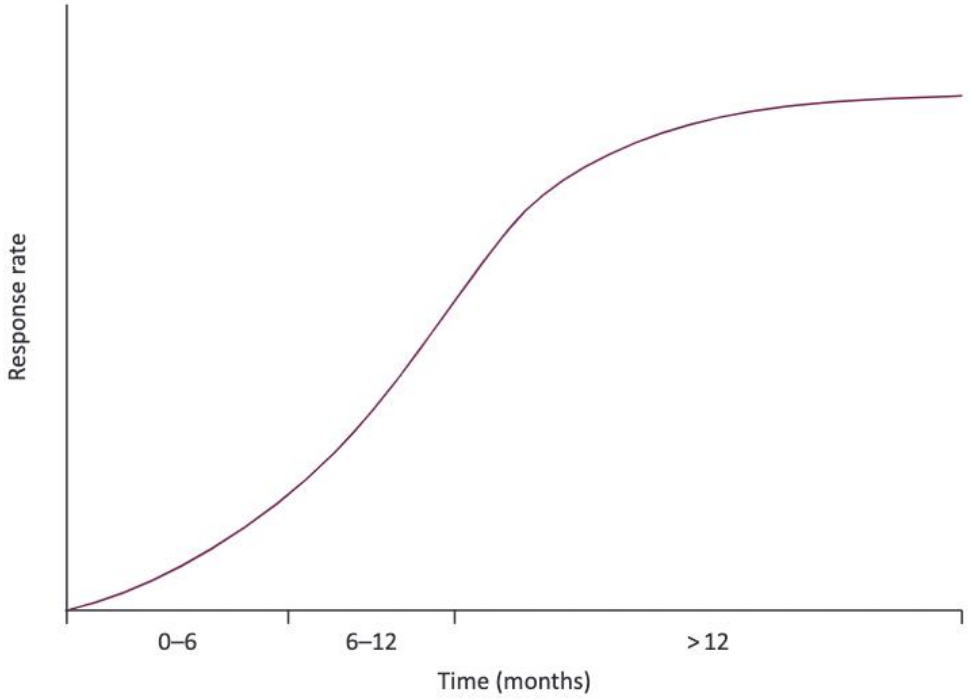


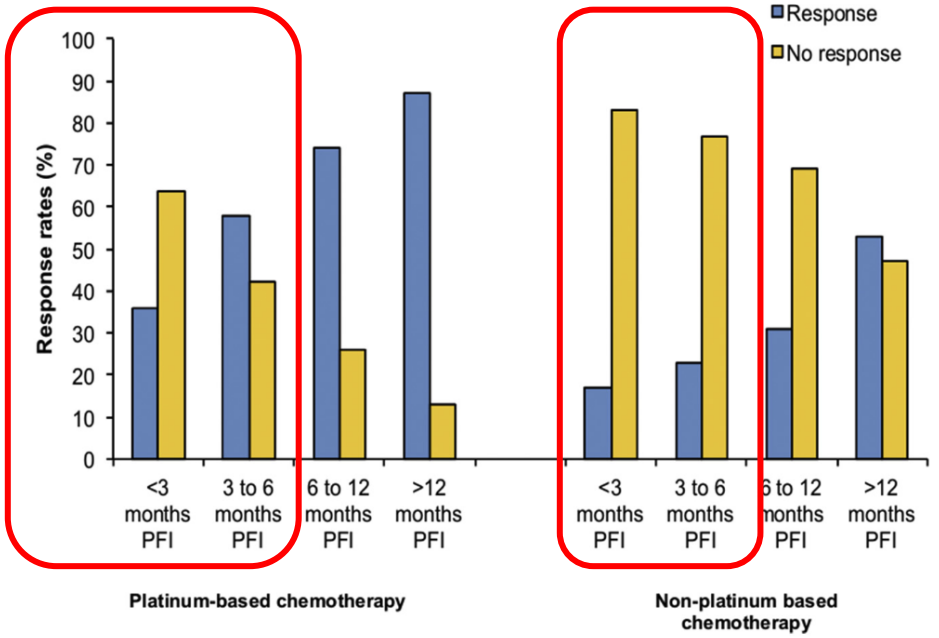
Platinum-based



Baert et al Ann Oncol 2020

Response to platinum relates to PFI as a continuous variable





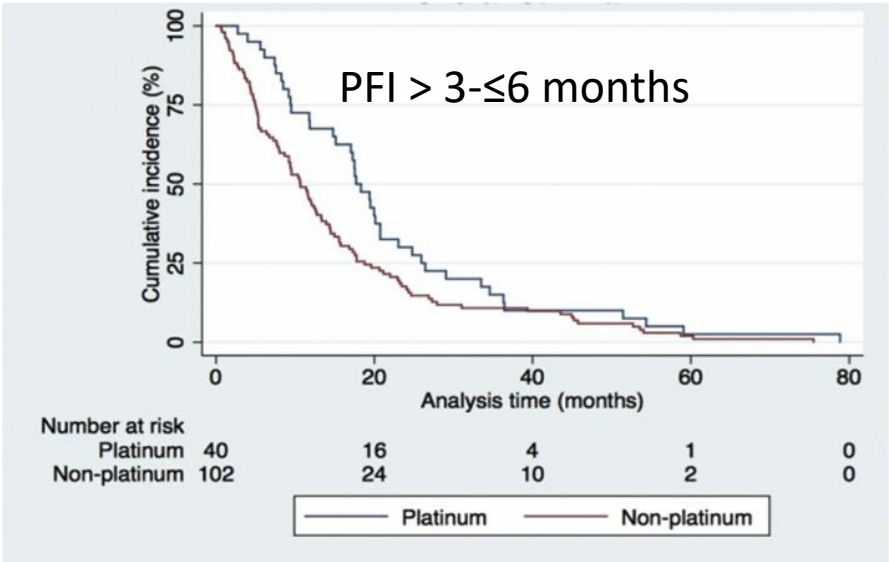
Median Overall Survival from treatment:

Platinum:

17.67 months (95% CI: 14.79–20.75)

Non-platinum:

10.62 months (95% CI: 8.02–12.72) [P = 0.022]



Beart et al Ann Oncol 2020

Lindemann et al Gynecol Oncol 2018

Platinum-sensitivity and platinum-resistance

- Patients who have previously responded to platinum-based therapy

DEMONSTRATED PLATINUM SENSITIVITY

- Patients with complete resection of tumour and no evaluable disease ?
- Patients who relapse after stage I disease, never having received chemotherapy?

ASSUMED PLATINUM SENSITIVITY

Platinum-sensitivity and platinum-resistance

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DEMONSTRATED PLATINUM SENSITIVITY

- Patients with complete resection of tumour and no evaluable disease ?
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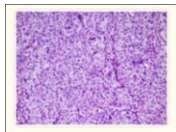
ASSUMED PLATINUM SENSITIVITY

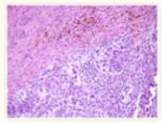
- Tumours that do not respond to platinum rechallenge, or progress while on platinum therapy
- Includes patients who have a symptomatic progression soon after completing treatment with platinum-based therapy

PLATINUM RESISTANCE

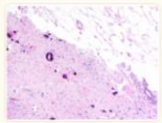
Chemotherapy Response Score [CRS]- histopathological evaluation at interval cytoreductive surgery



CRS 1
No or minimal tumor response. Mainly viable tumor with no or minimal regression-associated fibroinflammatory changes, limited to a few foci; cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration.

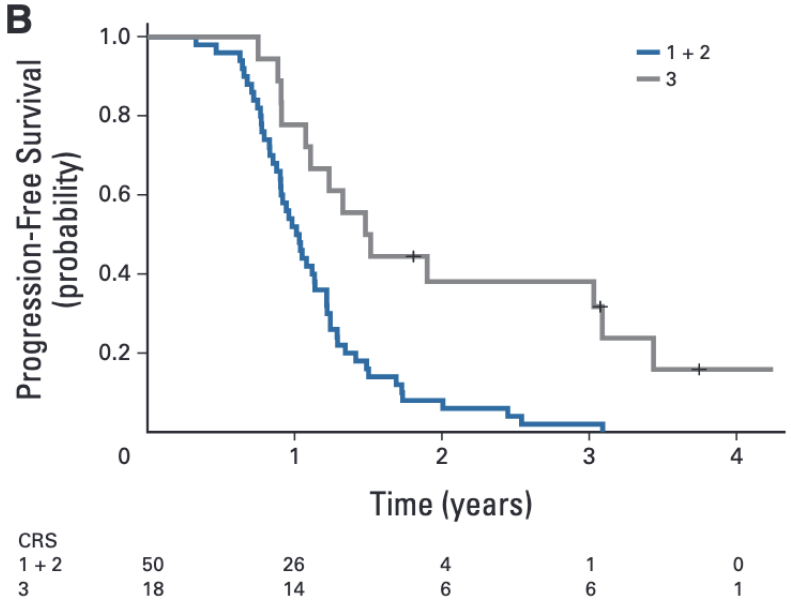


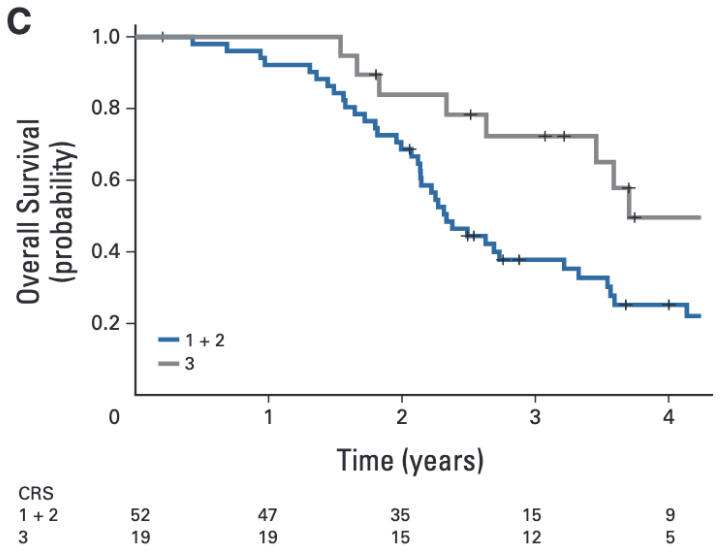
CRS 2
Appreciable tumor response amid viable tumor that is readily identifiable. Tumor is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with viable tumor in sheets, streaks, or nodules to extensive regression-associated fibroinflammatory changes with multifocal residual tumor, which is easily identifiable.



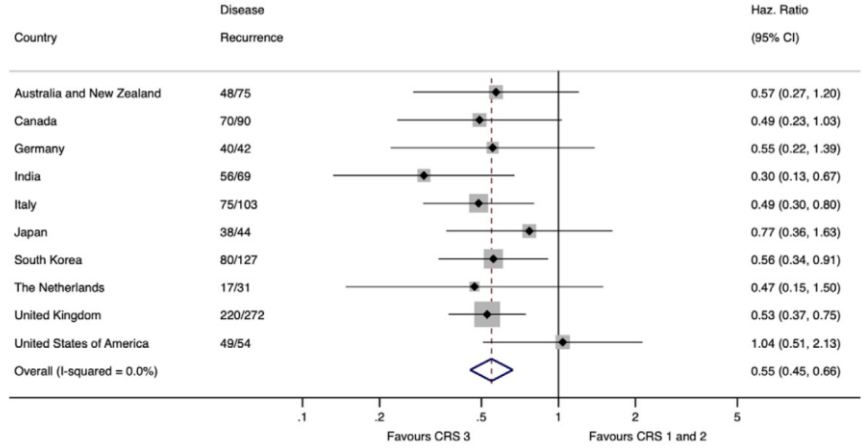
CRS 3
Complete or near-complete response with no residual tumor or minimal, irregularly scattered tumor foci seen as individual cells, cell groups or nodules up to 2 mm maximum size. Mainly regression-associated fibroinflammatory changes or very little residual tumor in the complete absence of any inflammatory response.

Böhm et al J Clin Oncol 2015;
Cohen et al Gyne Oncol 2019;
Lawson et al Am J Surg Path 2020

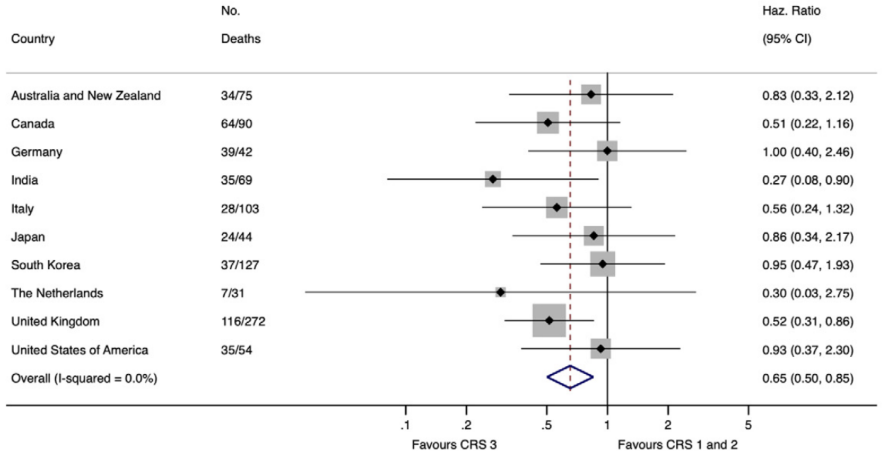




a) PFS adjusted Forest plot.

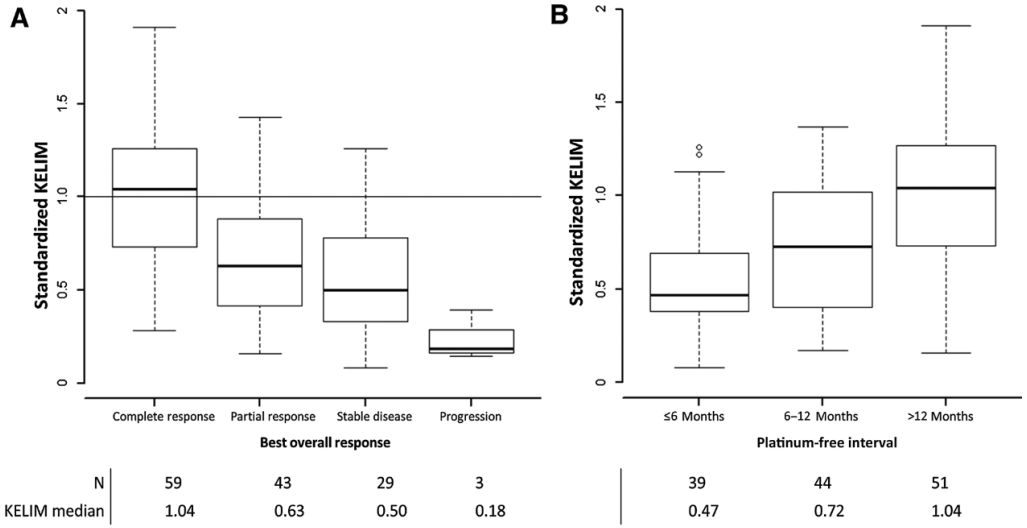


b) OS adjusted Forest plot.



CA125 monitoring and the KELIM score (**CA-125** ELIMination rate constant K)

CA125 elimination rate during the first 100 days of treatment - requires 3 CA125 time-points

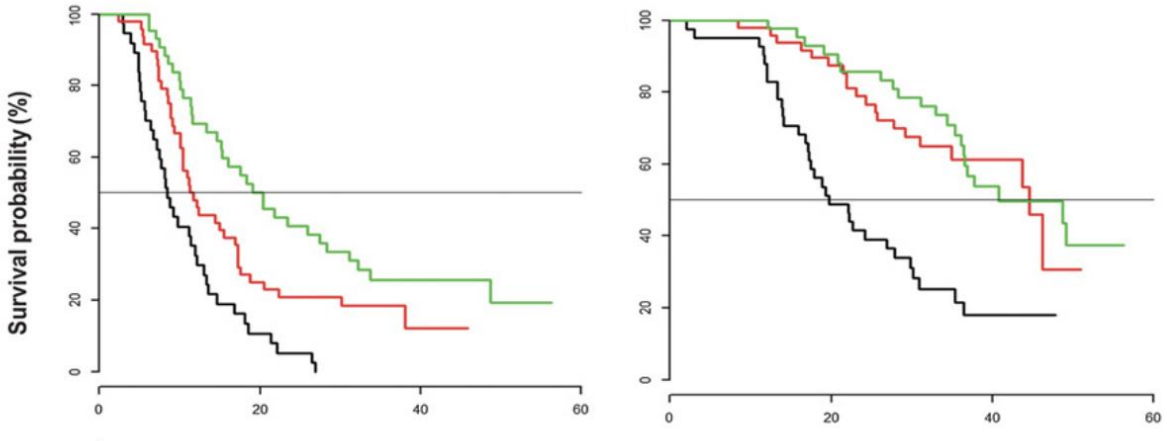


N	59	43	29	3
Std KELIM median	1.04	0.63	0.50	0.18

39	44	51
0.47	0.72	1.04

PFS

OS



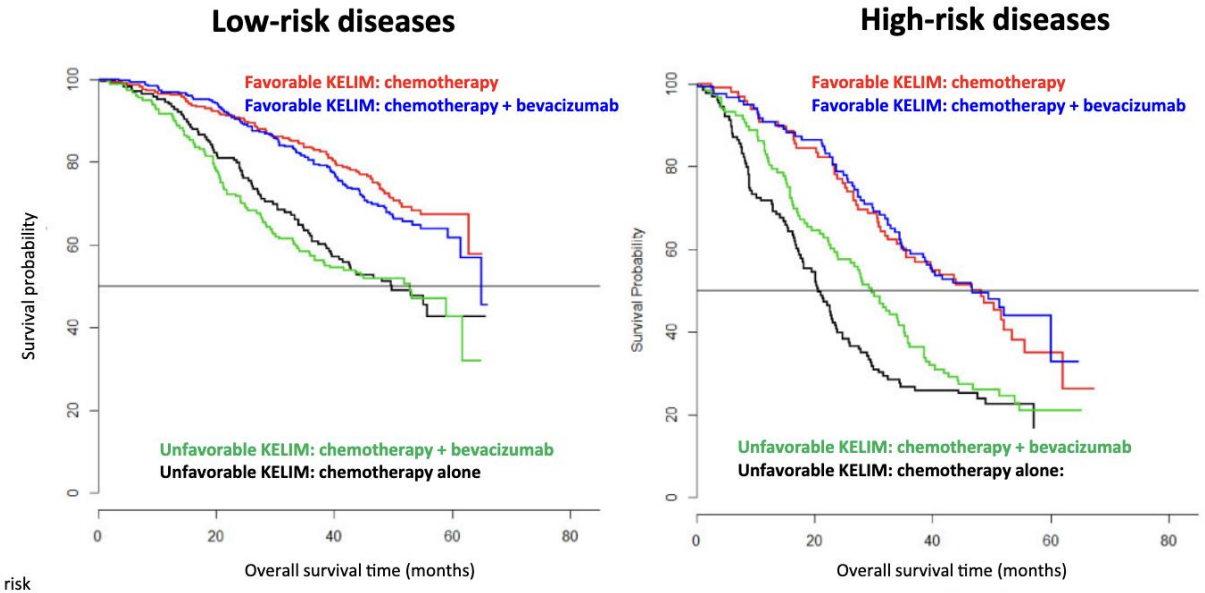
Number at risk								
Std KELIM (tercile)								
Unfavorable < 0.50	38	4	0	0	42	20	5	0
Intermediate [0.50–1.00]	49	12	2	0	49	42	12	0
Favorable > 1.00	43	21	6	0	43	38	15	0

CHIVA Trial- neoadjuvant chemotherapy

You et al Clin Cancer Res 2020;26:4625–32

ICON7 analysis of outcome in relation to KELIM score

ICON 7 Overall survival

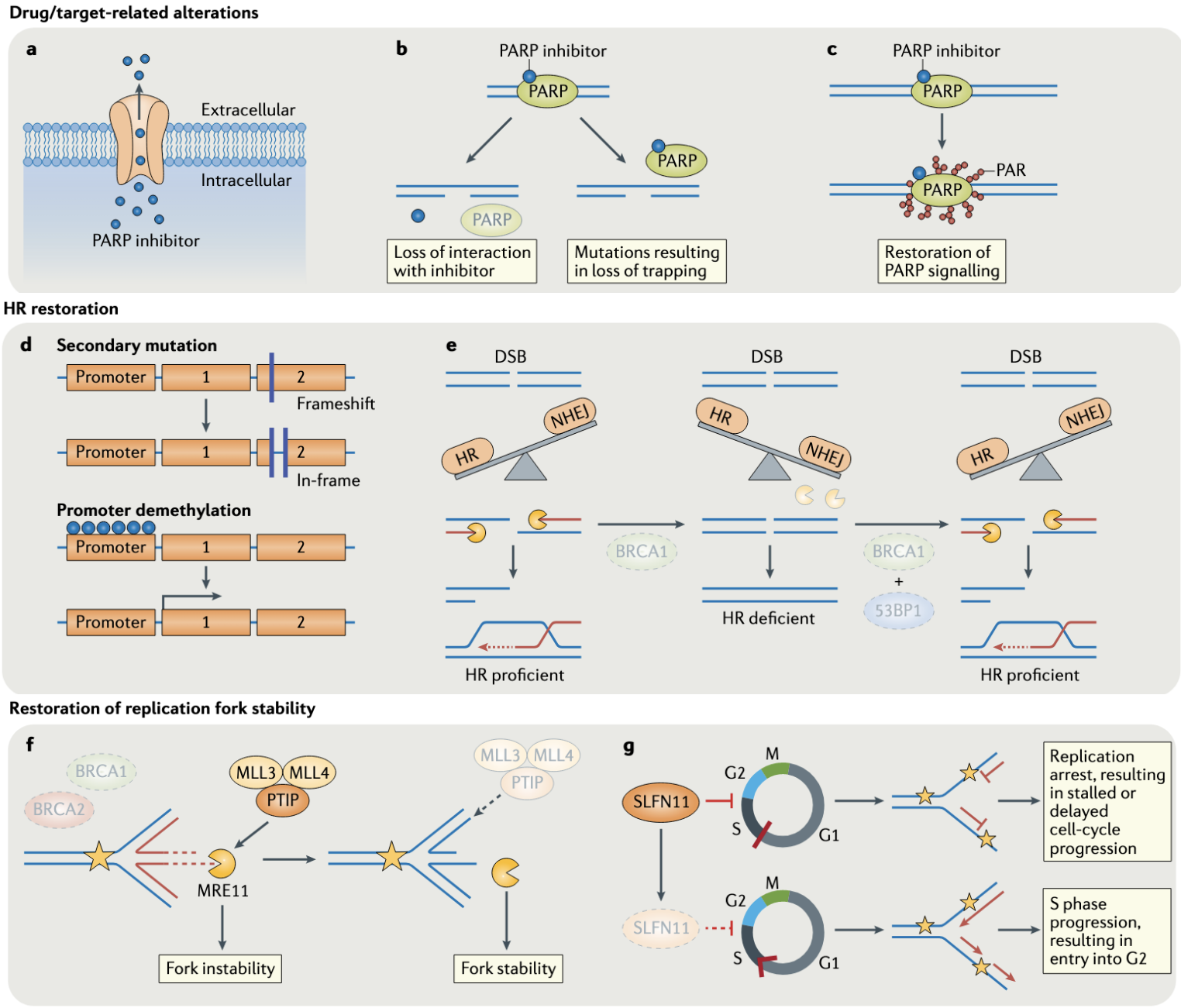


https://www.biomarker-kinetics.org/CA-125

Modeled CA-125 KELIM™ in patients with stage III-IV high grade serous ovarian carcinomas treated with first line adjuvant chemotherapy

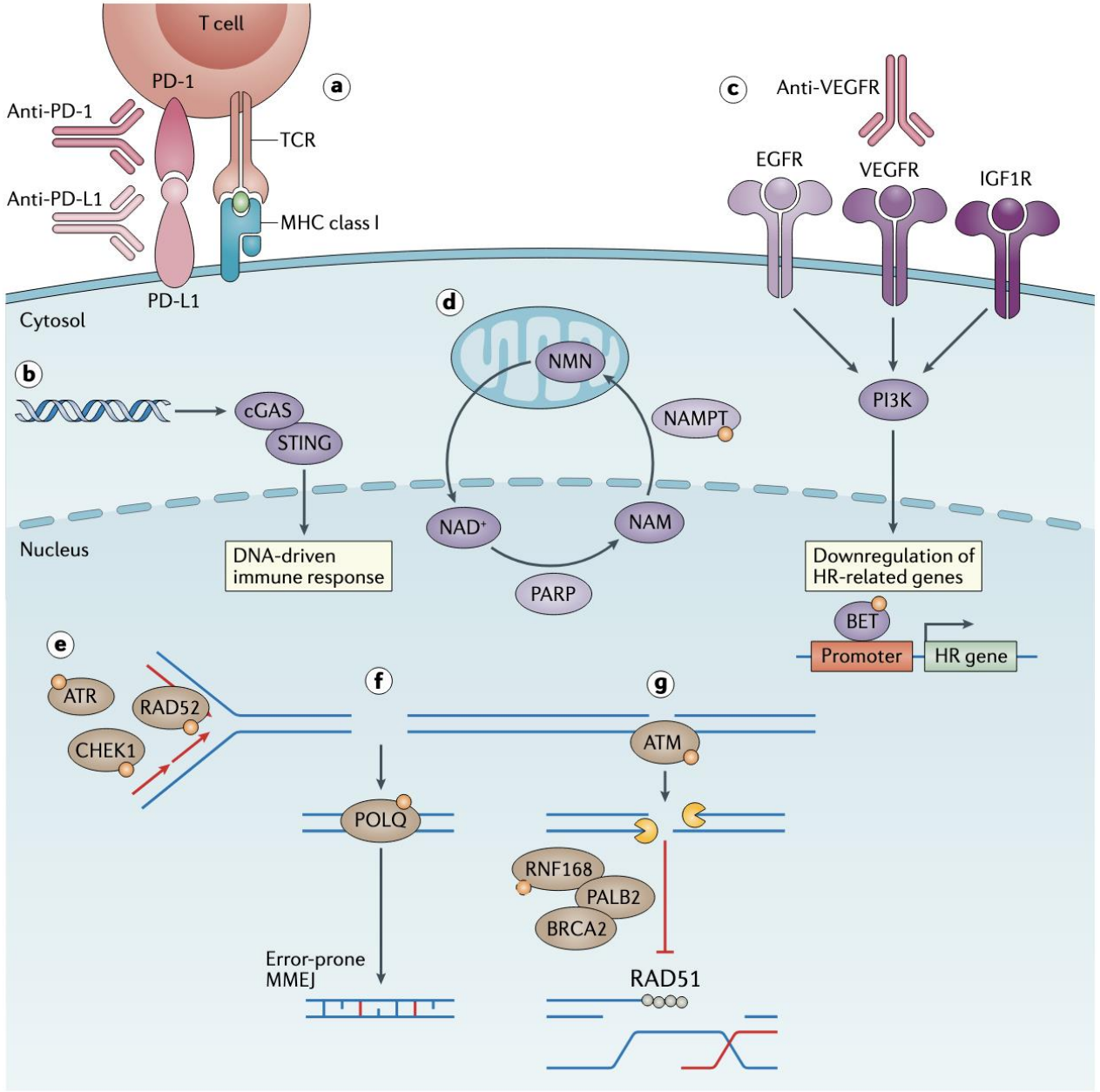
Colomban et al JCNI Spectrum 2020 *doi: 10.1093/jncics/pkaa026*

PARP inhibitor failure- exploiting DNA Damage Response Modifiers



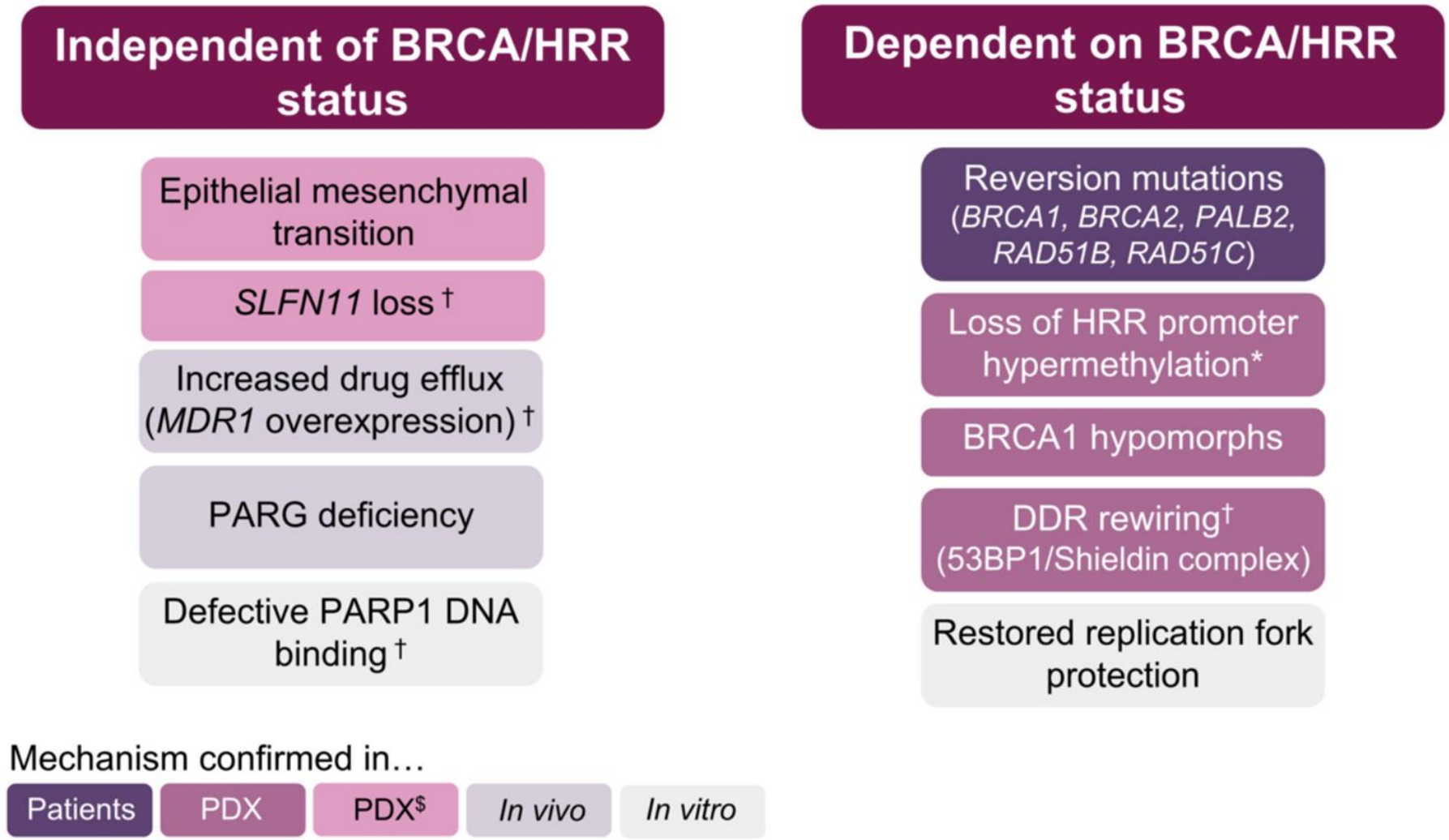
Dias et al Nat Rev Clin Oncol 2021

Strategies to augment the effect of PARP inhibitors



Dias et al Nat Rev Clin Oncol 2021

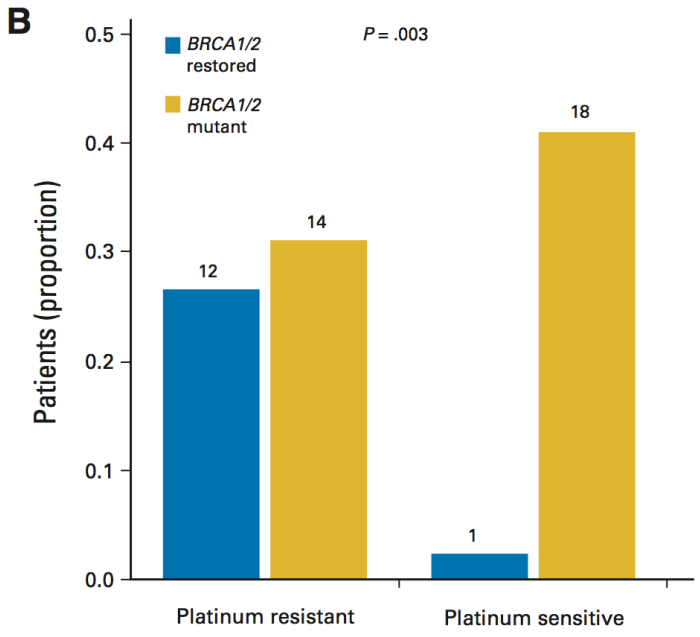
Application of resistance mechanisms to the clinic



Prados-Carvajal et al Cancers 2021

BRCA^{mut} Reversions

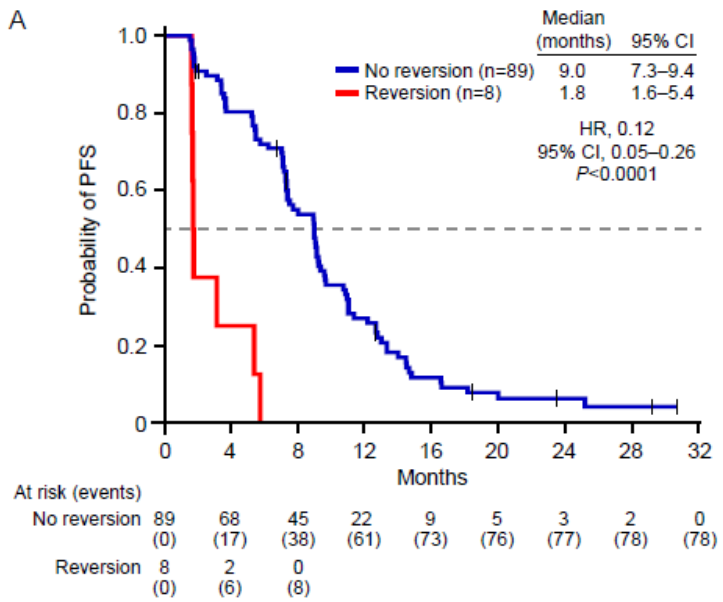
Recurrent ovarian cancers



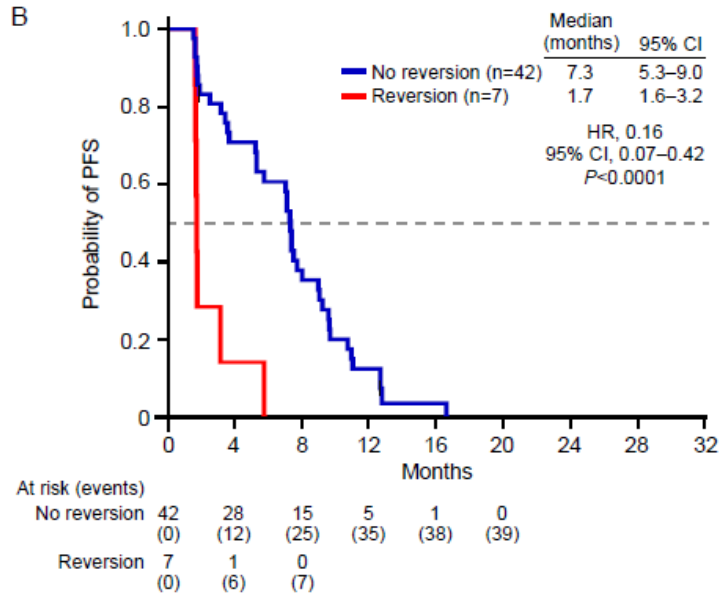
Norquist et al (2011) JCO 29:3008

ARIEL 2 - PFS with rucaparib according to *BRCA*^{mut} reversion

All cases

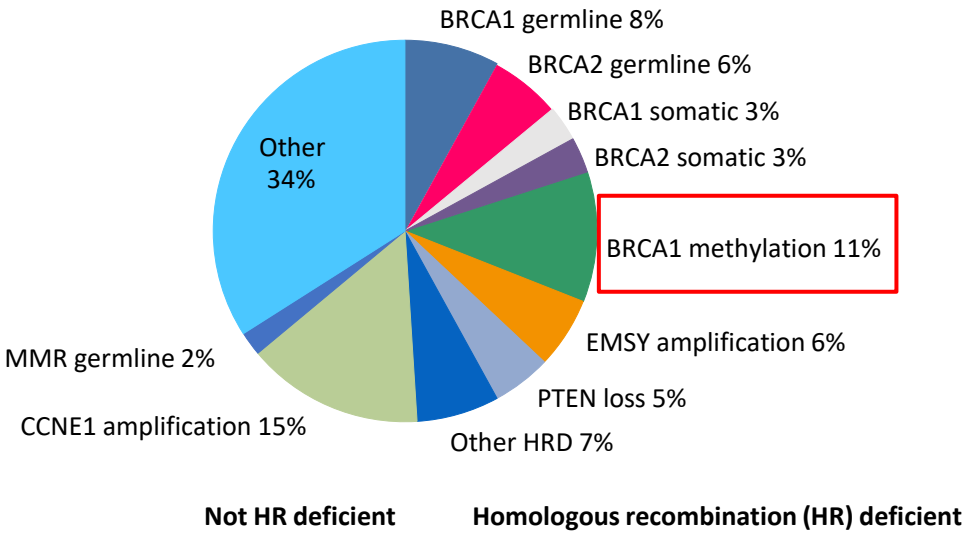


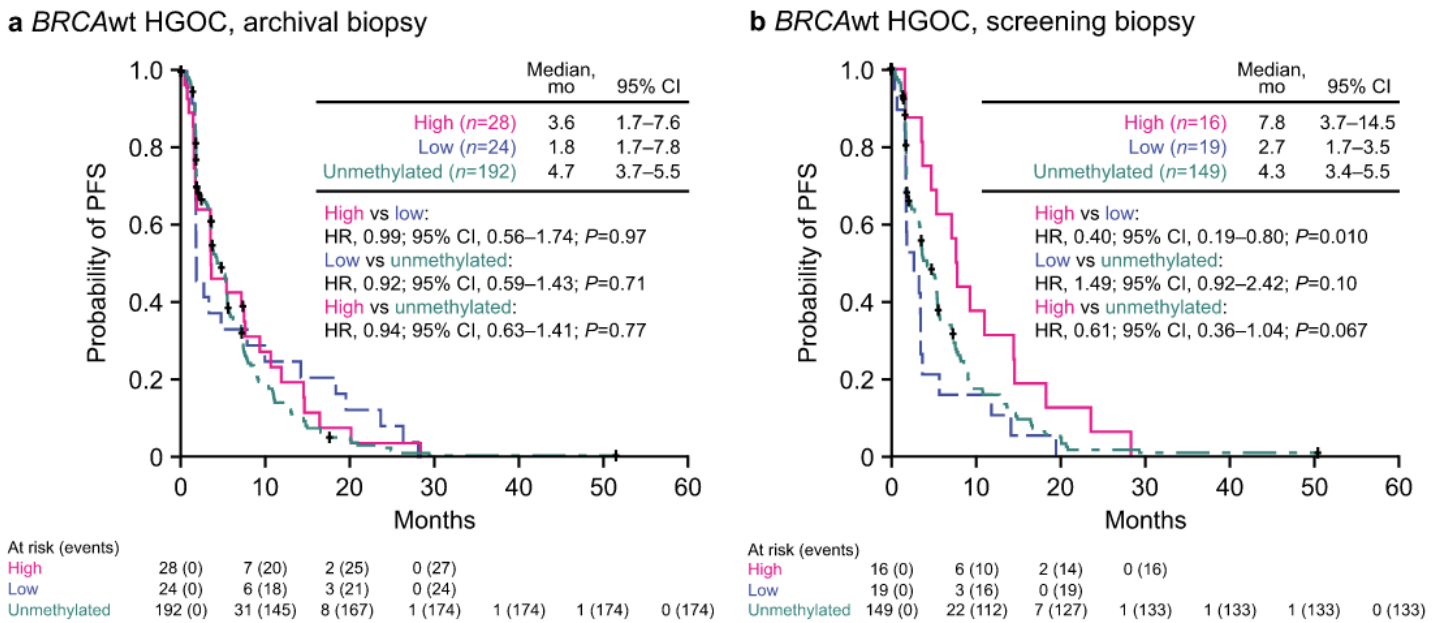
Platinum resistant/refractory cases



Lin et al (2019) Cancer Disc. 9:210

BRCA1 methylation- ARIEL2 rucaparib





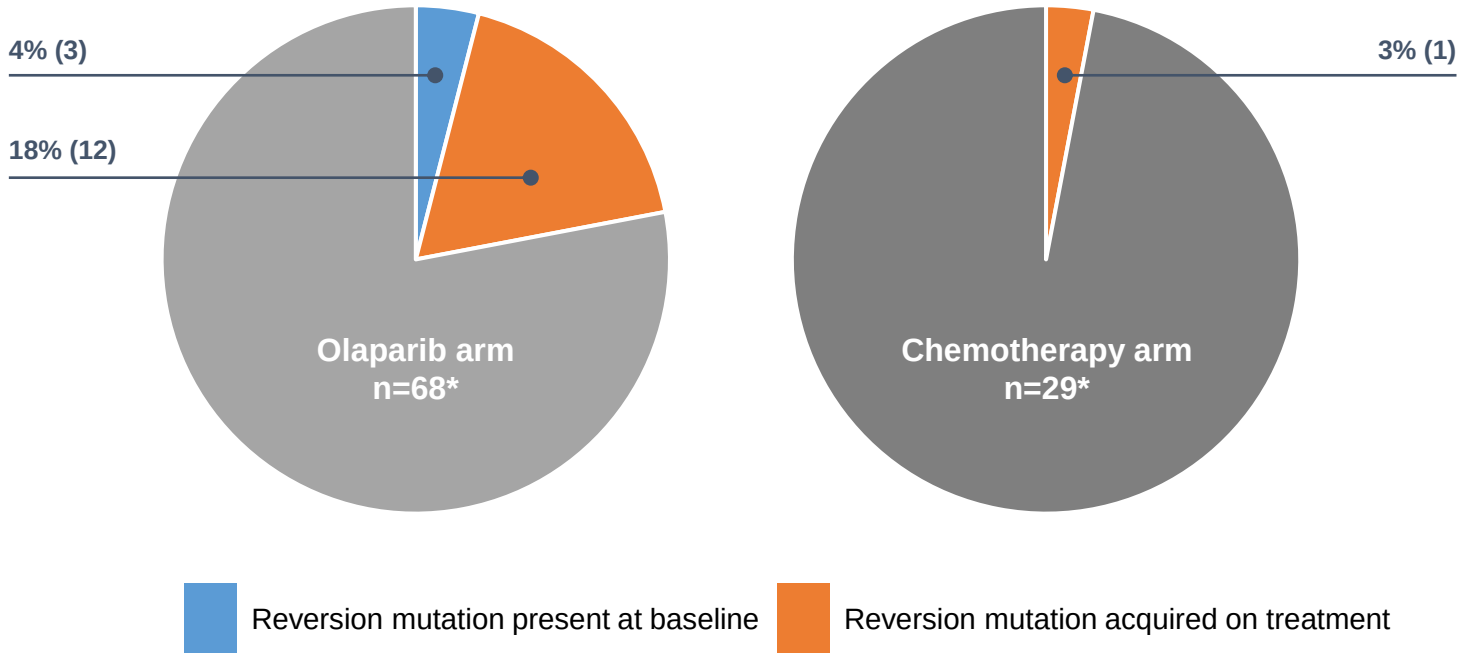
Courtesy of D Levine. The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, 2011

Swisher et al Nat Comm 2021

Does olaparib lead to generation of *BRCA* mutation reversion?

22% of patients in the olaparib arm of SOLO-3 had BRCA reversions detected in their ctDNA at disease progression[3]

- **BRCA reversions are a mechanism of resistance** to PARPi inhibitors and platinum-based chemotherapy[1]
- In SOLO-3, no responses to olaparib were seen for patients with BRCA reversions identified at baseline[2]



*Evaluable patients who had paired plasma samples collected at baseline and disease progression

SOLO-3 study investigated Olaparib as a treatment versus chemotherapy for platinum sensitive relapsed BRCA1/2 mut ovarian cancer. Olaparib is not licenced as a treatment in Europe. The data is shown here to demonstrate the impact of BRCA reversions on outcomes.

1. Leath CA, et al. IGCS, 2022. 2. Penson RT, et al. SGO, 2022; 3. Lukashchuk N, et al. ASCO 2022

Summary

- Drug resistance remains a key challenge to the treatment of ovarian cancer
- Resistance can evolve with time and treatment
- The definition should be mechanistic or proven, not time-defined
- Apart from a *BRCA*^{mut} reversion, biological markers of resistance are not well defined
- Understanding the biological processes underlying PARP inhibitor resistance provides opportunities to gain a greater benefit from this class of drug, and treatment strategy