2025 DEBATES AND DIDACTICS in Hematology and Oncology

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Recurrent Epithelial Ovarian Cancer:

Incorporating New Agents and Sequencing Therapies

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Disclosures

Has no relevant financial relationships

Goals:

- Define the role of the platinum free interval in treatment selection
- What is the role of surgery in recurrent ovary cancer?
- Review current treatment strategies with an eye towards the future
  - What is the status of PARP inhibitors in the recurrent setting?
  - Biomarker directed therapy
  - Clinical trials of interest
    - Where are we going from here?

Why talk about recurrent disease?

70-80% Remission with platinum based chemotherapy and surgery

PARP inhibitors have improved median PFS and OS

80% Recurrence by 18 mos
44% PARPi exposed recur by 3 yrs

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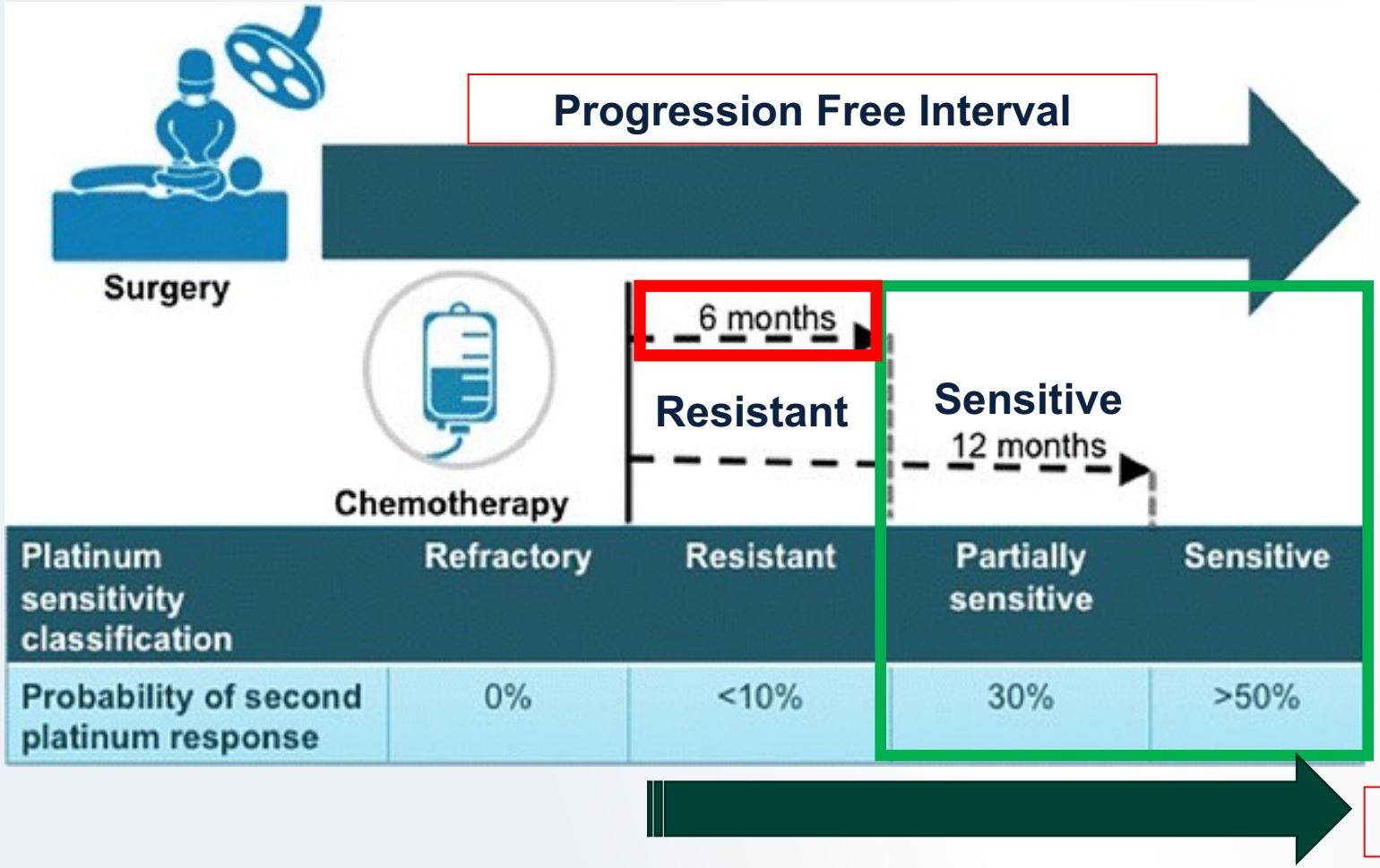
Recurrent Ovarian Cancer Treatment: The great platinum fork in the road

Defining Platinum Resistance



Platinum Resistant Disease:

- Represents 25% of EOC after first line treatment
- Eventual common pathway of most EOC

Oronsky, B., Ray, C.M., Spira, A.I. et al. Med Oncol (2017) 34: 103. https://doi-org.libproxy.usouthal.edu/10.1007/s12032-017-0960-z

Prognostic Impact of the Platinum Free Interval
(And the biologic correlates)

Platinum Responsiveness:	Time to Recurrence	Plat Response Rate:	Median PFI	Median OS
Resistant	<6 mos	<15%	3 mos	9-12 mos
Sensitive	>6 mos	30-90%	9-12 mos	24-36 mos

Refractory

- Low grade serous
- Mucinous
- Clear Cell

- Endometrioid
- High grade serous
  - HRP

- High grade serous
  - BRCAm
  - HRD

Sensitive

Recurrent Platinum Sensitive Ovary Cancer: Is there a surgical option?

Trial	DESKTOP III	SOC-1	GOG-213
Design	Randomized Phase III (Europe)	Randomized Phase III (China)	Randomized Phase III (U.S.)
Selection	AGO Score: ECOG 0, no ascites, prior R0	PET/CT-based resectability	Investigator discretion (no formal score)
Chemo	Platinum-based	Platinum-based	Platinum ± Bevacizumab (~84%)
Primary Endpoint	Overall Survival (OS)	Progression-Free Survival (PFS)	Overall Survival (OS)
Median OS	53.7 mo (surgery) vs 46.0 mo	Immature OS data	50.6 mo (surgery) vs 64.7 mo
OS HR	0.75 (p=0.02)	NA (immature)	1.29 (p=0.08)
PFS	18.4 vs 14.0 mo	17.4 vs 11.9 mo	No difference
Benefit Limited to R0?	Yes	Yes	Yes (post-hoc)
Conclusion	OS benefit with R0 and proper selection	PFS benefit with strict imaging	No OS benefit; possible harm with surgery

du Bois et al. (2020); Shi et al. (2021); Coleman et al. (2021).

Recurrent Platinum Sensitive Ovary Cancer: Is there a surgical option?

Patient selection is KEY

The downside for poorly selected patient is as significant as the benefit in the appropriately selected patient

Recurrent Platinum Sensitive Ovary cancer

Recurrent Platinum Sensitive Ovarian Cancer
Platinum Doublets

Carboplatin + Paclitaxel vs Carboplatin alone

- CP=>ORR 60-75% (Gonzalez-Martin et al. GEICO 2005)

Carboplatin + PLD vs Carboplatin + paclitaxel

- ORR 58-66% (du Bois etal. Calypso 2010)
- Improved PFS and toxicity profile over CP

Carboplatin + Gemcitabine:

- ORR 47-60%

Carboplatin + Topotecan:

- ORR 30-50%
- rarely used due to hematologic toxicity

Anti-Angiogenesis Agents in Recurrent PSOC:

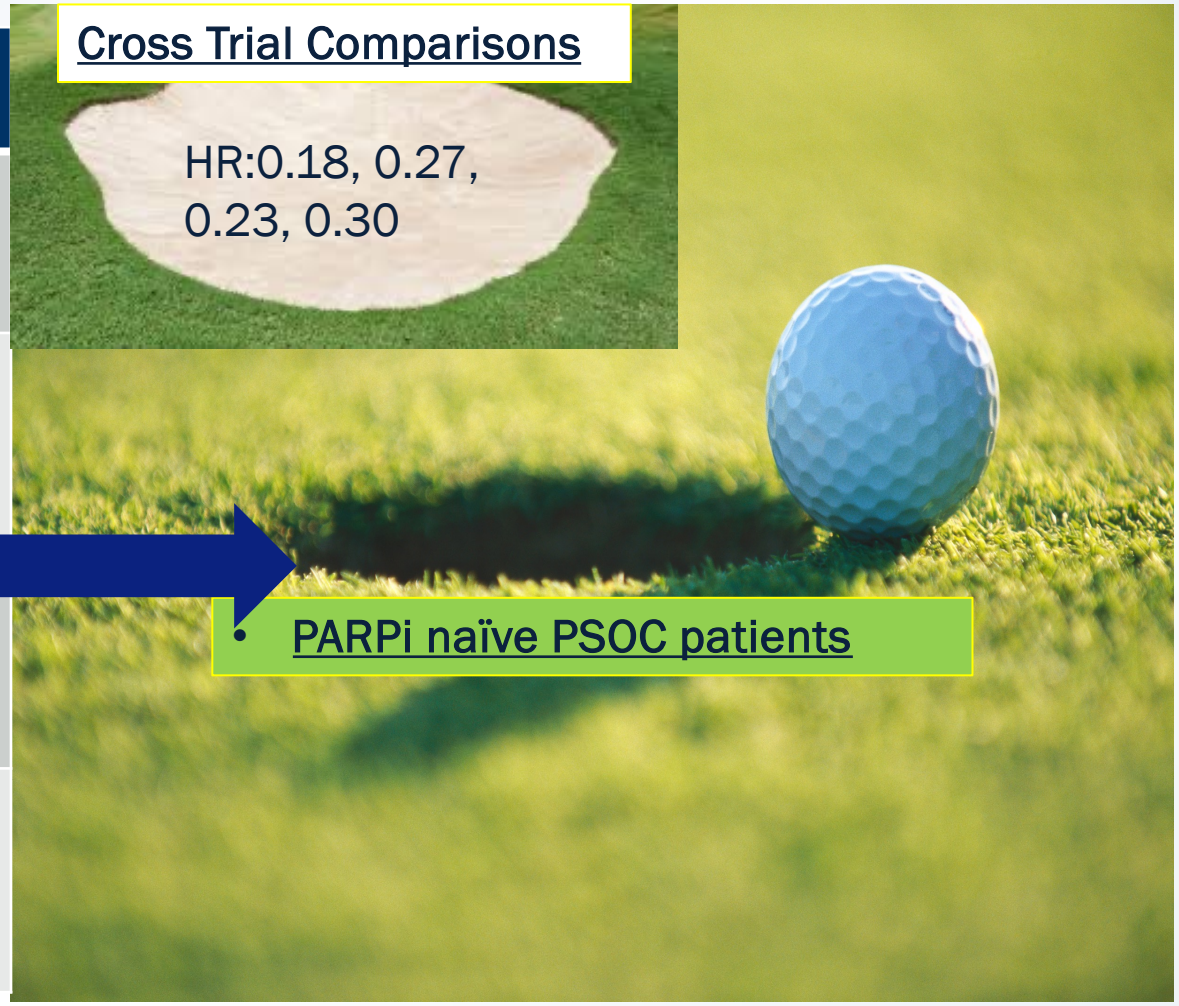
Bevacizumab (Anti-VEGF)

- OCEANS (2012)
  - Assess the role of bevacizumab in the recurrent platinum sensitive setting
  - Bevacizumab + Carbo + Gem with Bev maintenance vs Chemo alone
  - PFS 12.4 mos; HR 0.48 (p=0.0001)

- GOG 213 (2015, 2022)
  - Carbo +paclitaxel + bevacizumab with bev maintenance vs Chemo Alone
  - PSOC
  - PFS 13.8 mos; HR 0.63; OS 42.2 vs 37.3 (p=0.05)

PARp for the course:
Is there a role for PARPi maintenance in PSOC?

Trial	PARP Inhibitor	Population	PFS (months)	HR (PFS)	OS Data
Study 19	Olaparib	BRCA-mut and non-BRCA	BRCA: 11.2 vs 4.3	0.18	Not powered for OS
NOVA	Niraparib	gBRCA+, HRD+, non-HRD	gBRCA: 21.0 vs 5.5; HRD: 12.9 vs 3.8	0.27 (gBRCA); 0.38 (HRD)	No OS benefit
ARIEL3	Rucaparib	BRCA+, HRD+, non-HRD	BRCA: 16.6 vs 5.4	0.23	OS immature
SOLO2	Olaparib	BRCA-mut only	19.1 vs 5.5	0.30	51.7 vs 38.8 mo (HR 0.74; NS)



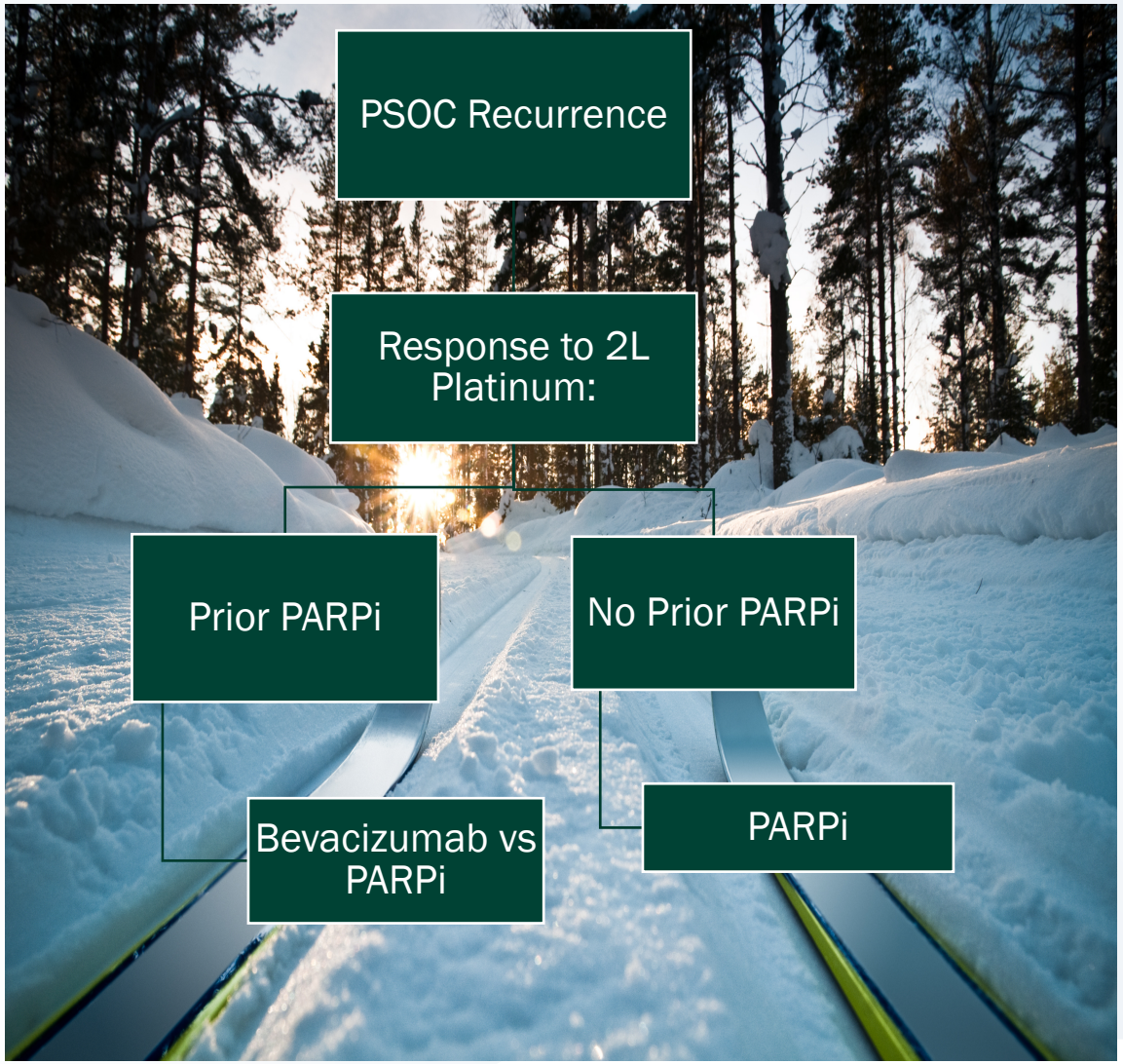
Après PARPi: Is there data for PARPi after PARPi?

Maintenance olaparib rechallenge in patients with platinum-sensitive relapsed ovarian cancer previously treated with a PARP inhibitor (OReO/ENGOT-ov38)

- Significant but **MODEST** PFS benefit (2 mo) in both BRCA mutant and non-mutant population
- Heavily pretreated
- no new MDS signal

KGOG NIRVANA-R trial: Niraparib+bevacizumab maintenance following platinum response prior exposure to PARP (Cho et al. ASCO 2025)

- 6-mo PFS 68% median 11.5 mos
- 65% >3 lines of therapy
- Biomarker analysis pending
- Treatment free interval predictive of response



Regulatory and Clinical Summary of PARP Inhibitors: (Platinum Sensitive Maintenance)

Category	Summary
Setting	Recurrent disease maintenance after response to platinum-based chemo
Initial FDA Approvals	All three agents approved for platinum-sensitive maintenance
Label Withdrawals (2022–2024)	Rucaparib & Niraparib: removed for non-BRCA due to lack of OS benefit
Current Indications	BRCA-mutated /HRD patients with platinum-sensitive recurrence (esp. olaparib)
Clinical Considerations	Genomic testing (BRCA, HRD) essential; OS benefit limited to BRCA+

Non-PARP Maintenance Alternatives:

GLORIOSA: A randomized, open-label, phase 3 study of mirvetuximab soravtansine with bevacizumab vs. bevacizumab as maintenance in platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer.

- FR-alpha high (2+/75%)
- Recurrent PSOC (allows for prior PARPi)
- 2nd Line Platinum + Bevacizumab
- Maintenance: Bevacizumab vs Bevacizumab + Mirv
- Phase II: 69% ORR; median PFS 13.3 mos

Future Oncol. 2024;20(32):2423-2436.
doi: 10.1080/14796694.2024.2372241.Epub 2024 Jul 31.

Platinum Resistant Ovary cancer

The Unfortunate likely common pathway…

Platinum Resistant Ovarian Cancer:

Is Platinum Resistance, Chemo resistance?

Single Agent Efficacy:

Paclitaxel: 22-30% ORR
- Weekly treatment, similar PFS, less toxicity

Liposomal Doxorubicin:
- ORR 17%; PPD rates are significant

Topotecan:
- Similar response to paclitaxel, PLD
- Higher incidence of Grade 3-4 neutropenia

Gemcitabine
- Multiple Platinum Resistant studies: ORR 14-22%
- Grade 3-4 neutropenia

What about Combination therapy?

Combination Cytotoxics:

Limited efficacy with increased toxicity

Gemcitabine/Cisplatin:

- Phase II=>ORR 16%, 54 stable disease
- PFS 5 mos
- increased toxicity

Incurable problem, increased toxicity, limited response

Investigational new Drugs 2004 Nov;22(4):475-80.
doi: 10.1023/B:DRUG.0000036690.14585.a3.

Targeting Angiogenesis:

Aurelia Trial:

Open label Phase III RCT

361 patients; Physician's Choice Chemo vs **Chemo+ Bevacizumab**

PROC 2 prior line limit:

- Weekly paclitaxel 80mg/m2 (day 1, 8, 15, 22) every 4 wks
- Pegylated Liposomal Doxorubicin 40mg/m2 every 4 wks
- Topotecan 4mg/m2 weekly every 4 wks OR 1.25mg/m2 day 1-5 every 3 wks

Pujade-Lauraine et al. Clin Oncol. 2014;32(13):1302. Epub 2014 Mar 17.

Aurelia Trial:

Improving chemotherapy sensitivity in platinum resistant EOC

Physician choice chemo + bevacizumab:

31% ORR vs 13% chemo alone (13.5 mos follow up)

Decrease recurrence HR 0.48 (CI 0.38-0.60)

PFS 6.7mos vs 3.6 mos

GI perf 2.2% (4 pts)

Impact of bevacizumab:

Paclitaxel+ Bev: ORR 53% vs 30% Taxol alone

- PFS 10 mos vs 4 mos; HR 0.46 (0.30-0.71)

Topo+ Bev: ORR 17% vs 0%

- PFS 6 mos vs 2 mos HR 0.32 (0.21-0.49)

PLD + Bev: ORR 14% vs 8%

- PFS 5 mos vs 4 mos (0.39-0.83)

**Not powered to discern difference between chemotherapy backbones

Pujade-Lauraine et al. Clin Oncol. 2014;32(13):1302. Epub 2014 Mar 17.

Mirvutuximab soravtansine: FR alpha targeted microtubule inhibitor conjugate (ADC)

Can Biomarkers select for improved outcomes in PROC?

Soraya: Phase II

- IHC Folate receptor alpha high ≥2+/75%
- **Objective Response Rate (ORR):** 32.4% (95% CI: 23.6–42.2)
- PFS: 5.5 mos/OS: 15.5 mos
- FDA approval

FIRST BIOMARKER DIRECTED TX in Ovarian Cancer

Mirasol (Randomized phase III confirmatory trial)

- 453 platinum resistant ovary cancer patients
- 1-3 prior lines of treatment
- ORR: 42% vs 16%
- **Overall Survival: 16.5 vs 12.8.**

FIRST OS improvement in PROC

FORWARD 2

- 14 pts PROC
- **MIRV+ IO?**
- ORR 43% w/ ICPI (pembro)
- DOR 6.9 PFS 5.2 mos

N Engl J Med. 2023;389(23):2162. , Biomedicines2025 Jan 12;13(1):168.

Emerging Agents in PROC:
Rosella Trial (May 2025)

Repotrectinib

- Selective Glucocorticoid receptor modulator
- Phase II Recolriant + nab-paclitaxel vs nab-paclitaxel alone
- Repotrectinib improved ORR, PFS & OS in PROC with minimal toxicity

Confirmatory phase III trial (ASCO 2025)

- PROC 1-3 prior lines; no biomarker requirement
- 381 pts; OS: HR 0.69 (0.52-0.92); 15.97 mos vs 11.5 mos (p=0.0121)
- No new safety signals when normalized for nab-pac exposure

J Gynecol Oncol 2024 Jul;35(4):e111.doi: 10.3802/jgo.2024.35.e111.

What's in the pipeline for PROC? Clinical Trials of Promise…

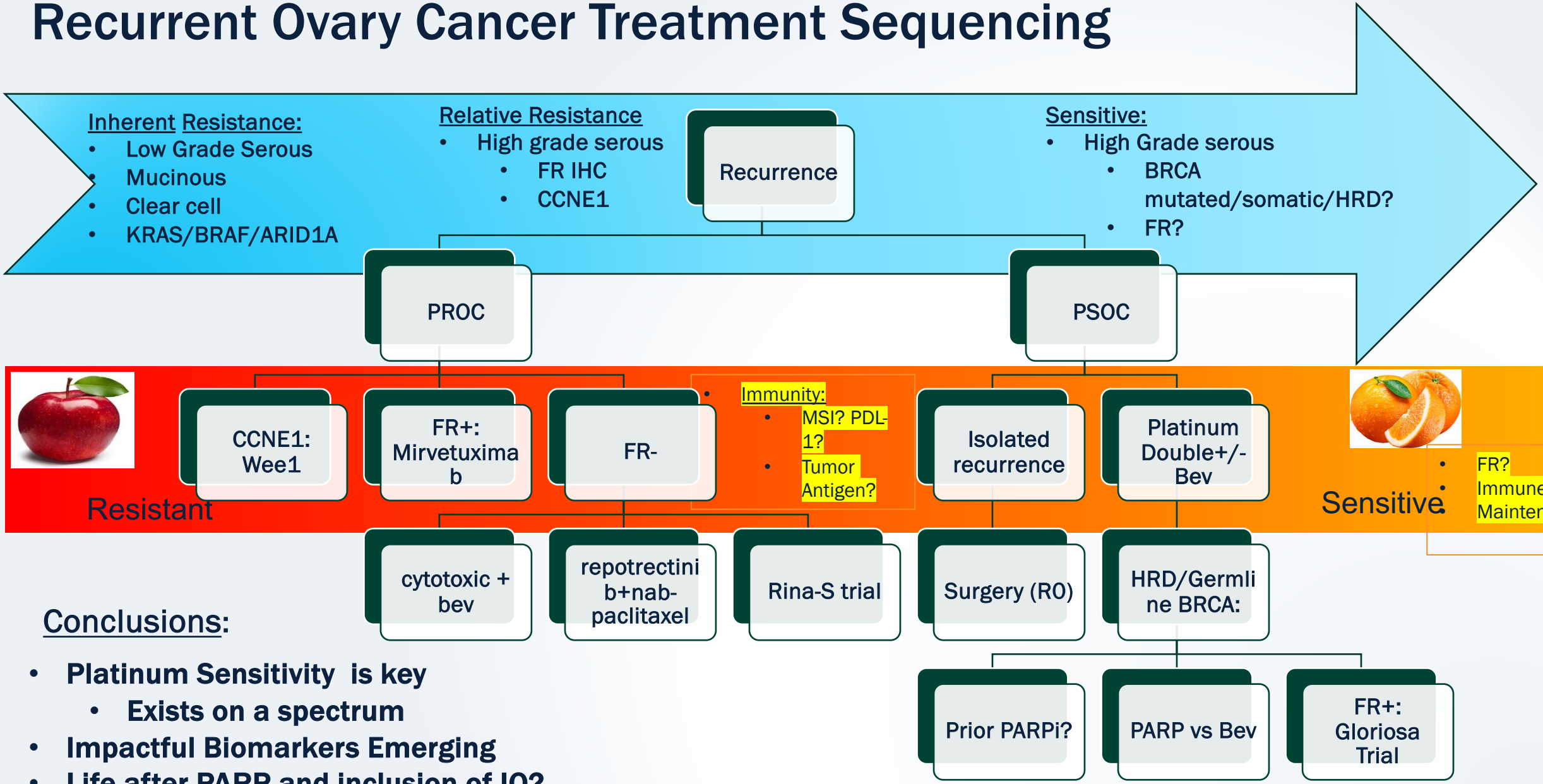
DENALI Phase 1b/2:

- Wee-1 (azenosertib)
- Cyclin E 1 over-expression vs CCNE1 amplification
- SGO 2025 phase Ib:
  - ORR 34.9%
  - Cyclin E1 IHC predicted response
    - ORR 31.3%

RAINFOL-OV2 Phase 1/2

- RINA-S (rinatabart sesutecan)
- Non-Biomarker tethered Fra-ADC
  - 100mg/m2 ORR 22.7%; 4.5% CR rate
  - 120mg/m2 ORR 55.6%; 11.1% CR rate
  - Disease control rate 86%-88%
  - Phase III on-going (Rina-S 120mg/m2 vs IC Chemo)

Recurrent Ovary Cancer Treatment Sequencing



Conclusions:

- **Platinum Sensitivity is key**
  - **Exists on a spectrum**
- **Impactful Biomarkers Emerging**
- **Life after PARP and inclusion of IO?**
- **Clinical Trials are integral**