Rucaparib a new option in first line maintenance treatment: peculiarity of drug and indications

PHARMA& SPONSORED LECTURE

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COI – Elisa Piovano

- Travel grants: MSD, AZ, GSK
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- A fee is expected for this presentation

I casi che saranno presentati sono a scopo educazionale e non corrispondono a casi reali

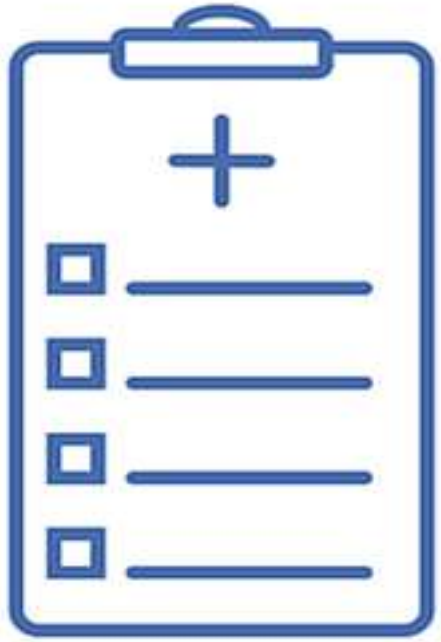
Rucaparib as 1L maintenance therapy: 3 clinical cases

BRCAm

BRCAwt / HRD+

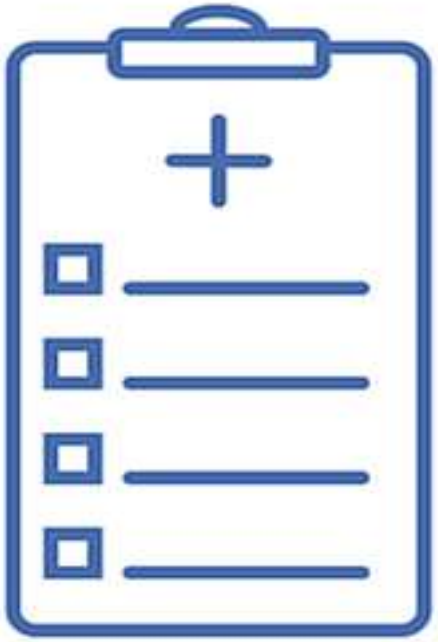
HRD-

For educational purposes

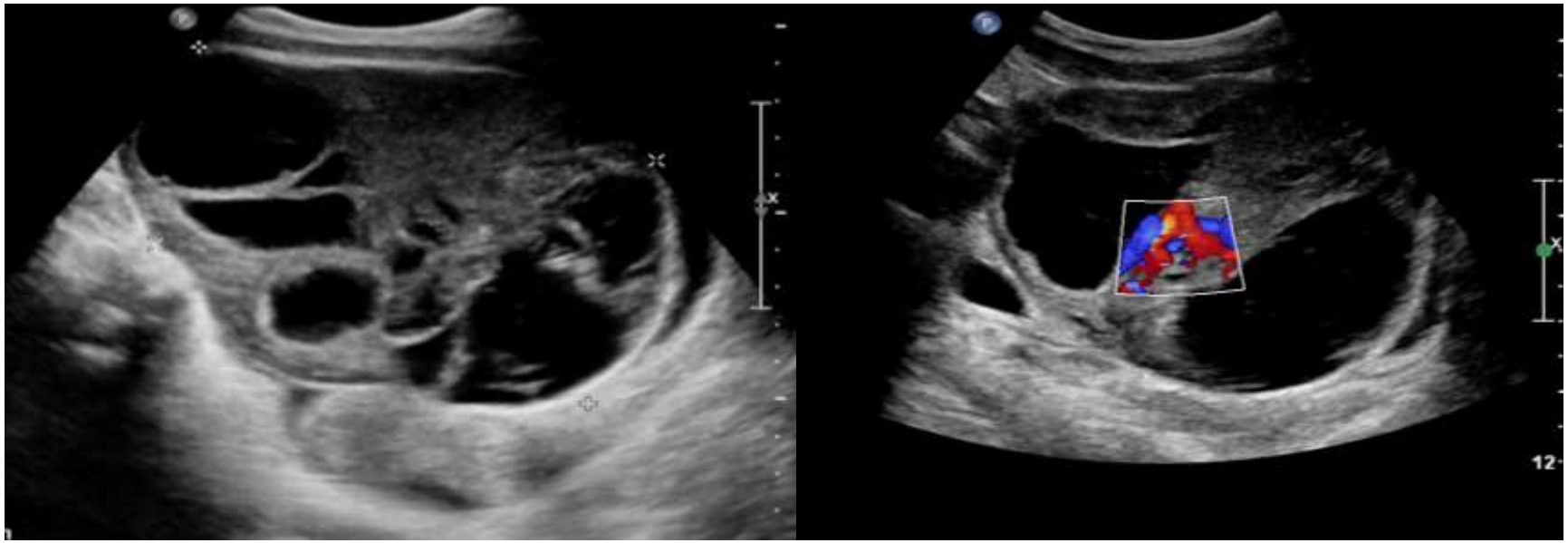


- **Age 67**
- Oncological family history: Maternal grandmother with ovarian cancer at 60 y, Mother gastric lymphoma at 72 y
- **Arterial hypertension** in therapy with Enalapril 5 mg 1 cp die and Amplodipine 10 mg 1 cp die; **Familial hypercholesterolemia** in therapy with Rosuvastatin 10 mgX2
- Access to the E.D. for worsening **constipation, dyspnea, cough and asthenia** and radiological CT finding of **pneumonia** → hospitalization. Urinary antigen + for *Str. Pneumoniae*
- CT T+A performed in the E.D also highlights an **adnexal mass with suspicion of peritoneal carcinomatosis**

For educational purposes



- II level TV-US: left adnexal **MULTI-SOL mass, color score 3**, low fluid level in the pelvis



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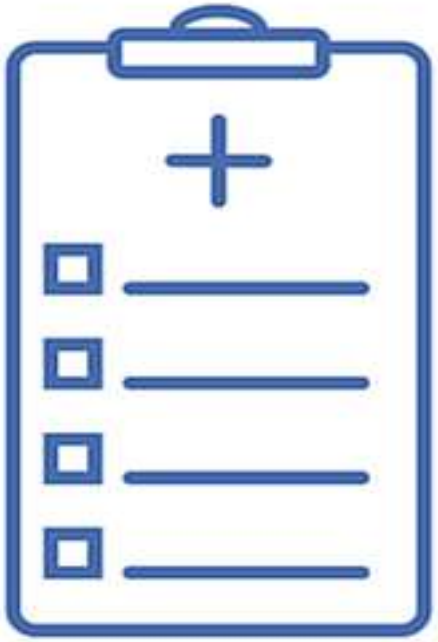


- **Ca125 870, HE4 162**, CEA and Ca19.9 neg
- During hospitalization antibiotic therapy is started, but **nephritic syndrome** begins with hematuria, edema and hypertension from glomerular nephritis associated with the ongoing infection → **Moderate CKD results**

For educational purposes

- **MDT**: diagnostic LPS, left adnexectomy, FS and surgical staging in case of neoplasia of adnexal origin and positive evaluation of cytoreducibility
- **PDS** with intraoperative evidence of pelvic-parietocolic-right diaphragmatic peritoneal carcinomatosis (small nodes of 5-10 mm) – **RT 0**
- ***Carcinoma of ovarian origin***
- ***Mixed serous-endometrioid histology, HG***
- *IIC: PAX8 (+), CK 5/6 (+focal), p53 (< 1%, mut), WT1 +, p16 -, Napsin -, ER 70%, PgR 20%, non dMMR*
- ***FIGO IIIB***
- ***HRD +, sBRCA1m***

GENE	ESONE	TIPOLOGIA	EFFETTO	COVERAGE	VAF%	DETTAGLI ALTERAZIONE			CAT
BRCA1	10	INDEL	frameshift	2116	**47**	c.1016dup	p. (Val340Glyfs*6)	p. (V340Gfs*6)	**A**
TP53	4	INDEL	frameshift	3402	**63,2**	c.365dup	p. (Thr123Aspfs*26)	p. (T123Dfs*26)	**B**

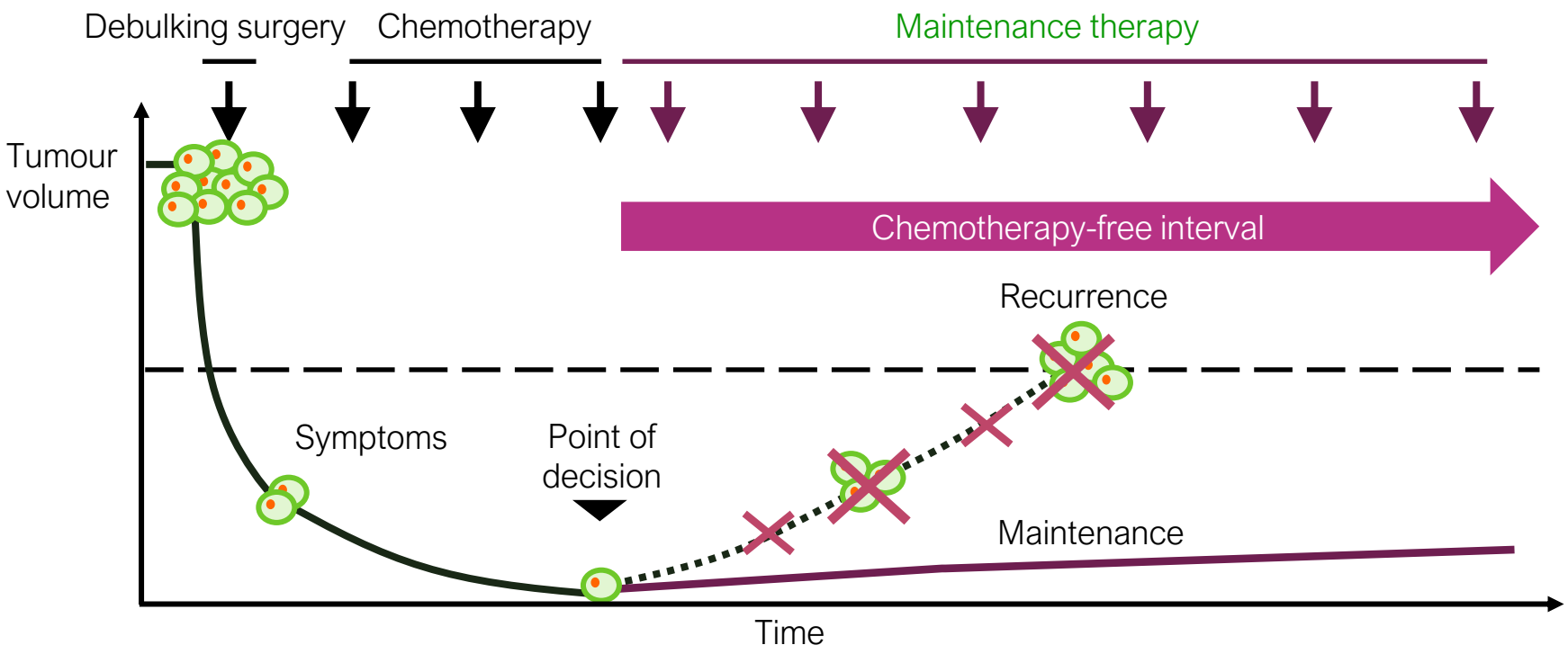
For educational purposes

- **MDT**: CT with carboplatin-paclitaxel 1:21, 6 cycles and genetic oncological consultation
- **Ca125 95** before starting CT
- **Creatinine clearance 50 ml/min** (67 yr, 64 kg, serum creatine 1.1) = Moderate renal impairment
- Carboplatin dose reduction

- **Ca125 turns negative after the I cycle**
- **KELIM 1.4** favorable score
- CT scan at the end of CT: NED

For educational purposes

>70% of patients with advanced OC will recur within 3–5 years in the absence of 1L maintenance therapy



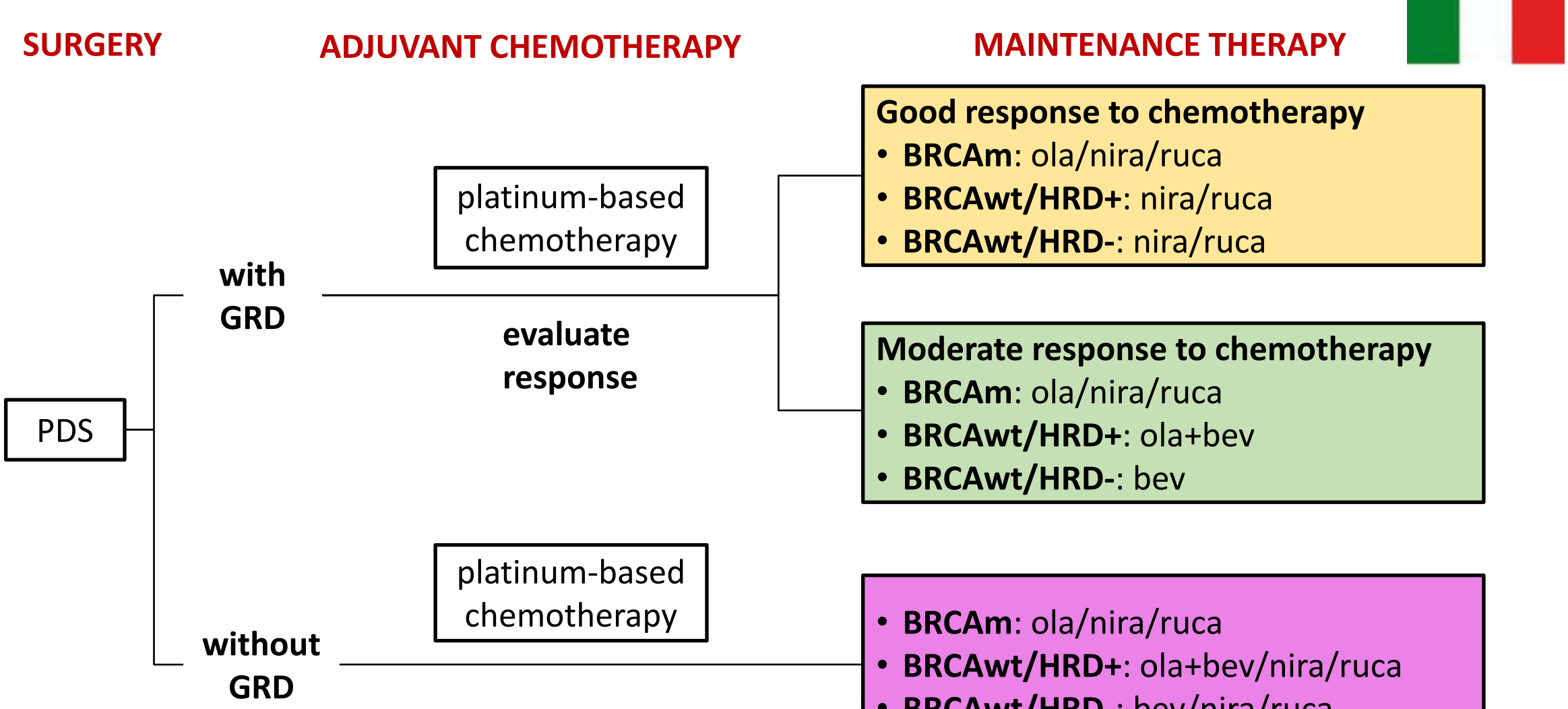
Goals of maintenance therapy

1. Prolong benefit following surgery and chemotherapy
2. Improve survival (PFS and hopefully OS)
3. Manageable toxicity and no negative effects on QoL

† = Common indicator of fatality - CA-125 = cancer antigen 125; PFS = progression-free survival.

Markman M, et al. *The Oncologist 2000;* Hanker LC, et al. *Ann Oncol.* 2012; Armstrong DK, et al. *The Oncologist* 2002; Fotopoulou C, et al. *Eur. J. Cancer Suppl.* 2014.

THERAPEUTIC ALGORITHM

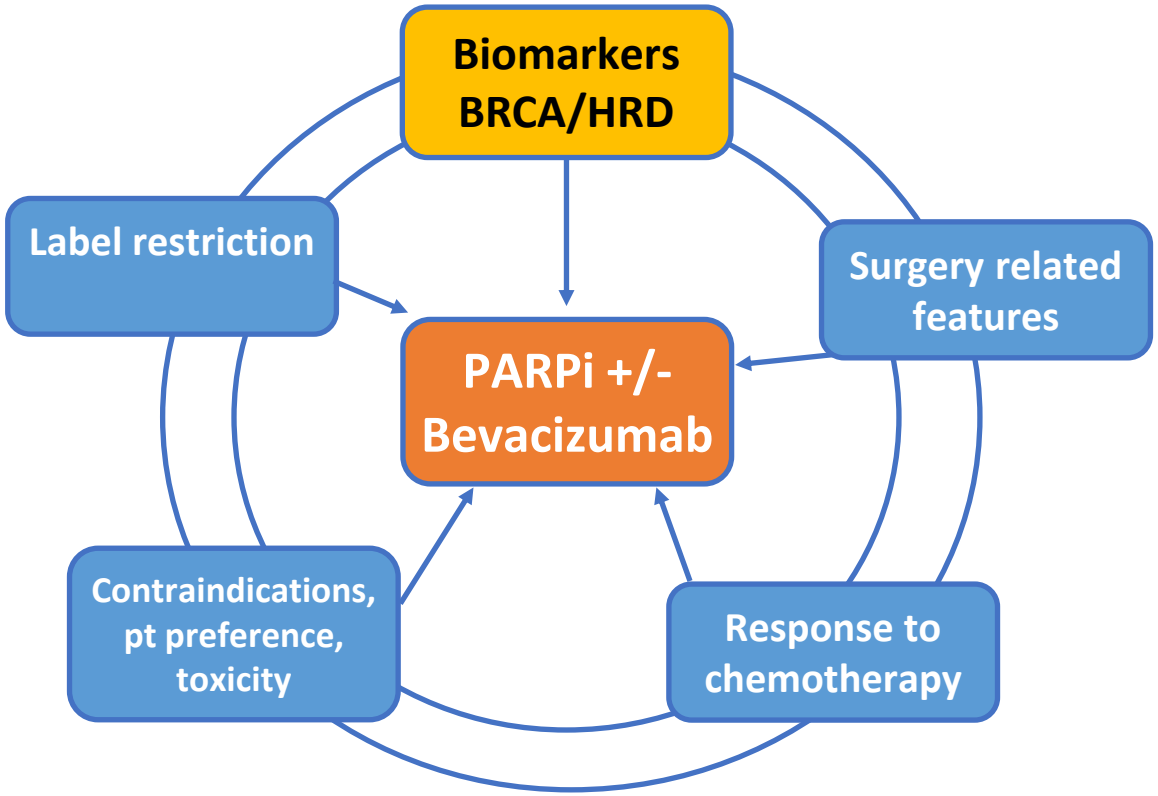


Niraparib is not reimbursed for stage III disease with RT=0 after PDS

Note that reimbursement policies may differ from approval indications and vary across countries

Adapted from *Colombo N, Gyn Oncol 2023*

Factors to consider when selecting the most effective first-line maintenance



Mutational status and PARPi benefit

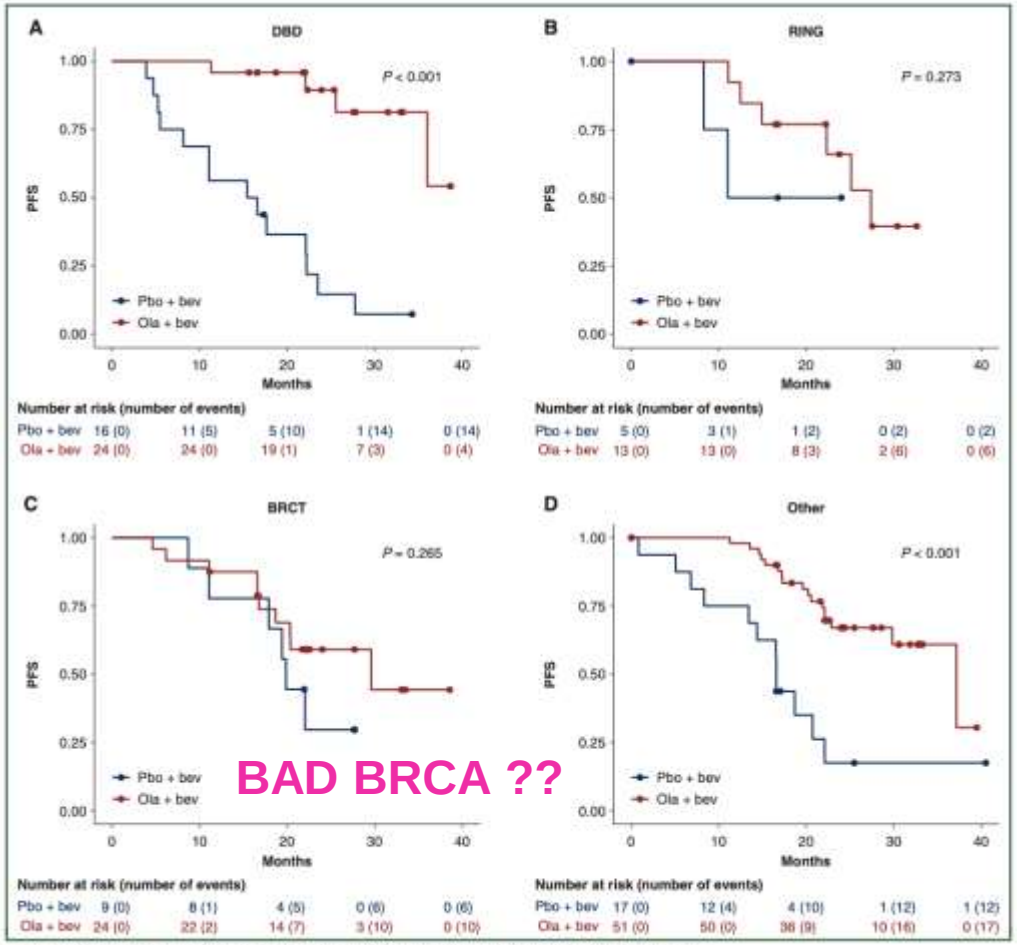
	SOLO-1[1]	PRIMA[2]	PAOLA-1[3]	ATHENA-MONO[4]	PRIME[5]
PARPi	Olaparib	Niraparib	Olaparib	Rucaparib	Niraparib
Bevacizumab	No	No	Yes	No	No
Population	BRCAmut	All comers	All comers	All comers	All comers (Chinese)
HRD test	NA	MyChoice	MyChoice	Foundation-One	BGI
PFS					
BRCAmut	0.33 (0.25–0.43)	0.40* (0.27–0.62)	0.31* (0.20–0.47)	0.31* (0.20–0.47)	0.40* (0.23-0.68)
BRCAwt/HRD+	-	0.50* (0.31-0.83)	0.43* (0.28-0.66)	0.58* (0.33-1.01)	0.58* (0.36-0.93)
BRCAwt/HRD-	-	0.68* (0.49-0.94)	1.0* (0.75-1.36)	0.65* (0.45-0.95)	0.41* (0.25-0.65)

*exploratory

The aim of the table is not the cross-trial comparison

1. Moore. NEJM 2018; 2. Gonzalez-Martin. NEJM 20193; 3. Ray-Coquard. NEJM 2019; 4. Monk. J Clin Oncol 2022; 5. Li.SGO 2022

Mutational status and PARPi benefit



BAD BRCA ??

Figure 2. **PFS according to the location of mutations in *BRCA1*.** (A) DBD. (B) RING. (C) BRCT. (D) Other locations.
Bev, bevacizumab; BRCT, C-terminal domain of *BRCA1*; DBD, DNA-binding domain; Ola, olaparib; Pbo, placebo; PFS, progression-free survival; RING, Really Interesting New Gene.

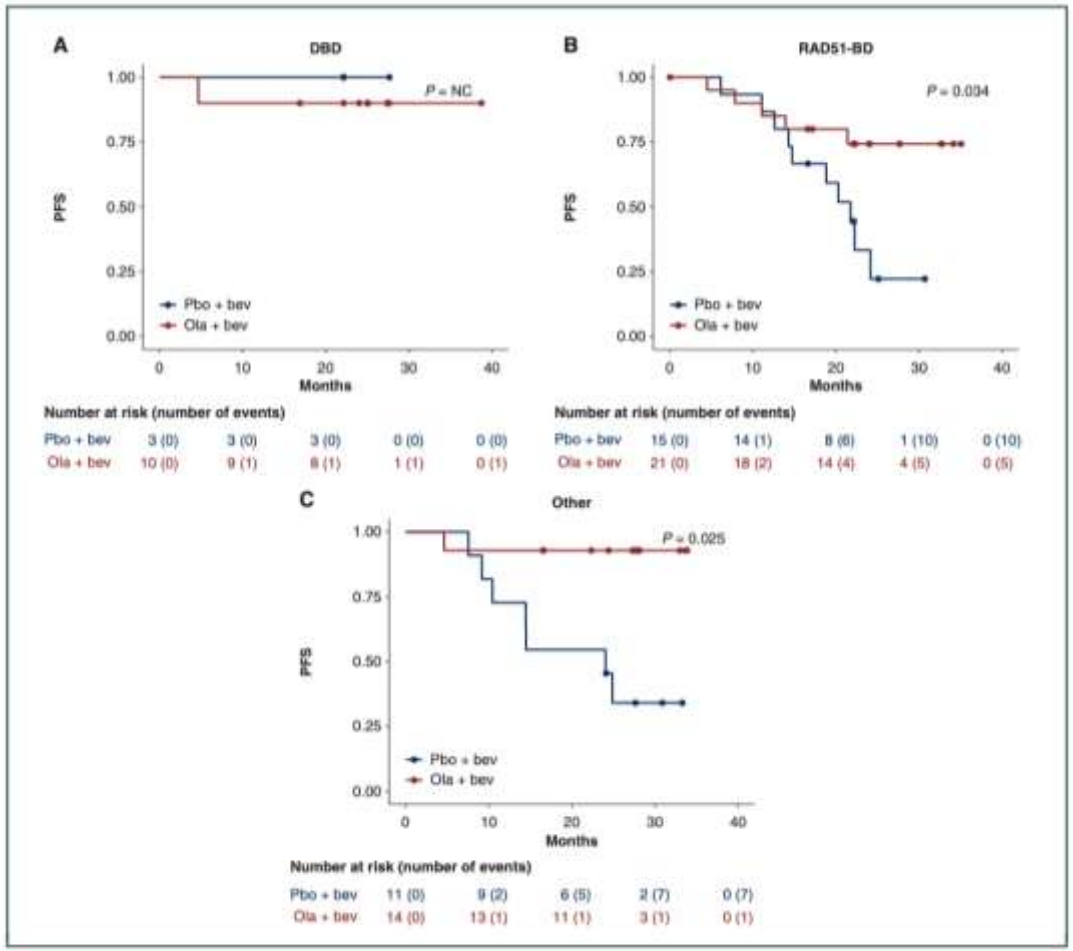
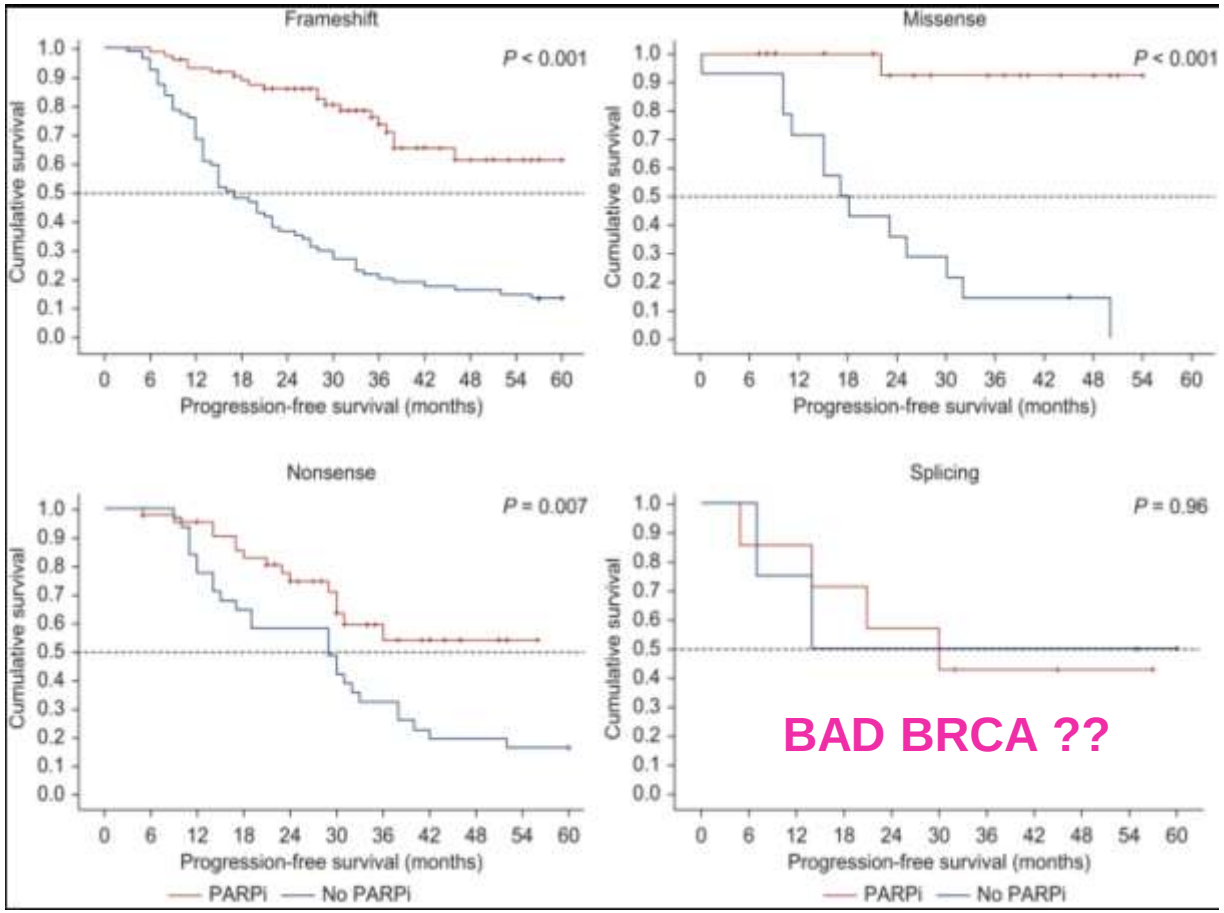


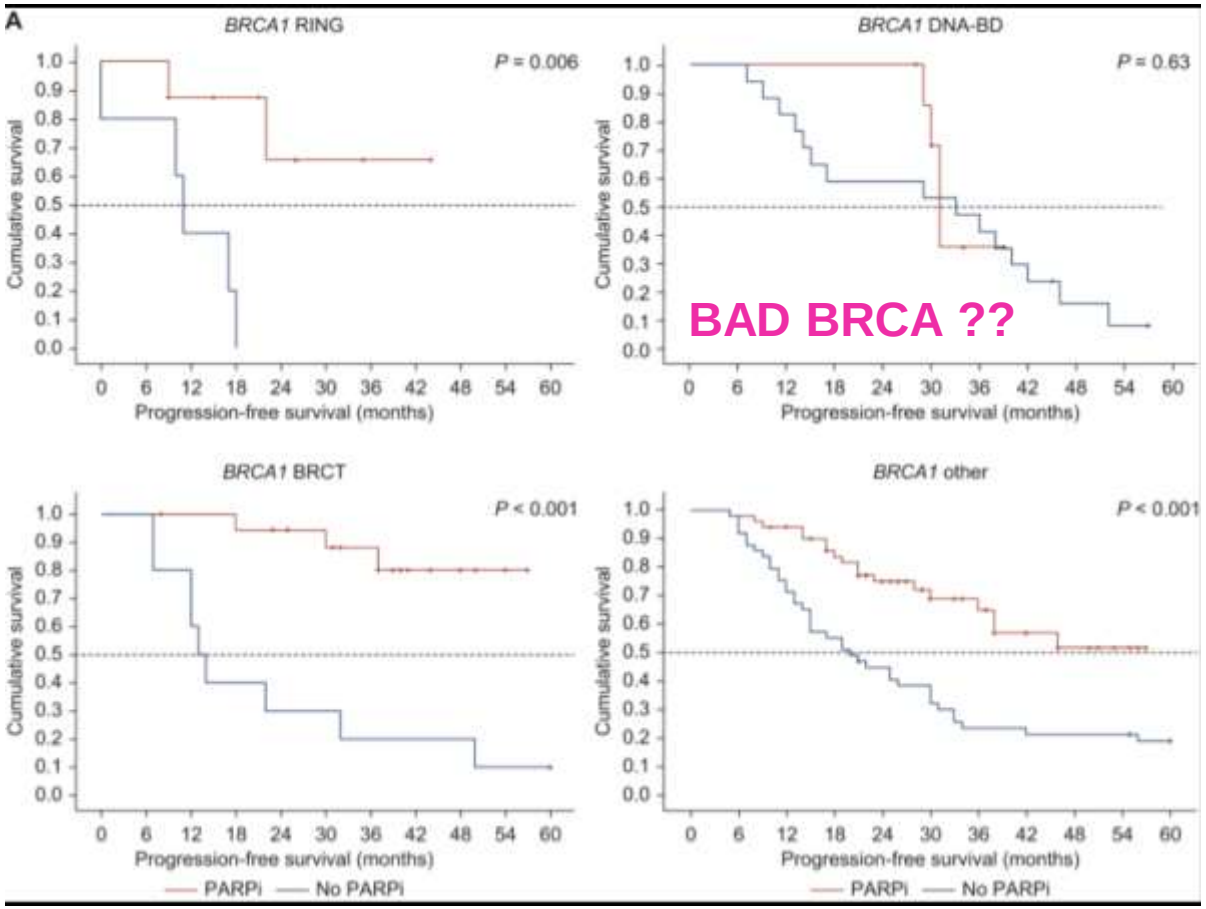
Figure 3. **PFS according to the location of mutations in *BRCA2*.** (A). DBD. (B) RAD51-BD. (C) Other locations.
Bev, bevacizumab; DBD, DNA-binding domain; NC, not calculated; Ola, olaparib; Pbo, placebo; PFS, progression-free survival; RAD51-BD, RAD51-binding domain.

Labidi-Galy SI Association of location of BRCA1 and BRCA2 mutations with benefit from olaparib and bevacizumab maintenance in high-grade ovarian cancer: phase II PAOLA-1/ENGOT-ov25 trial subgroup exploratory analysis. Ann Oncol. 2023 Feb;34(2):152-162.

Mutational status and PARPi benefit



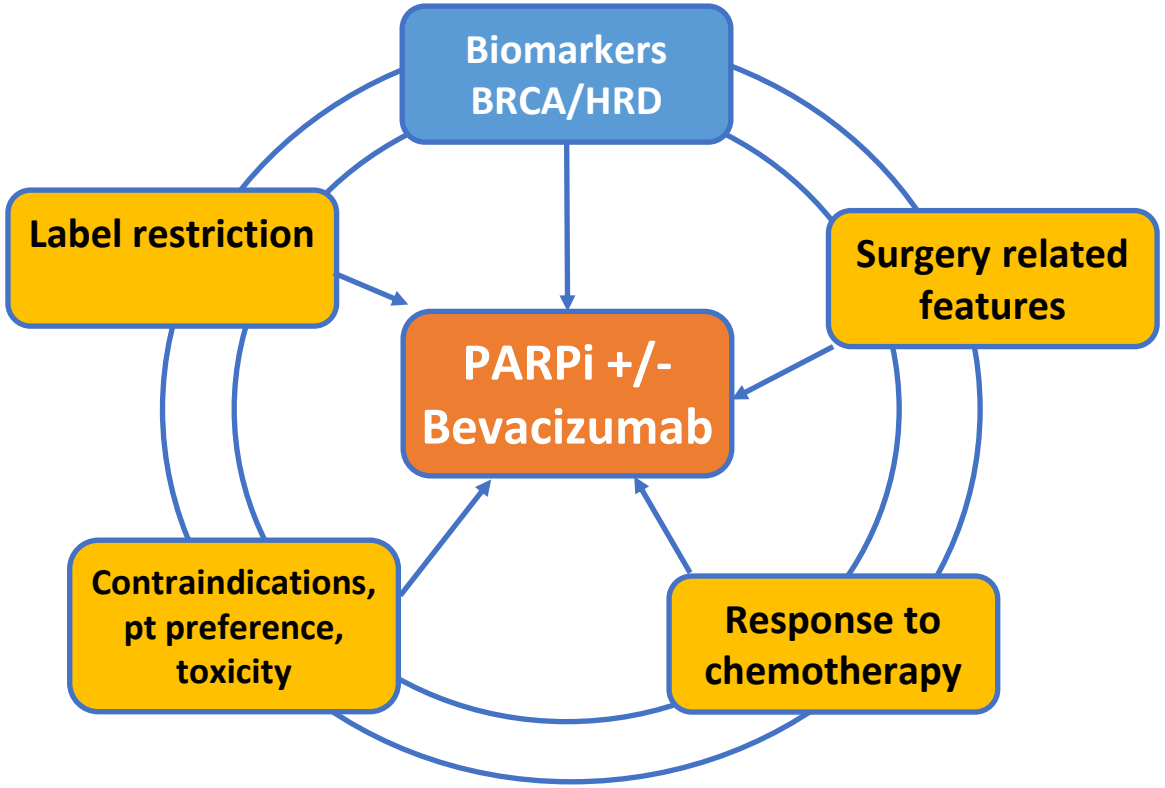
PFS in the overall population according to the <u>type of mutation</u>



Progression-free survival according to <u>functional domain</u> in the BRCA1-mutated population

Marchetti C et al Benefit from maintenance with PARP inhibitor in newly diagnosed ovarian cancer according to BRCA1/2 mutation type and site: a multicenter real-world study. ESMO Open. 2025 Apr;10(4):104533.

It is recommended that this patient receive maintenance therapy with PARPi. Which PARPi ? Should we add Beva ?



Which PARPi ? Should we add Beva ?

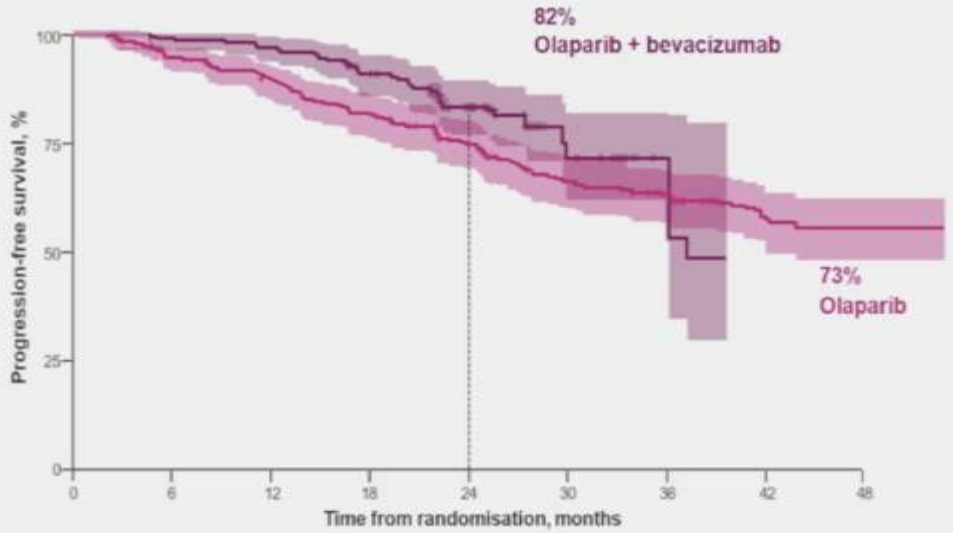
	Olaparib	Rucaparib	Niraparib	Ola + Beva
HRD + , sBRCA1m				
PDS, no RT, FIGO IIIB, mixed histotype				
Moderate renal impairment				
Arterial hypertension				

Ok !

?

Nicoletta Colombo, Isabelle Ray-Coquard, Shannon N. W…

A population-adjusted indirect treatment comparison of PAOLA-1 and SOLO1 showed an additive benefit from bevacizumab



	PAOLA-1 tBRCAm	SOLO1
	Olaparib + bev[a] (n=151)	Olaparib (n=254)
PFS at 12 months, %	96	88
PFS at 24 months, %	82	73
	HR 0.71 (95% CI, 0.45–1.09)[b]	

In SOLO1, the median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. Shaded region represents 95% CI.
In PAOLA-1, median follow-up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm. Shaded region represents 95% CI.
[a]These results are based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (PDS vs IDS), residual disease status after surgery, response to first-line treatment and age to SOLO1.
[b]CIs generated by bootstrapping.
bev, bevacizumab; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IDS, in…
Virgil…

Courtesy of Prof N. Colombo, from ESGO Meeting 2025 Rome

Agenzia Italiana del Farmaco

Attivazione web e pubblicazione schede di monitoraggio - Registro Olaparib (associazione con bevacizumab - cancro dell'ovaio)

Si informano gli utenti dei Registri Farmaci sottoposti a Monitoraggio che, a seguito della pubblicazione della Determina AIFA nella GU n.64 del 17.03.2022, a partire dal 18.03.2022 è possibile utilizzare, in regime di rimborsabilità SSN, il medicinale LYNPARZA per la seguente indicazione terapeutica:

- *Trattamento di mantenimento di pazienti adulte con cancro epiteliale dell'ovaio di alto grado avanzato (stadi III e IV secondo FIGO), cancro della tuba di Falloppio o cancro peritoneale primitivo, in risposta (completa o parziale) dopo completamento della chemioterapia di prima linea a base di platino in associazione con bevacizumab e il cui tumore presenti un deficit di ricombinazione omologa (homologous recombination deficiency, HRD), definito dalla presenza di instabilità genomica ed in assenza di una mutazione BRCA1/2.*

E	(se indicato C) Il tumore presenta un deficit di ricombinazione omologa (homologous recombination deficiency, HRD)?	Si	
		No	***blocca***
E	Se si, la paziente presenta il gene BRCA:	wild-type	***combobox***
		mutazione somatica/germinale BRCA1	***Blocco all'associazione olaparib + bevacizumab per pazienti HRD+ e selezionato mutazione BRCA1 o BRCA2***
		mutazione somatica/germinale BRCA2	

Which PARPi ? Should we add Beva ?

	Olaparib	Rucaparib	Niraparib	Olap+Beva
HRD + , sBRCA1m				
PDS, no RT, FIGO IIIB, mixed histotype, KelimS F				
Moderate renal impairment				
Arterial hypertension				

Which PARPi ? Should we add Beva ?

	Olaparib	Rucaparib	Niraparib	Cl… Beva
HRD + , sBRCA1m				
PDS, no RT, FIGO IIIB, mixed histotype, KelimS F				
Moderate renal impairment				
Arterial hypertension				

Label restriction

Label restriction

	Olaparib	Rucaparib	Niraparib	Ola + Beva
HRD + , sBRCA1m				
PDS, no RT, FIGO IIIB, mixed histotype, KelimS F				
Moderate renal impairment				
Arterial hypertension				

Label restriction

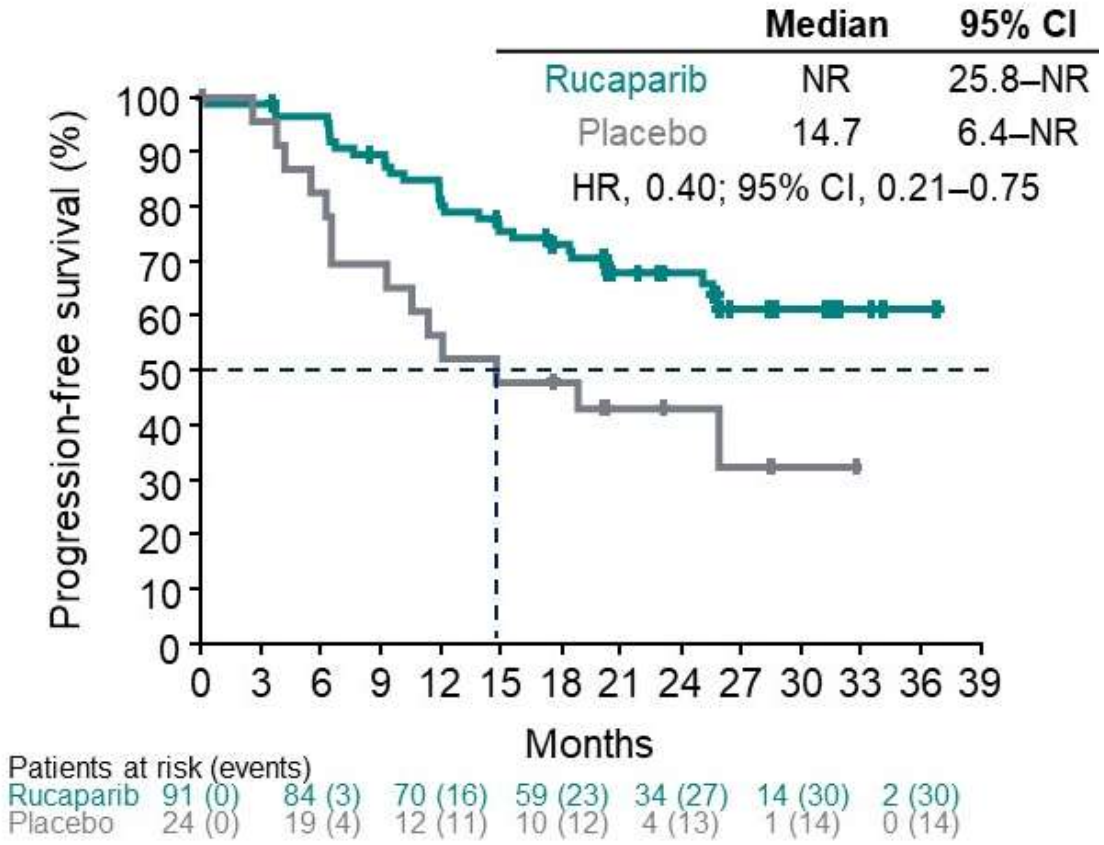
Label restriction

Per i pazienti con compromissione renale moderata (clearance della creatinina da 31 a 50 mL/min) la dose raccomandata di olaparib è di 200 mg (due compresse da 100 mg) due volte al giorno (equivalente ad una dose giornaliera totale di 400 mg)*

*Riassunto delle caratteristiche del prodotto (Olaparib)

ATHENA-MONO: Primary Endpoint – subgroup analysis

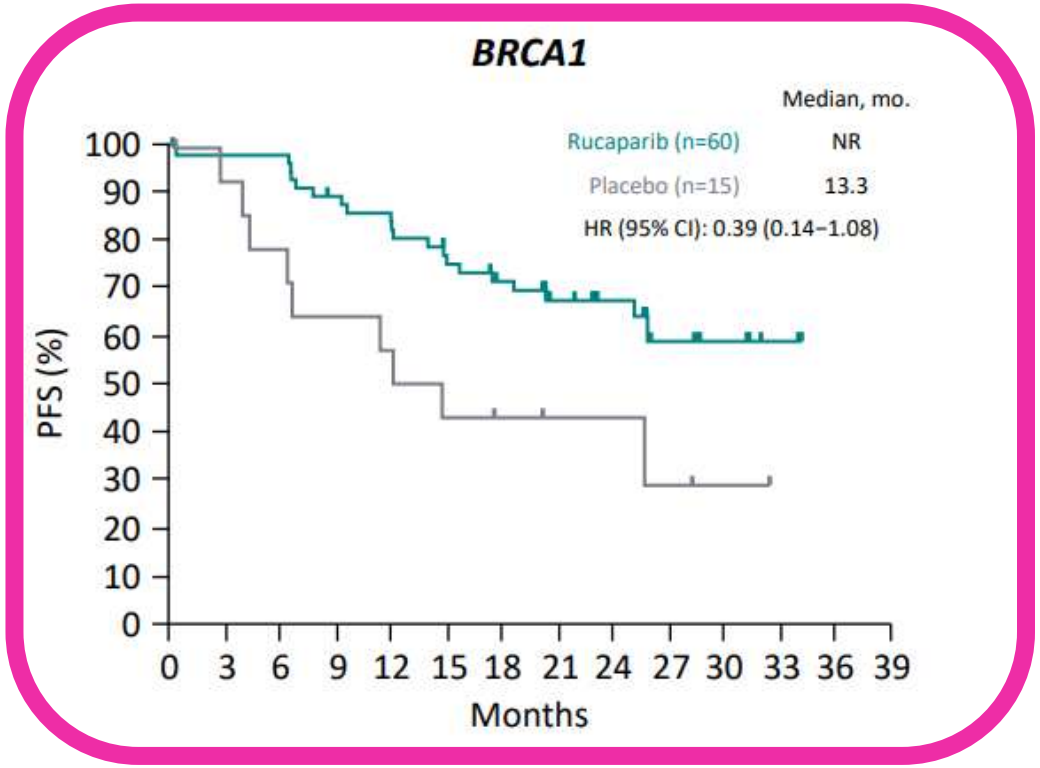
BRCAm

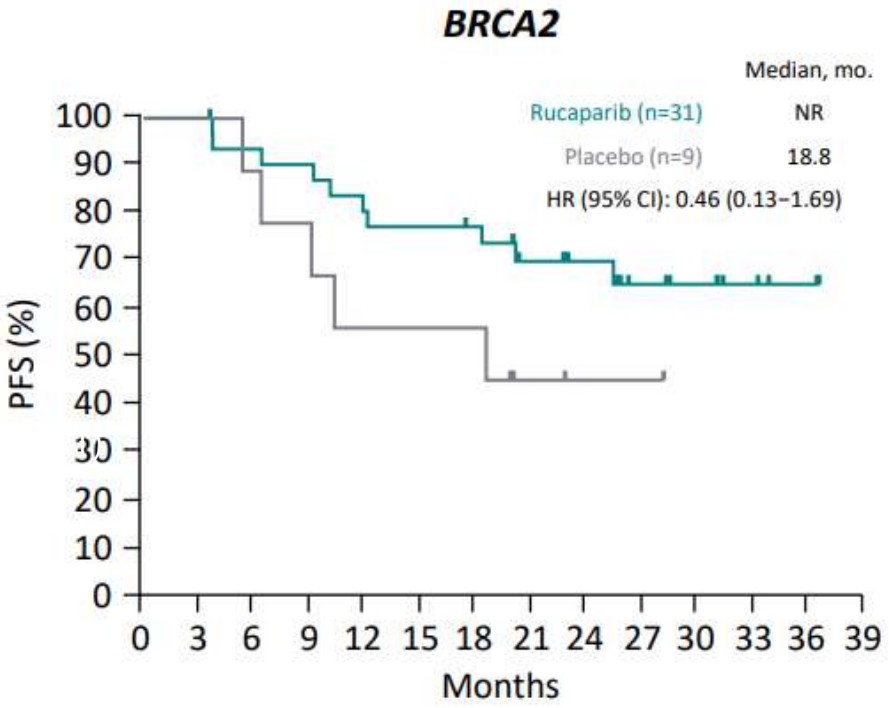


Monk B., ASCO 2022

ATHENA-MONO: Exploratory biomarkers analysis

PFS in Patients With Deleterious *BRCA1* or *BRCA2* Mutations





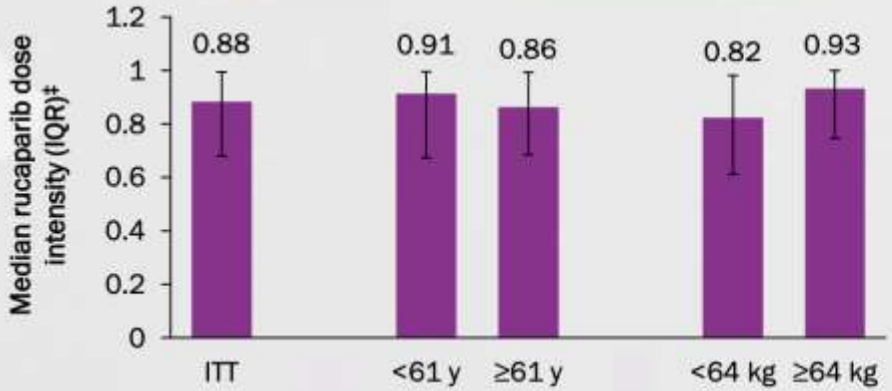
Ana Oaknin
Patients With Newly Diagnosed Ovarian Cancer Treated With Maintenance Rucaparib: Exploratory Biomarker Analysis From the Phase 3 ATHENA–MONO Study (GOG-3020/ENGOT-ov45; NCT03522246)
ESGO Congress 2022 Berlin

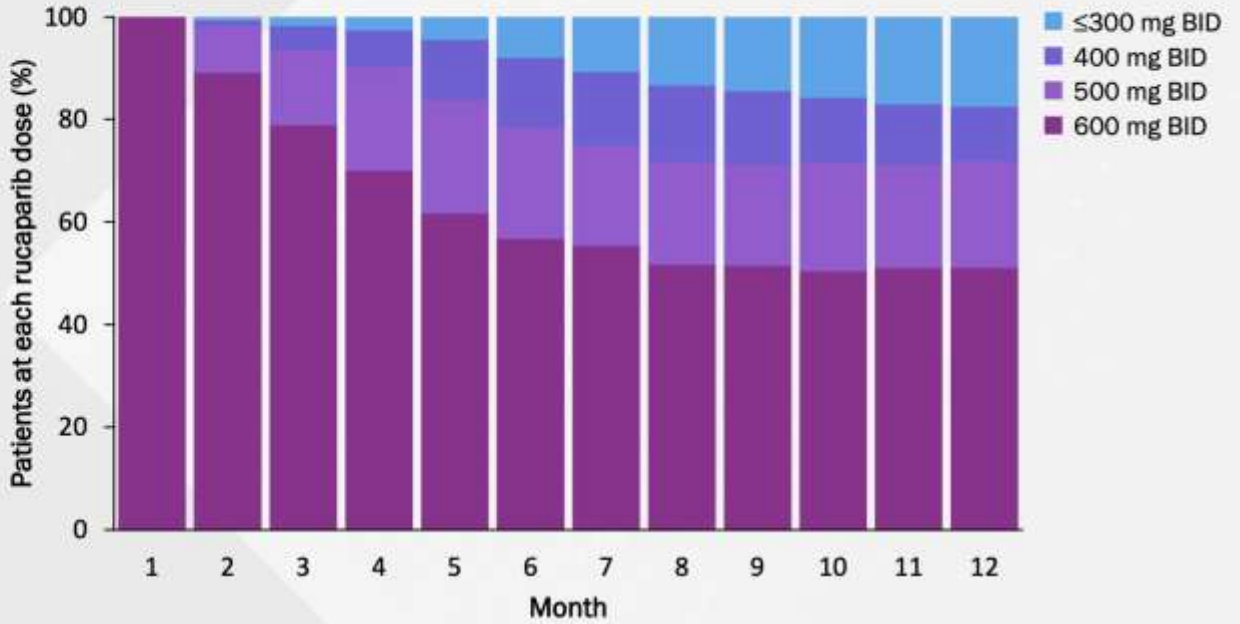
For educational purposes

- Starts Rucaparib **within 8 weeks** of the end of CT, **600 mgX2**,

Rucaparib Dose Intensity in ATHENA–mono

Starting dose	600 mg BID
Dose level: –1	500 mg BID
Dose level: –2	400 mg BID
Dose level: –3†	300 mg BID





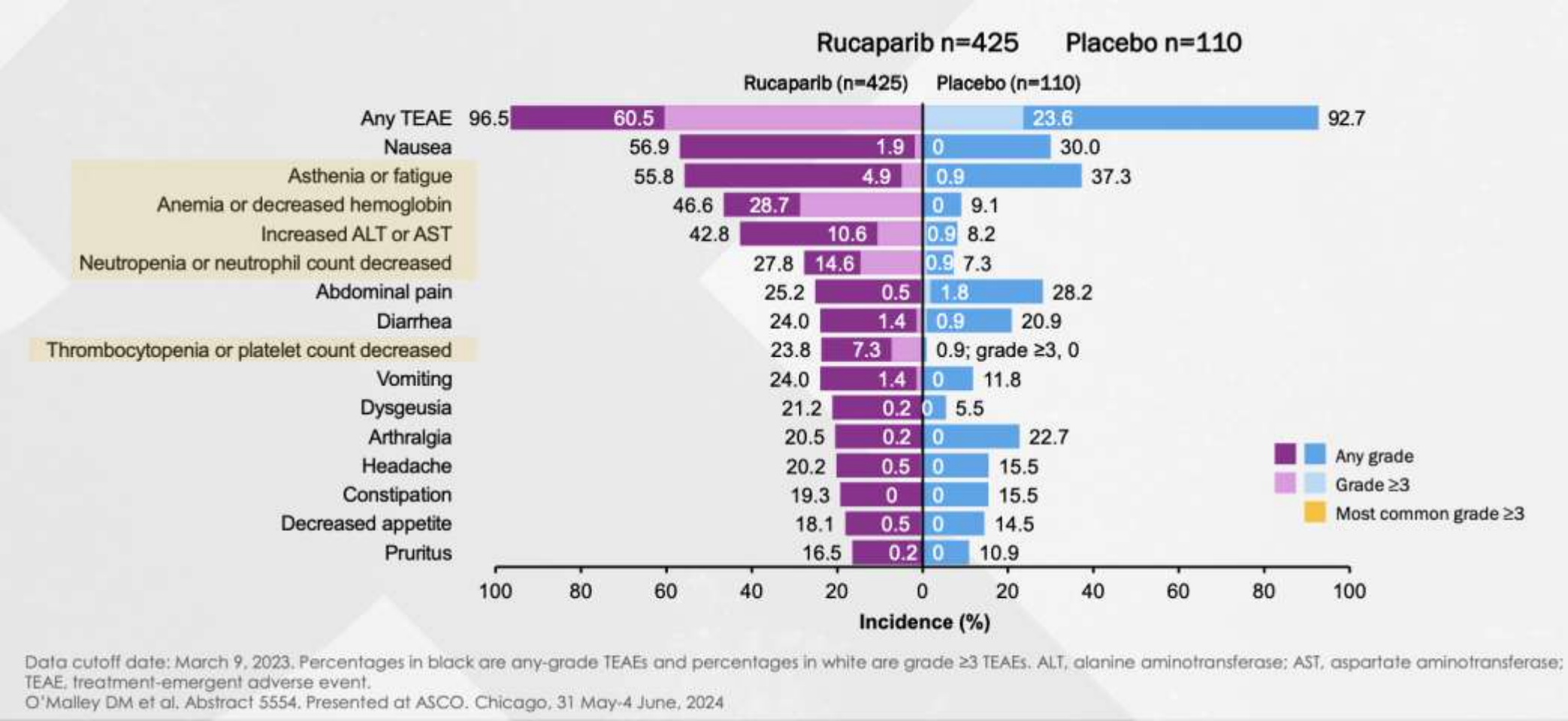
- More than 70% of patients continued to receive ≥500 mg BID rucaparib (>80% of starting dose) through month 12
- Median (IQR) dose intensity was 0.88 (0.680–0.995) in the rucaparib and 1.00 (0.970–1.000) in the placebo group

Data cut-off date: March 23, 2022

†Consultation with the sponsor's medical monitor was required before reducing to dose level –3. Dose reduction below 300 mg BID was possible upon consultation with the sponsor's medical monitor; ‡Dose intensity was calculated as time normalized actual dose received divided by the starting dose of 600 mg BID

1. Monk BJ et al. *J Clin Oncol*. 2022;40:3952–3964; 2. Monk BJ et al. Abstract: LBA5500. Presented at ASCO, June 3–7, 2022, Chicago

Most Common TEAEs (≥15%) of Any Grade Reported with Rucaparib



Data cutoff date: March 9, 2023. Percentages in black are any-grade TEAEs and percentages in white are grade ≥3 TEAEs. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.
O'Malley DM et al. Abstract 5554. Presented at ASCO. Chicago, 31 May-4 June, 2024

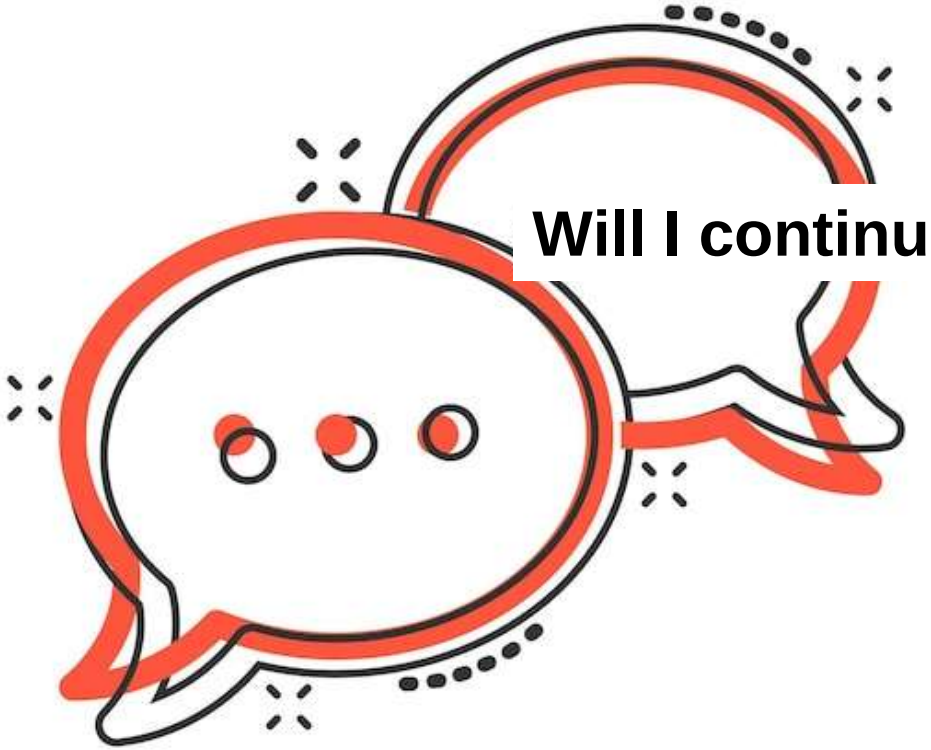
- Starts Rucaparib **within 8 weeks** of the end of CT, **600 mgX2**,

Table 1 Incidence of myeloid neoplasms post PARPi in patients with ovarian cancer enrolled in pivotal randomized clinical trials

First-line maintenance setting			
SOLO1 (OLA vs PBO; BRCAm)	**PRIMA (NIRA vs PBO)**	**ATHENA-MONO (RUCA vs PBO)**	**PAOLA1 (OLA+BEVA vs PBO+BEVA)**
Primary analysis: 1% vs 0%[5]	Primary analysis: 0.2% vs 0%[6]	Primary analysis: 0.5% vs 0%[7]	Primary analysis: 1.1% vs 0.4%[8]
7-year FU: 1.5% vs 0.8%[50]	3.5-year FU: 1.2% vs 1.2%[51]		5-year FU: 1.7% vs 2.2%[52]
Platinum-sensitive recurrent maintenance setting			
SOLO2 (OLA vs PBO; BRCAm)	**NOVA (NIRA vs PBO)**	**ARIEL3 (RUCA vs PBO)**	**OReO (OLA rechallenge vs PBO)**
Primary analysis: 2.1% vs 4%[11]	Primary analysis: 1.4% vs 1.1%[10]	Primary analysis: 1% vs 0%[9]	Awaited[53]
6-year FU: 8% vs 4%[13]	5.5-year FU: 3.5% vs 1.7%[12]	6-year FU: 3.8% vs 3.2%[48]	

BEVA, bevacizumab; BRCAm, BRCA-mutated patients; FU, follow-up; NIRA, niraparib; OLA, olaparib; PARPi, poly (ADP-ribose) polymerase inhibitor; PBO, placebo; RUCA, rucaparib.

*Caruso G, Gigli F, Parma G, et al. Int J Gynecol Cancer 2023;**33**:598–606.*



Will I continue therapy with rosuvastatin ?

For educational purposes

Drug-drug interactions

- Rosuvastatin could interfere with Rucaparib by **increasing the AUC of Rosuvastatin itself**

→ increasing risk for myopathy/rhabdomyolysis in a patient already affected by CKD !

- After **internistic consultation: dose reduction of Rosuvastatin** to 5 mg/day
- **Close monitor CPK** during the periodic tests performed for Rucaparib
- **Counseling to the patient**: promptly report the onset of muscle pain, weakness or cramps

For educational purposes

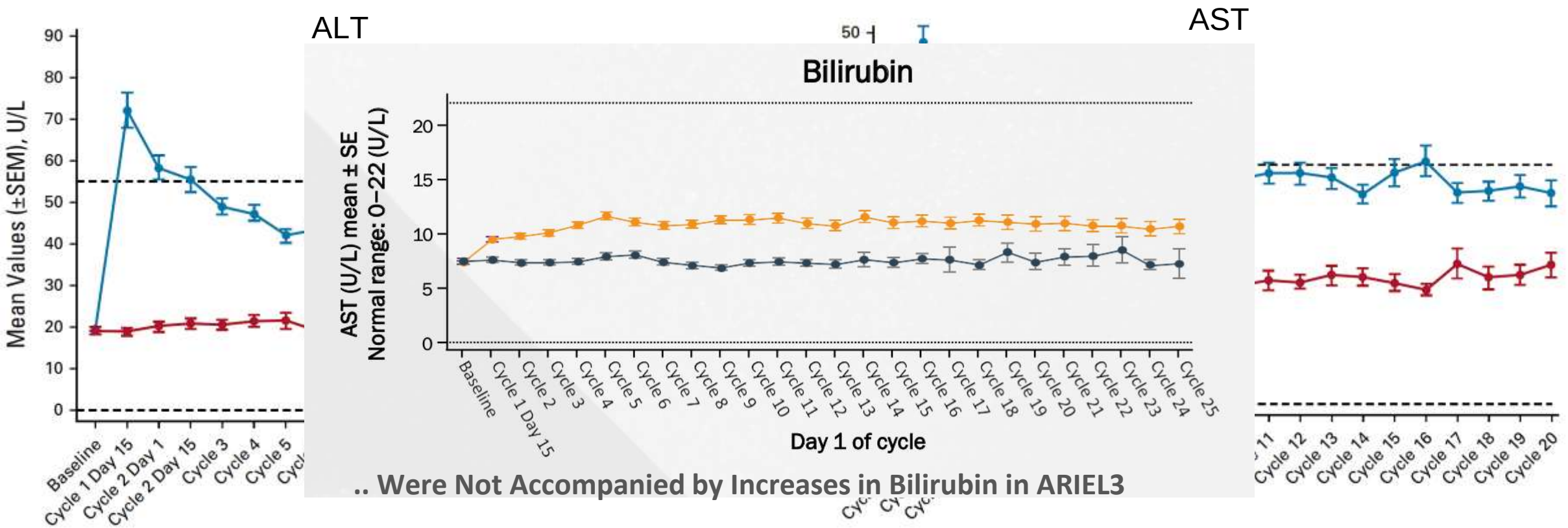
- **What type of surveillance (timing) would you choose for this patient?**
  - A) Weekly check-ups
  - B) Biweekly check-ups at least for the first 3 months
  - C) Monthly check-ups

- What type of surveillance (exams)?

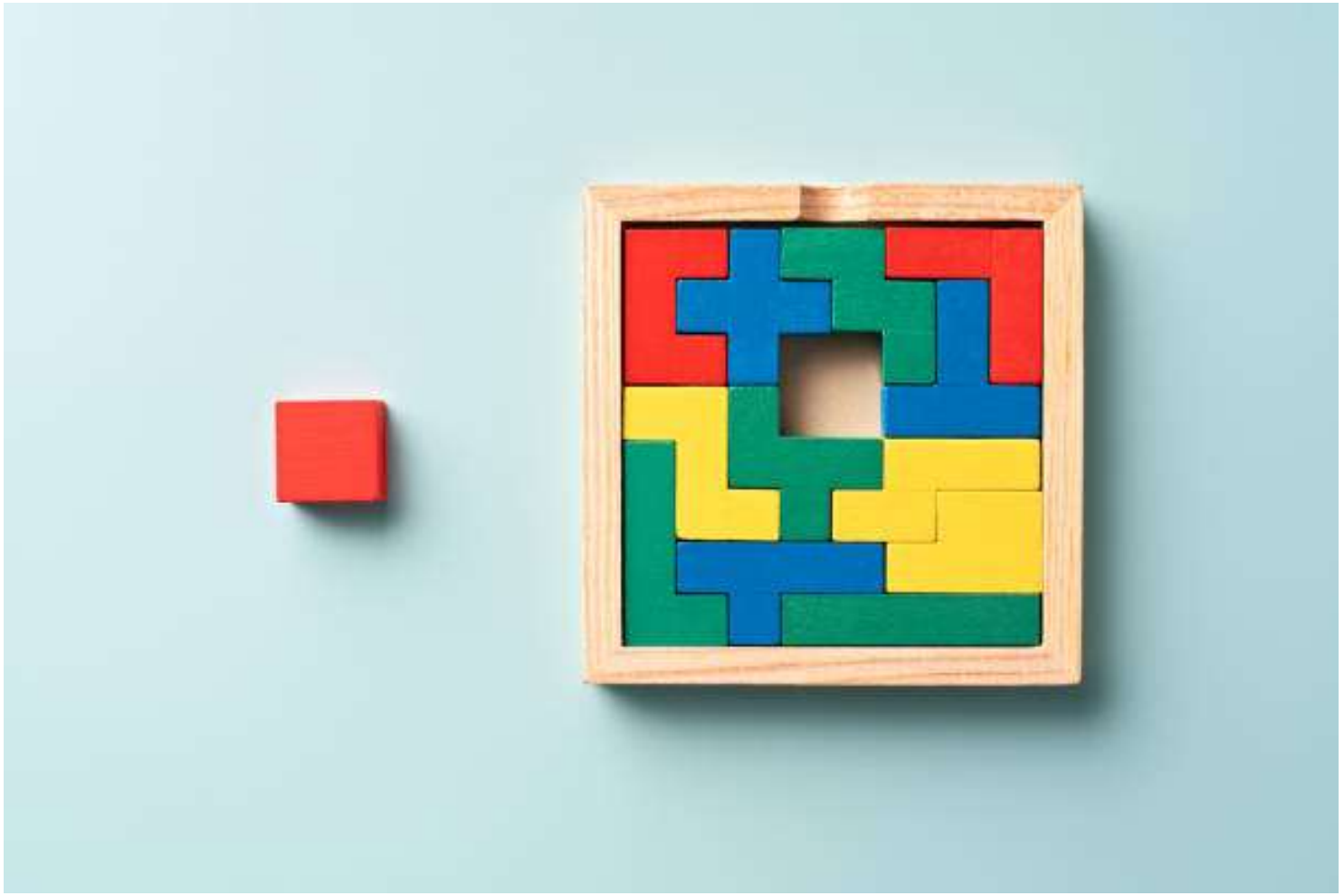
Counseling, Clinical visit, blood exam:
emocromo, creatinine, **AST, ALT, bilirubina**, CPK (for this pts)

For educational purposes

Changes from baseline in ALT and AST with rucaparib



Monk BJ et al. *J Clin Oncol*. 2022;40:3952–3964; Monk BJ et al. Abstract: LBA5500. Presented at ASCO, June 3–7, 2022, Chicago
Coleman RL et al. Lancet. 2017;390:1949–1961. pharmaand GmbH. Data on File. ATHENA CO-338-087. Clinical Study Report



Grazie ! ☺

RUCAPARIB, a new option in first-line maintenance treatment: peculiarity of drug and indications

PHARMA& SPONSORED LECTURE

Giuseppe Caruso, MD, PhD(c)

Division of Gynecologic Oncology, IEO Milan

Conflicts of interest

Financial interest	Sponsor
Honoraria for educational activities	**Pharma&**, Abbvie, AZ, GSK
Travel/accomodation	AZ, GSK

- A fee is expected for this presentation
- The clinical cases presented are intended solely for educational use

Rucaparib as 1L maintenance therapy: 3 clinical cases

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BRCAm

BRCAwt / HRD+

HRD-

MARIA GRAZIA, 76 yrs

Diagnosis | 1L treatment | Maintenance

Family Cancer History
• Maternal grandmother: breast cancer • Father: lung cancer (smoker)

Comorbidities
• Hypertension • Severe obesity (BMI 32 kg/m^2) • DM type 2

Dec 2024

- Diagnosis of HGSOC, FIGO stage IIICr, BRCAwt/HRD+
- No ascites or pleural effusion
- CA125 = 897 KU/L

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MARIA GRAZIA, 76 yrs

Diagnosis | **1L treatment** | Maintenance

Jan 2025 – Mar 2025

- MDT: Patient not deemed suitable for PDS (due to disease extent and frailty status)
- NACT (4 cycles): carboplatin + paclitaxel Q3W. AEs: neutropenia G3 – thrombocytopenia G1
- RECIST – **Partial response** (nearly complete)
- **KELIM score 1.29** (negative CA125 after NACT)
- Interval cytoreductive surgery (via robotics) – **RT = 0**
- **CRS 3**

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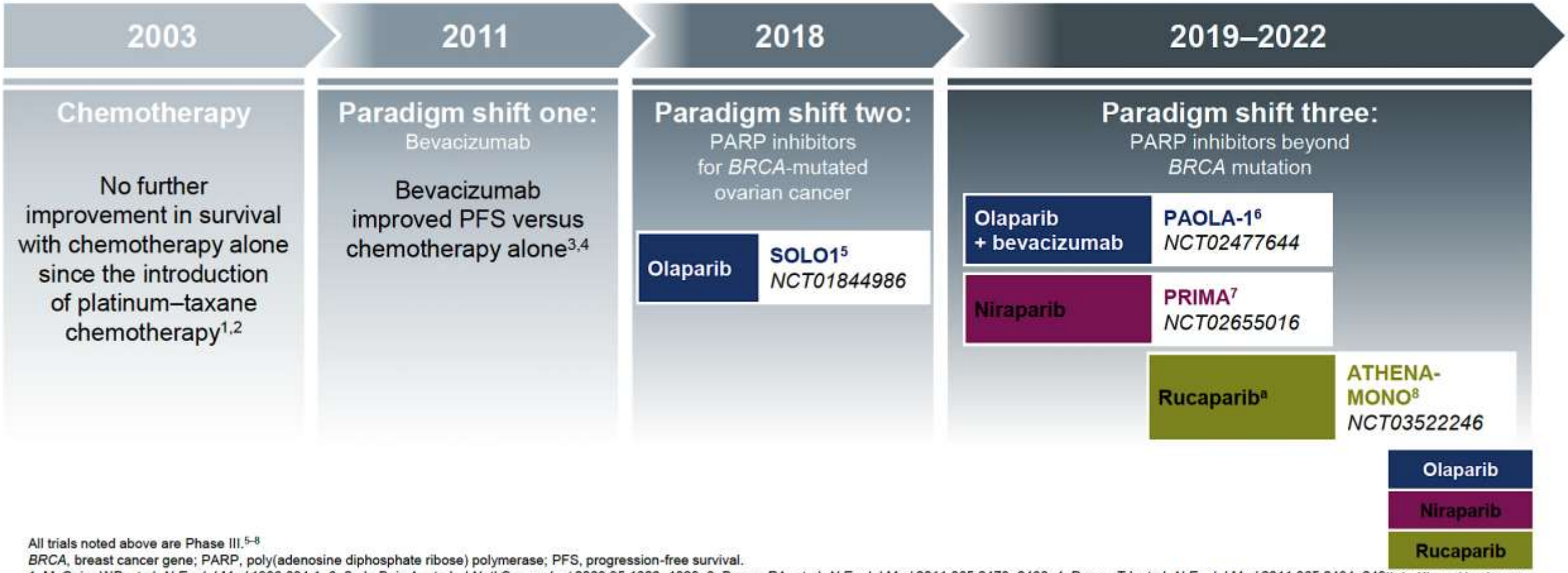
Significant progress has been made in the first-line management of ovarian cancer



All trials noted above are Phase III.[5–8]

BRCA, breast cancer gene; PARP, poly(adenosine diphosphate ribose) polymerase; PFS, progression-free survival.

1. McGuire WP, et al. *N Engl J Med* 1996;334:1–6; 2. du Bois A, et al. *J Natl Cancer Inst* 2003;95:1320–1329; 3. Burger RA, et al. *N Engl J Med* 2011;365:2473–2483; 4. Perren TJ, et al. *N Engl J Med* 2011;365:2484–2496; 5. ClinicalTrials.gov. NCT01844986. Available at: https://clinicaltrials.gov/ct2/show/NCT01844986 (accessed February 2024); 6. ClinicalTrials.gov. NCT02477644. Available at: https://clinicaltrials.gov/ct2/show/NCT02477644 (accessed February 2024); 7. ClinicalTrials.gov. NCT02655016. Available at: https://clinicaltrials.gov/ct2/show/NCT02655016 (accessed February 2024); 8. Monk JM, et al. *J Clin Oncol* 2022;40:3952–3964.

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GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

15.02.2025

AIFA
AGENZIA ITALIANA DEL FARMACO

E	*Campo obbligatorio ai fini dell'eleggibilità*	**(rucaparib)** **Carcinoma ovarico**
O	*Campo obbligatorio*	

Indicazioni autorizzate
Rubraca è indicato:
-come monoterapia per il trattamento di mantenimento di pazienti adulte con recidiva platino sensibile di carcinoma ovarico epiteliale ad alto grado, delle tube di Falloppio o peritoneale primario, in risposta (risposta completa o parziale) dopo chemioterapia a base di platino.

- come monoterapia per il trattamento di mantenimento di pazienti adulte con carcinoma ovarico epiteliale, delle tube di Falloppio o peritoneale primario, avanzato (stadio III e IV secondo FIGO) e ad alto grado, in risposta (risposta completa o parziale) dopo il completamento della chemioterapia di prima linea a base di platino

Indicazione rimborsata SSN:
- come monoterapia per il trattamento di mantenimento di pazienti adulte con carcinoma ovarico epiteliale, delle tube di Falloppio o peritoneale primario, avanzato (stadio III e IV secondo FIGO) e ad alto grado, in risposta (risposta completa o parziale) dopo il completamento della chemioterapia di prima linea a base di platino

	Indicazione		
E	Età	≥18 aa	*solo F*
	2 - Scheda Eleggibilità e Dati Clinici (EDC)		
	Caratteristiche della malattia		
E	Paziente con carcinoma ovarico epiteliale, delle tube di Falloppio o peritoneale primario, di alto grado, di nuova diagnosi, confermato istologicamente, in stadio avanzato (stadio FIGO III-IV)	Si	
		No	*blocco*
E	Tipo istologico	Adenocarcinoma sieroso	
		Adenocarcinoma endometrioide	
		Carcinoma a cellule chiare	
		Carcinoma epiteliale misto	
		Adenocarcinoma mucinoso	*blocco*
		Carcinoma a cellule transizionali	*blocco*
		Tumore di Brenner maligno	*blocco*
		Carcinoma indifferenziato	*blocco*
		Adenocarcinoma NOS	*blocco*

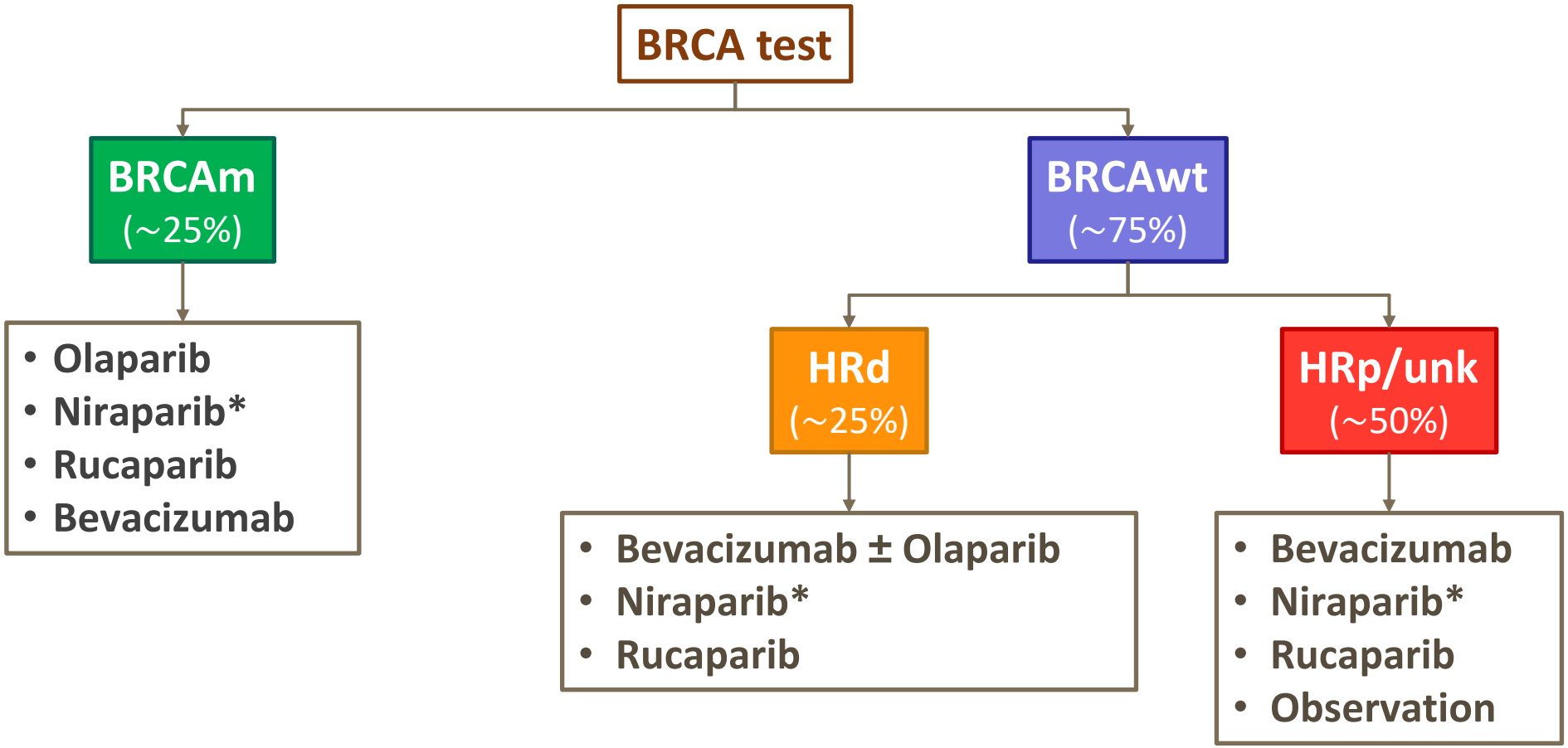
Including also:

- **Non-BRCAm, stage III, PDS, RT=0**
- **Clear cell**
- **Mixed histology**

MORE DRUGS
MORE OPTIONS

MORE OPPORTUNITIES
TO FIND THE RIGHT DRUG
FOR THE RIGHT PATIENT

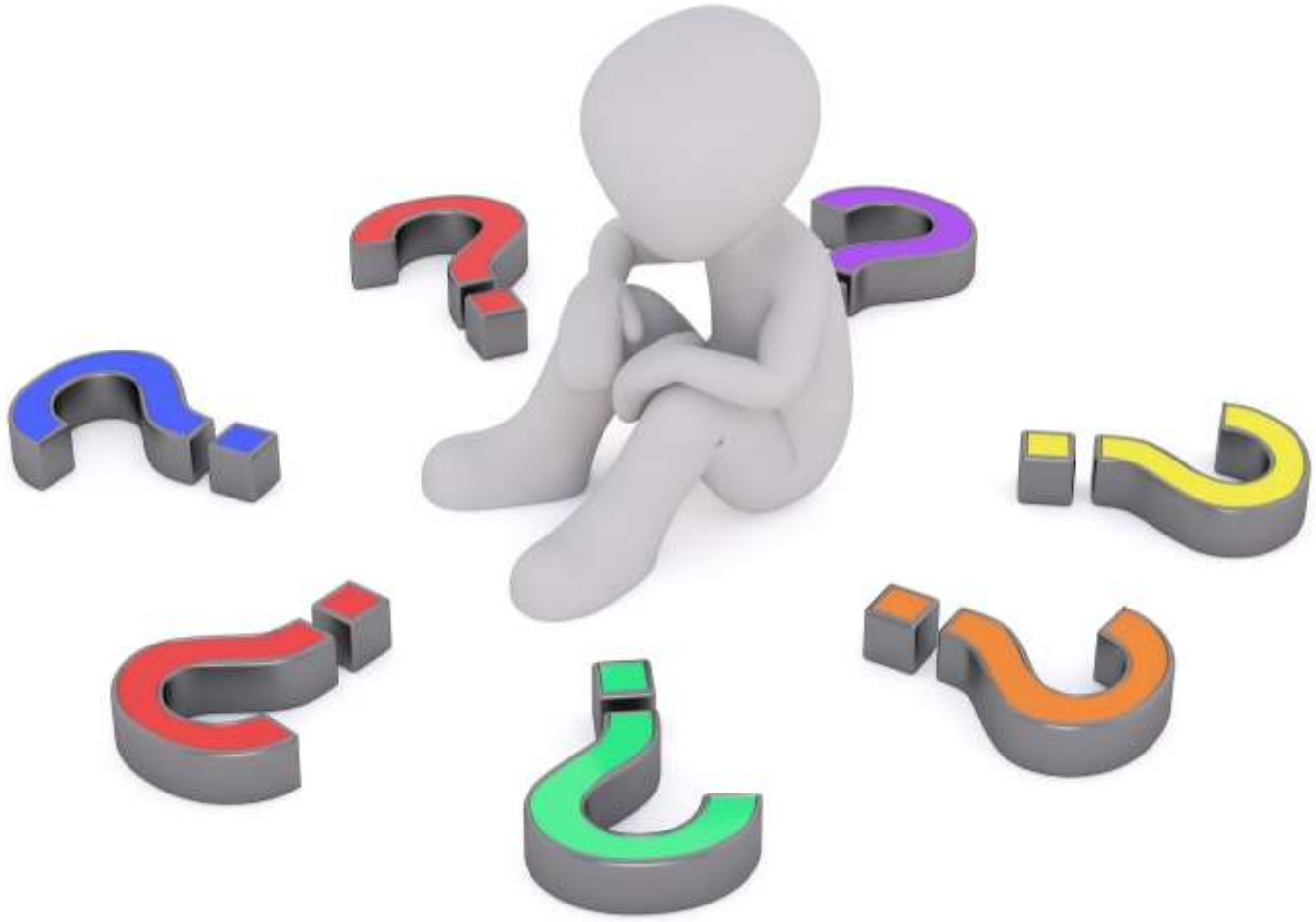
FIRST-LINE MAINTENANCE THERAPY: STATE OF THE ART



*Niraparib is not reimbursed for stage III disease with RT=0 after PDS

Adapted from *Caruso et al. IJGC 2023*

FIRST-LINE MAINTENANCE THERAPY: WHICH ONE?



Question n. 1

Which maintenance therapy option would you choose for this patient?

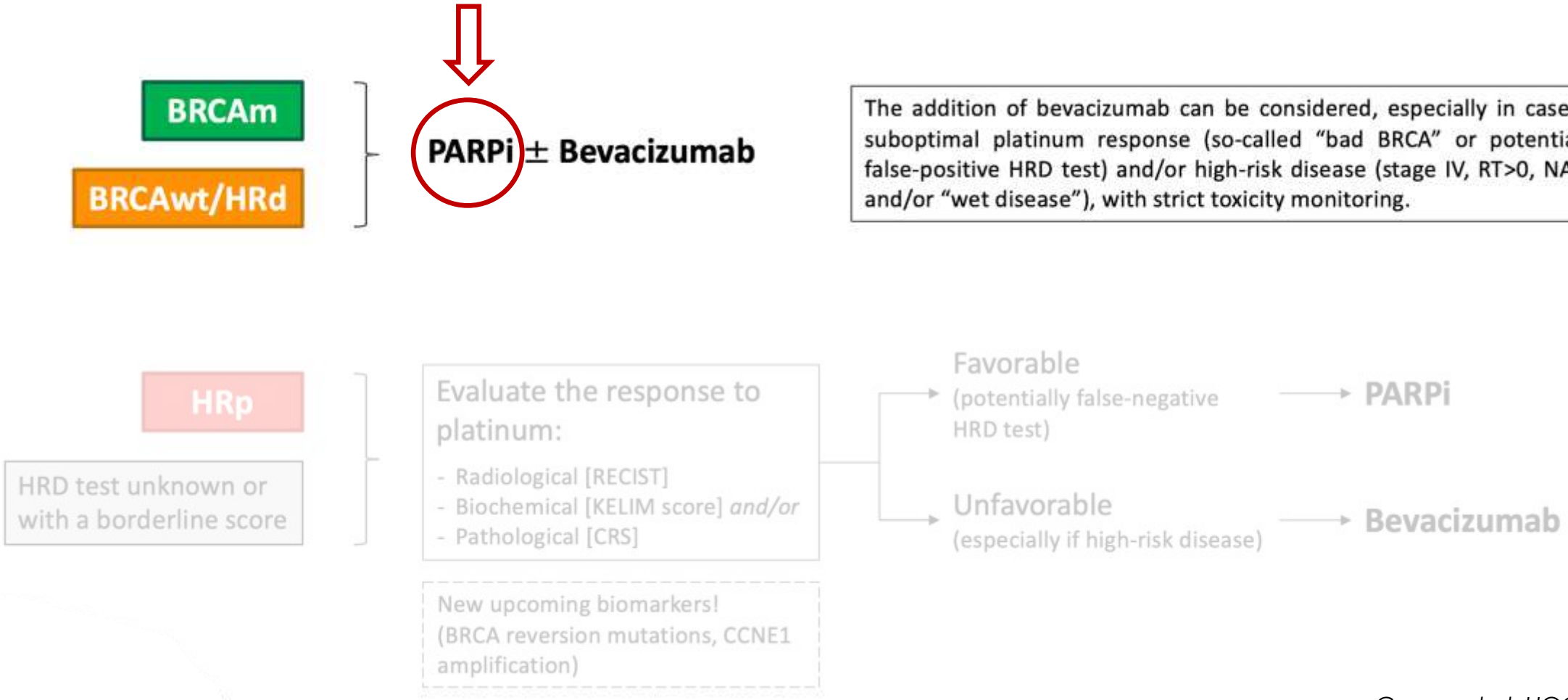
1. **Bevacizumab alone**
2. **Bevacizumab + PARPi**
3. **PARPi alone**
4. **Observation**

RECAP

- 76 yr, hypertension, obesity
- HGSOC, BRCAwt/HRD+
- Stage IIIC (no ascites or pleural effusion)
- Favorable KELIM score
- RT=0 after robotic IDS
- CRS 3

How to choose the best first-line maintenance option

Mutational status



Caruso et al. IJGC 2023

Mutational status and PARPi benefit

	SOLO-1[1]	PRIMA[2]	PAOLA-1[3]	ATHENA-MONO[4]	PRIME[5]
PARPi	Olaparib	Niraparib	Olaparib	Rucaparib	Niraparib
Bevacizumab	No	No	Yes	No	No
Population	BRCAmut	All comers	All comers	All comers	All comers (Chinese)
HRD test	NA	MyChoice	MyChoice	Foundation-One	BGI
BRCAmut	0.33 (0.25–0.43)	0.40* (0.27–0.62)	0.31* (0.20–0.47)	0.31* (0.20–0.47)	0.40* (0.23-0.68)
BRCAwt/HRD+	-	0.50* (0.31-0.83)	0.43* (0.28-0.66)	0.58* (0.33-1.01)	0.58* (0.36-0.93)
BRCAwt/HRD-	-	0.68* (0.49-0.94)	1.0* (0.75-1.36)	0.65* (0.45-0.95)	0.41* (0.25-0.65)

+++

++

+

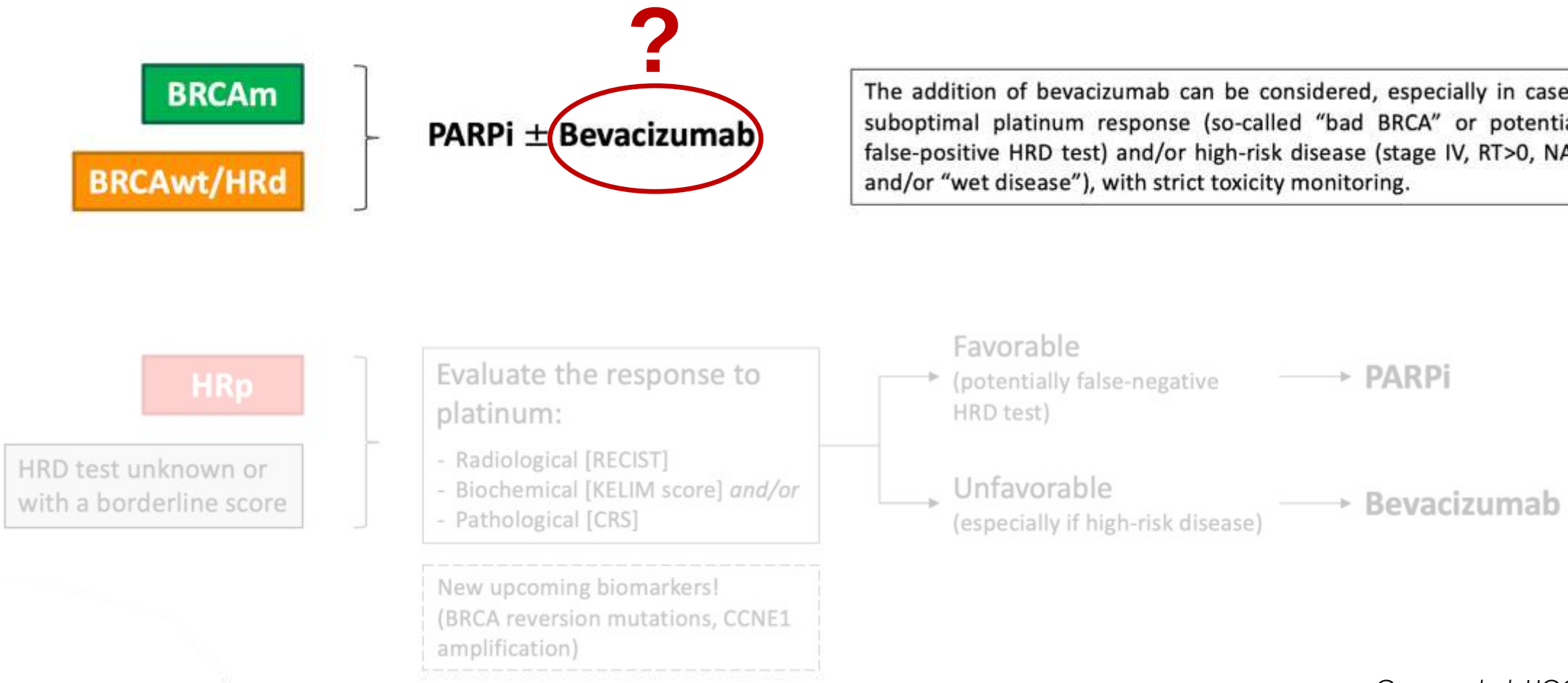
*exploratory

The aim of the table is not the cross-trial comparison

1. Moore. NEJM 2018; 2. Gonzalez-Martin. NEJM 20193; 3. Ray-Coquard. NEJM 2019; 4. Monk. J Clin Oncol 2022; 5. Li.SGO 2022

How to choose the best first-line maintenance option

Mutational status



Caruso et al. IJGC 2023

How to choose the best first-line maintenance option

Addition of bevacizumab?

The addition of bevacizumab can be considered, especially in case of suboptimal platinum response (so-called "bad BRCA" or potentially false-positive HRD test) and/or high-risk disease (stage IV, RT>0, NACT and/or "wet disease"), with strict toxicity monitoring.

Caruso et al. IJGC 2023

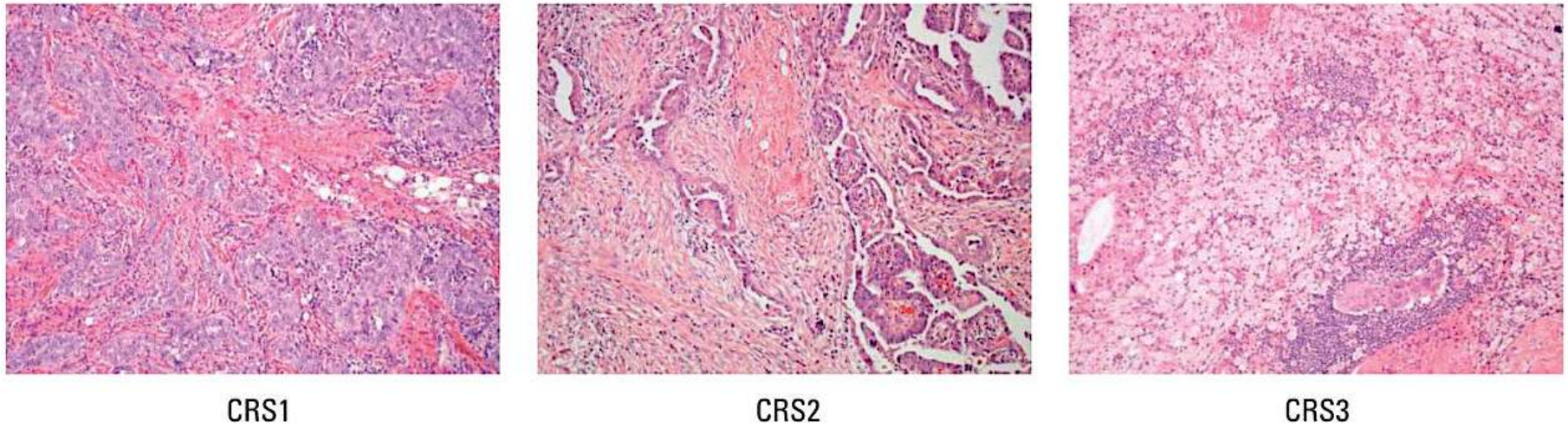
How to choose the best first-line maintenance option

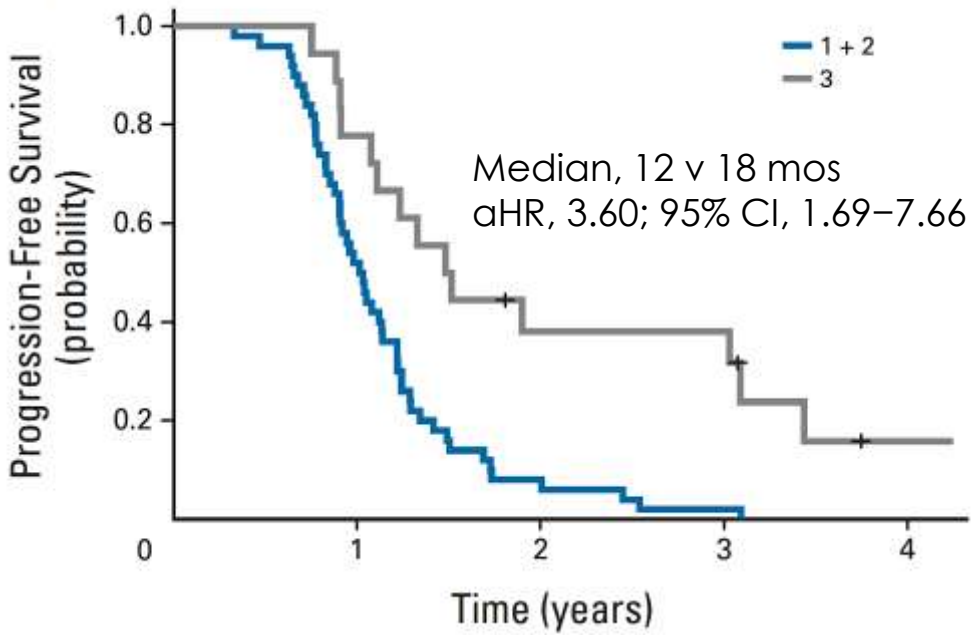
Response to platinum

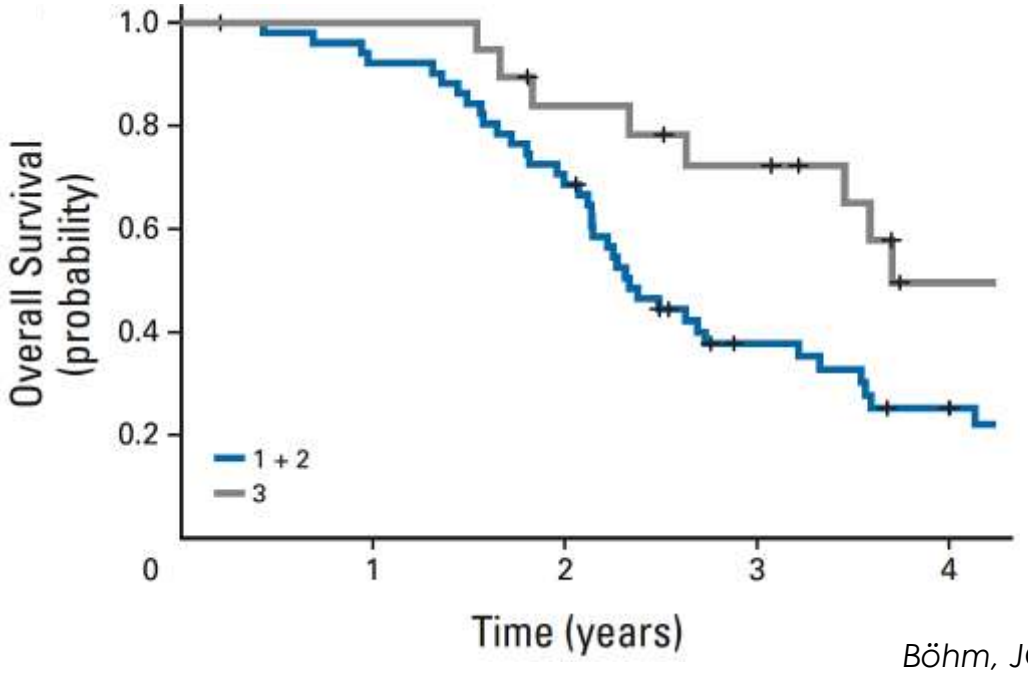
- **KELIM score** (if elevated CA125)
- **Residual tumor**
- **RECIST** (if measurable disease)
- **CRS (Böhm's score)** (if IDS)

CRS and platinum/PARPi benefit

- Omental samples
- Highly reproducible (*kappa, 0.67*)
- **CRS 3: 94.3% NPV for progression <6 months**







Böhm, JCO 2015

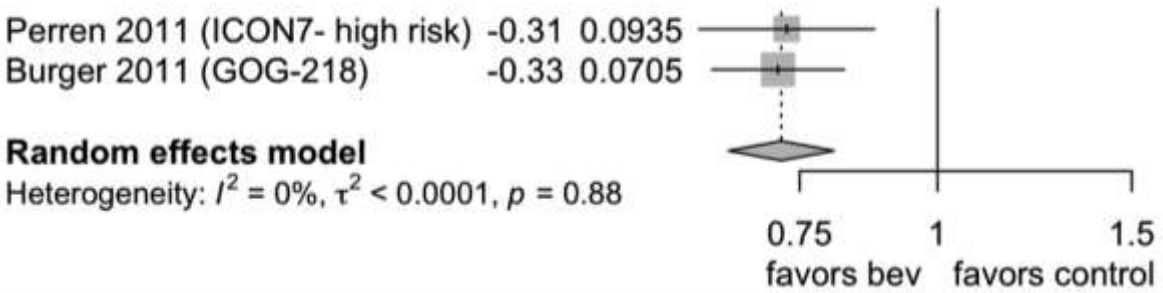
The use of bevacizumab in the modern era of targeted therapy for ovarian cancer: A systematic review and meta-analysis

2021

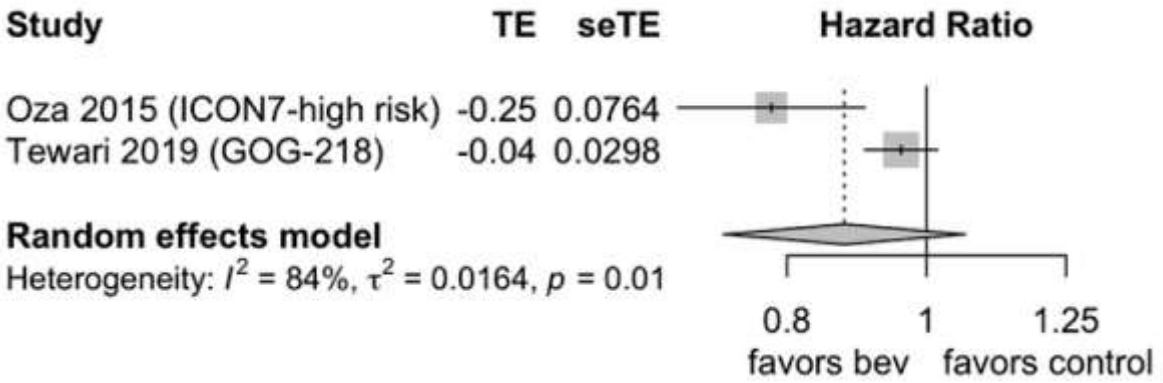
Shiru Liu [a,1], Lawrence Kasherman [a], Rouhi Fazelzad [b], Lisa Wang [c], Genevieve Bouchard-Fortier [d], Stephanie Lheureux [a], Monika K. Krzyzanowska [e,*]

3,401 pts

PFS



OS



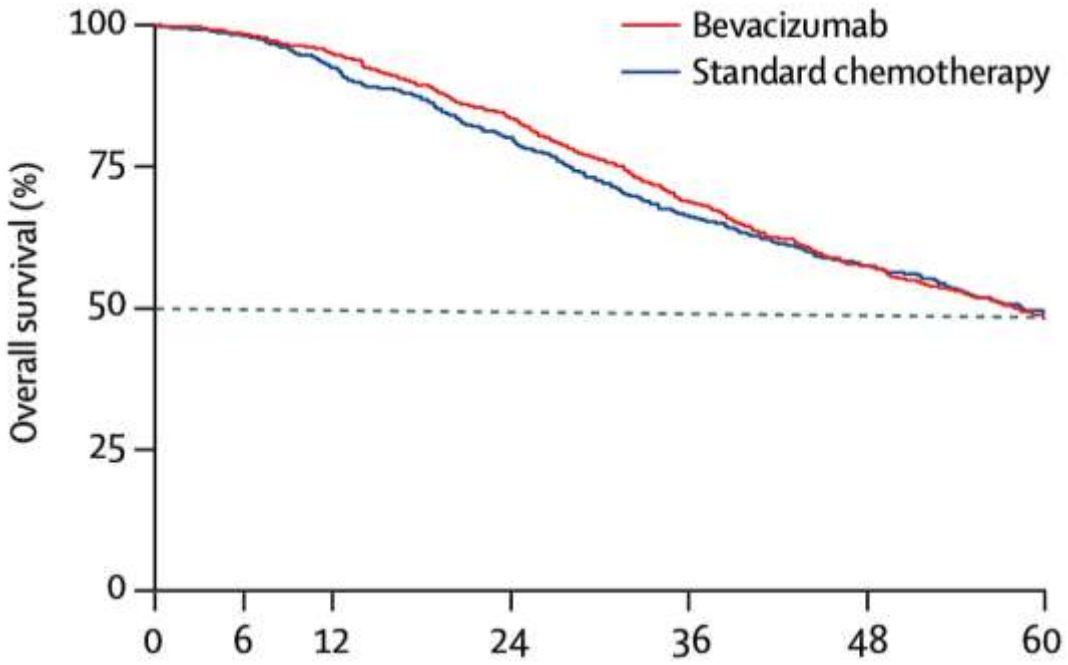
Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial

THE LANCET Oncology

pharma &

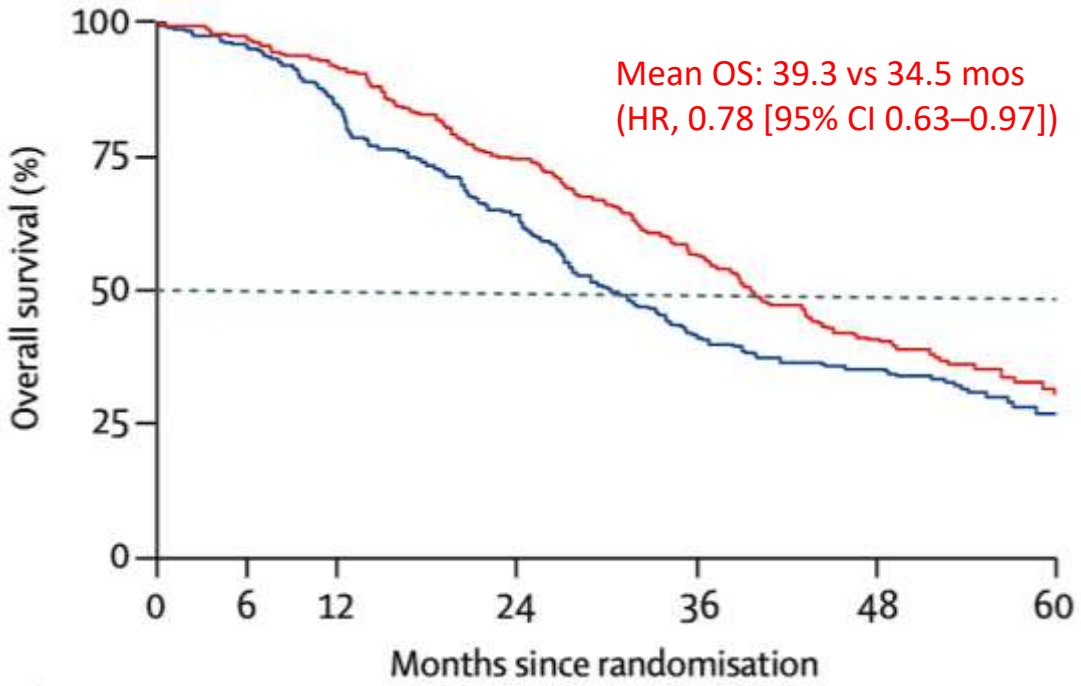
Oza et al., 2015

All patients 1528 pts



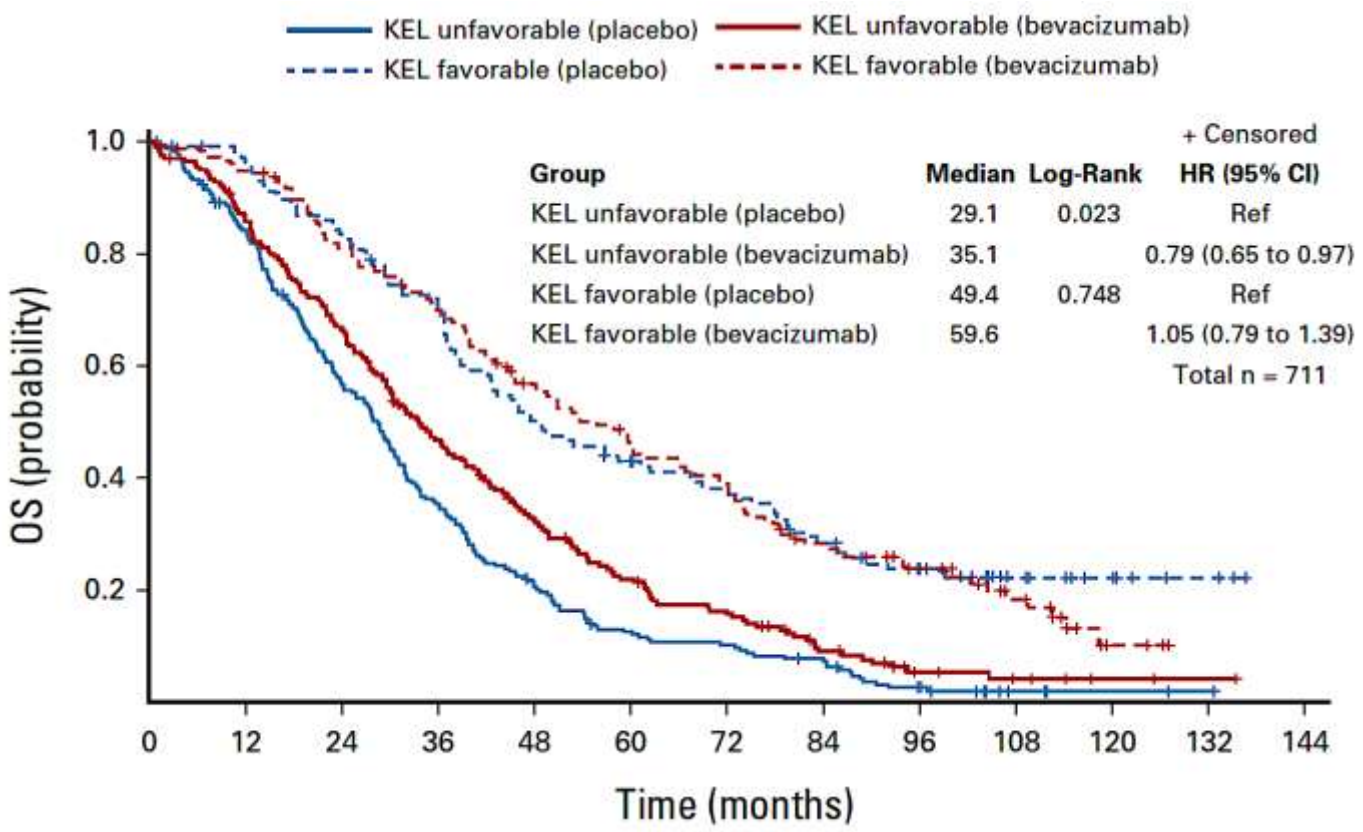
Exploratory analysis in high-risk patients

(stage IV, inoperable, or RT >1 cm)



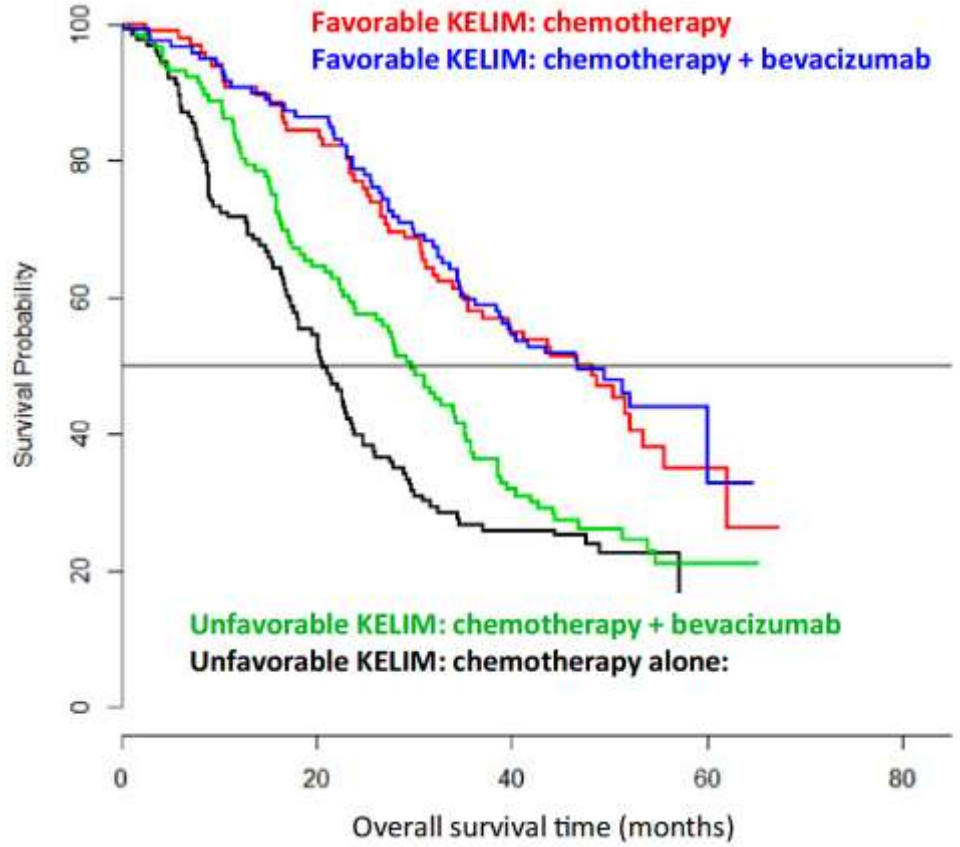
KELIM score and Bevacizumab benefit

GOG-0218



You, JCO 2022

ICON-7

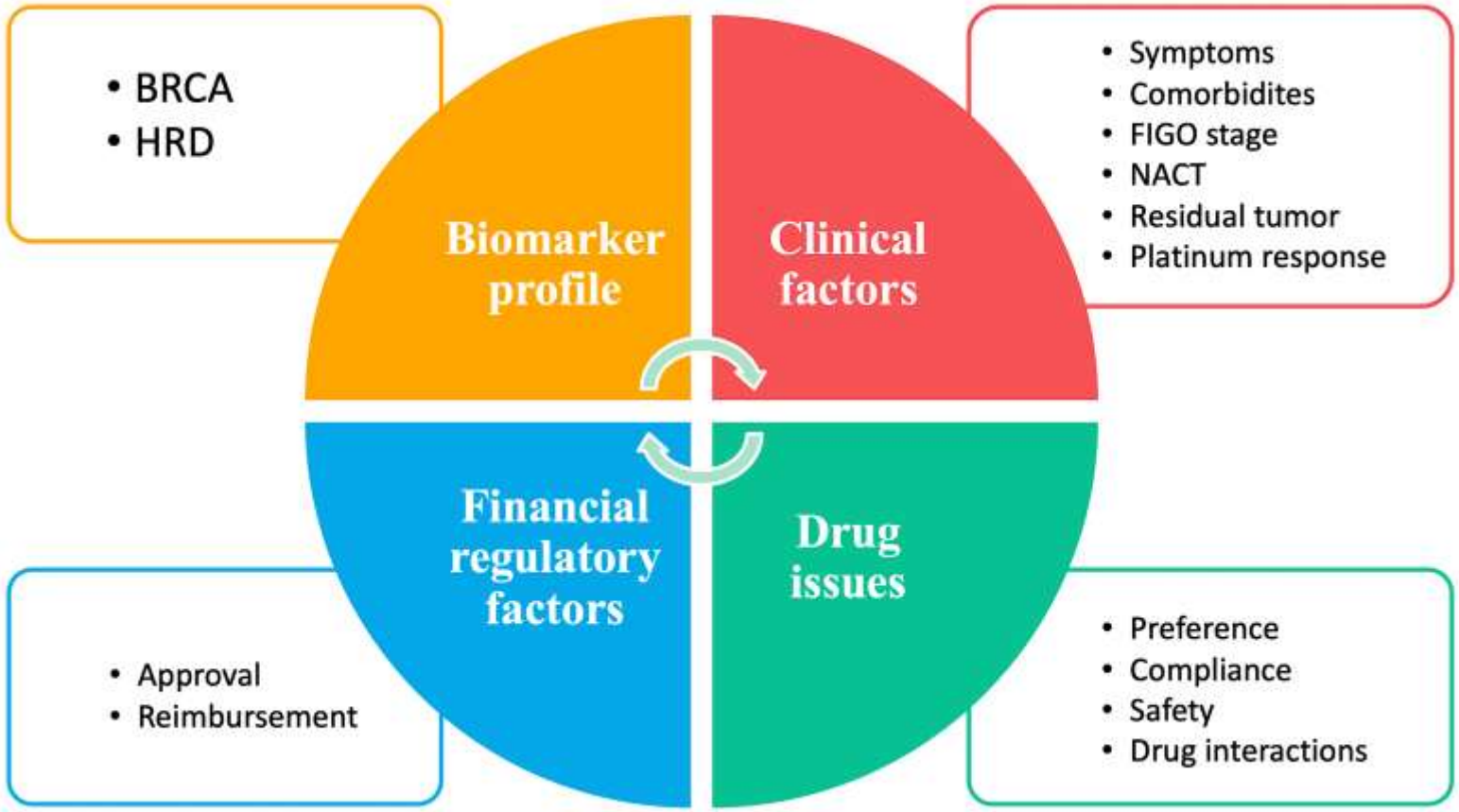


Colomban, JNCI 2020

Bevacizumab should be prioritized in high-risk patients with poorly chemosensitive disease

How to choose the most effective first-line maintenance option

Several other factors



Caruso et al. IJGC 2023

Safety profile across first-line maintenance trials:
Summary

	SOLO1[1]		PRIMA[2]		ATHENA-MONO[3]		PAOLA-1[4]	
	Olaparib	Placebo	Niraparib	Placebo	Rucaparib	Placebo	Bevacizumab + olaparib	Bevacizumab + placebo
n	260	130	484	244	185	49	535	267
AE leading to								
Dose reduction	28.8%	3.1%	71.7%	10.2%	49.4%	8.2%	41%	7%
Dose interruption	**52.7**%	16.9%	**80.8**%	23.0%	**60.7**%	20.0%	**54**%	24%
Discontinuation	11.9%	3.1%	16.0%	3.7%	11.8%	5.5%	20%	6%
Grade ≥3 AEs	39.6%	20%	70.5%	18.9%	60.5%	22.7%	57%	51%

Rate of treatment discontinuations was higher in PAOLA-1 than in PRIMA, SOLO1, and ATHENA-MONO

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended. **Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.** AE, adverse event 1. Di Silvestro P, et al. *J Clin Oncol* 2022. doi: https://ascopubs.org/doi/full/10.1200/JCO.22.01549 [Epub ahead of print]; 2. Gonzalez-Martin A, et al. *N Engl J Med* 2019;381:2391–2402; 3. Monk JM, et al. *J Clin Oncol* 2022. doi: http://ascopubs.org/doi/full/10.1200/JCO.22.01003 [Epub ahead of print]; 4. Ray-Coquard IL, et al. Presented at European Society for Medical Oncology Congress; 27th September – 1st October 2019; Barcelona, Spain; abstract LBA2, Gonzalez-Martin A, et al. ESMO 2024

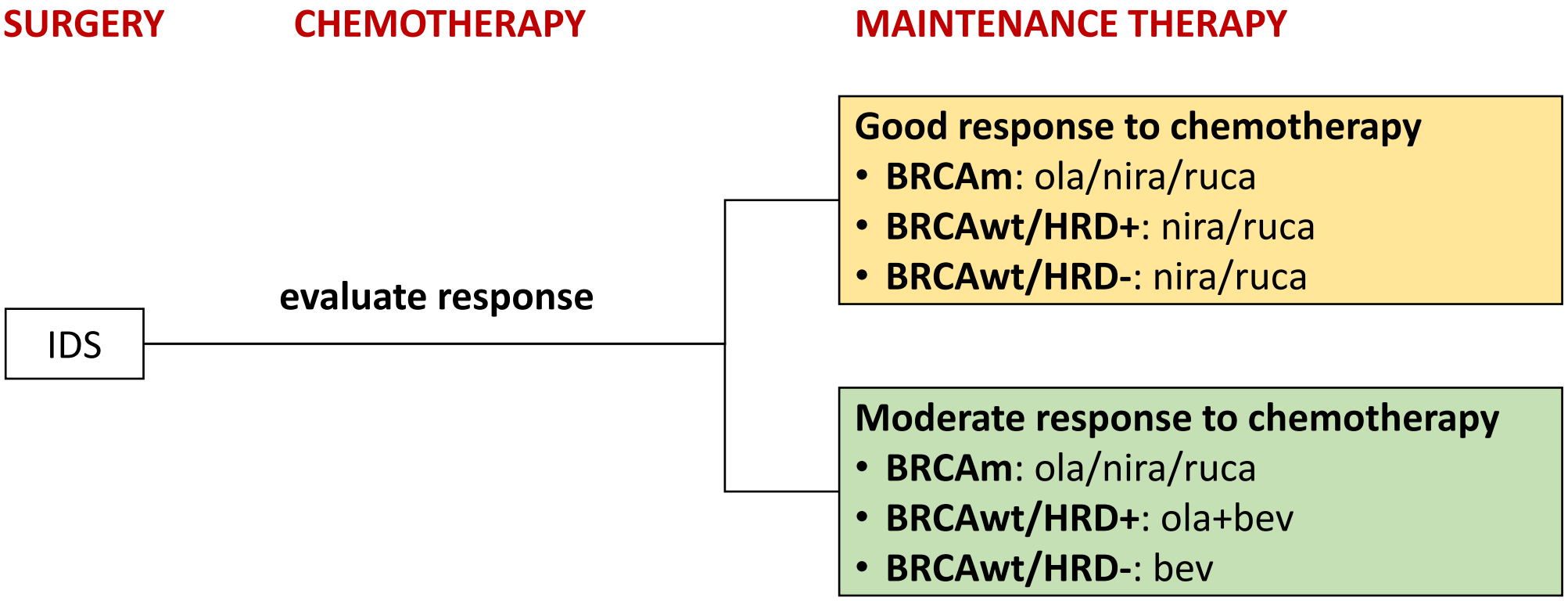
How to evaluate platinum response (after NACT-IDS)

Pathology (CRS)	KELIM	Surgical outcome
1 = Partial (CRS 2)	0 = KELIM < 1	0 = Residual tumor
3 = Near-complete/complete (CRS 3)	1 = KELIM ≥ 1	1 = No residual tumor

Interpretation of total scores	
Total score	Response definition
< 3	Moderate
≥ 3	Good

Adapted from *Colombo N, Gyn Oncol 2023*

THERAPEUTIC ALGORITHM



Adapted from *Colombo N, Gyn Oncol 2023*

Question n. 2

Which PARPi would you choose for this patient?

1. Olaparib
2. Niraparib
3. Rucaparib

RECAP

- 76 yr, hypertension, obesity
- BRCAwt/HRD+
- Stage IIIC with RT=0 after IDS
- Hematological toxicity (w/ thrombocytopenia) during CHT

Incidence of main PARPi-related AEs

Any-grade

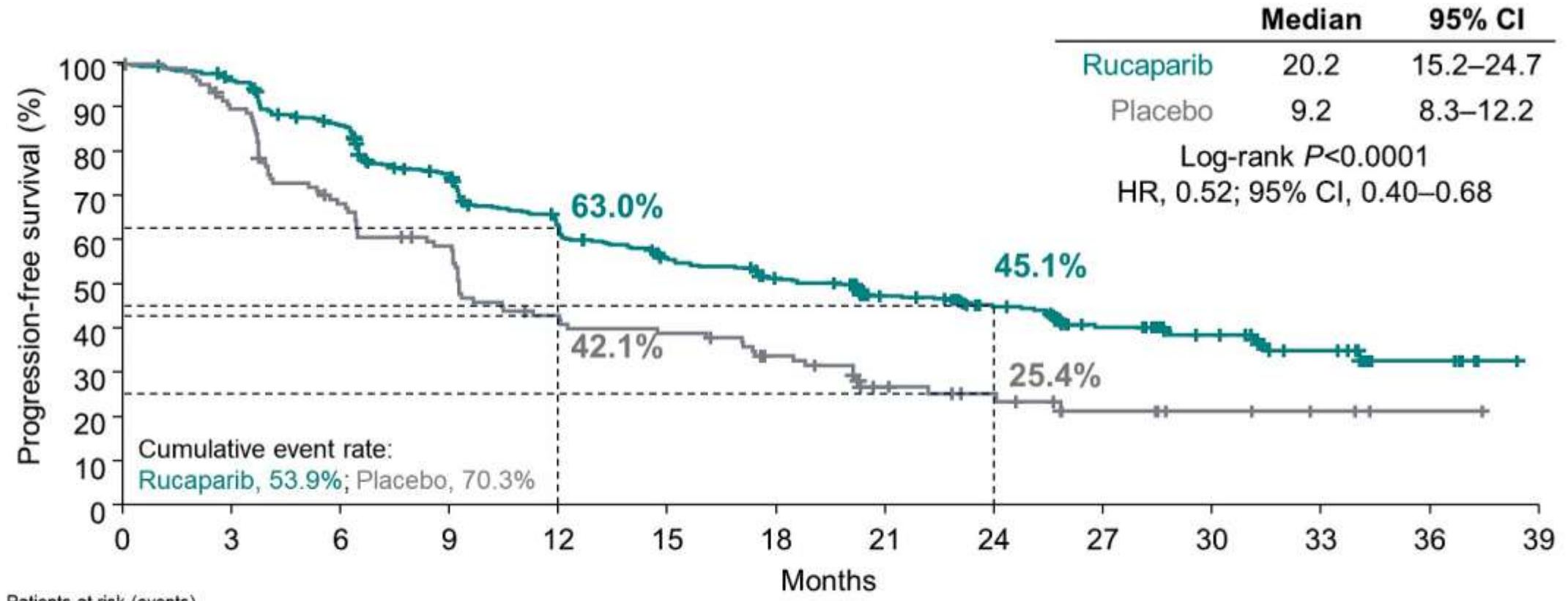
	SOLO1	PRIMA	PAOLA-1	ATHENA
Anemia	39%	63.4%	41%	46.6%
Neutropenia	23%	26.4%	18%	27.8%
Thrombocytopenia	11%	**45.9%**	8%	23.8%
Hypertension	-	**16.9%**	**46%**	-

Grade 3-4

	SOLO1	PRIMA	PAOLA-1	ATHENA
Anemia	22%	31%	17%	28.7%
Neutropenia	9%	12.8%	6%	14.6%
Thrombocytopenia	1%	**28.7%**	2%	7.1%
Hypertension	-	**6%**	**19%**	-

Adapted from: Friedlander M, Lee YC, Tew WP. Am Soc Clin Oncol Educ Book. 2023 Jun;43:e390876.

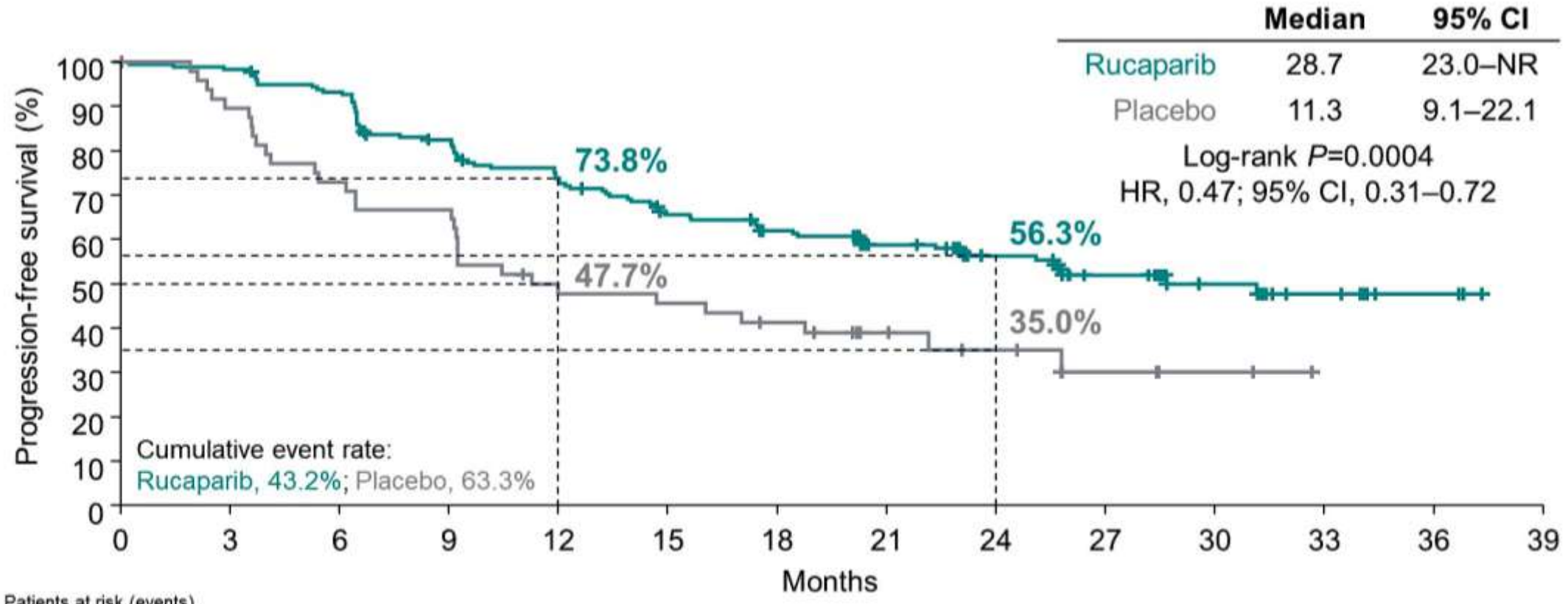
ATHENA-MONO: Primary Endpoint – PFS in the ITT population



Data cutoff date: March 23, 2022.
HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Monk B., ASCO 2022

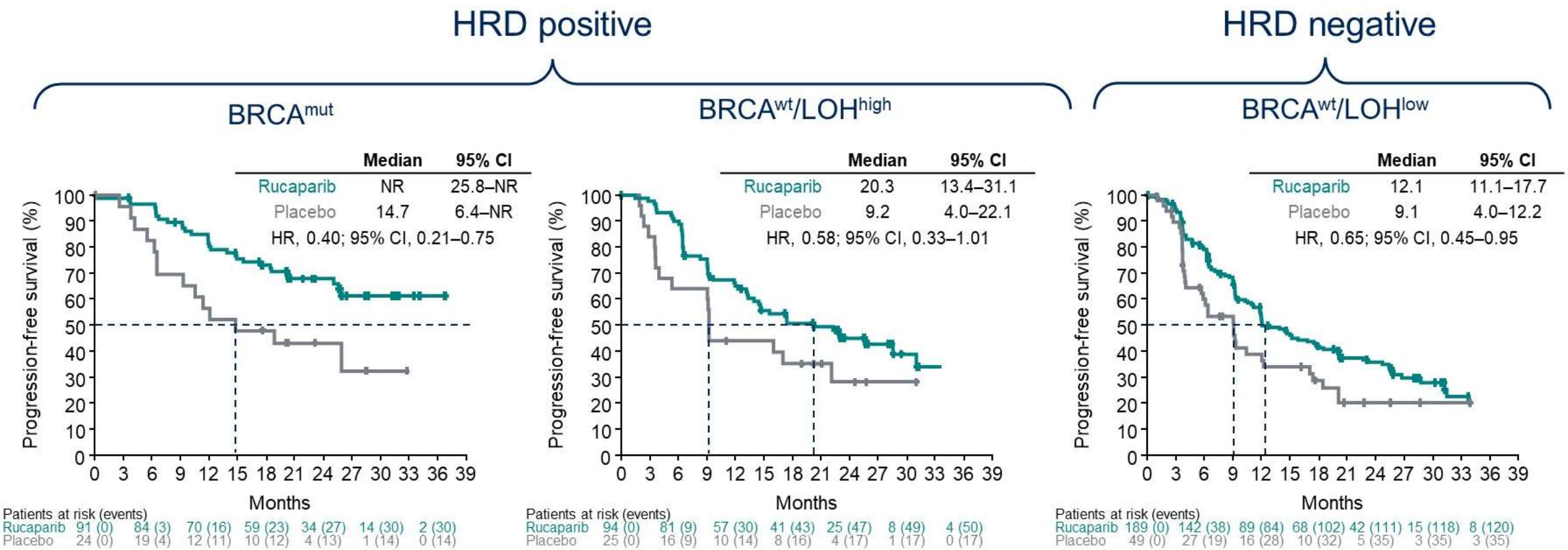
ATHENA-MONO: Primary Endpoint – PFS in the HRD+ population



Data cutoff date: March 23, 2022.
HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; PFS, progression-free survival.

Monk B., ASCO 2022

ATHENA-MONO: Primary Endpoint – subgroup analyses



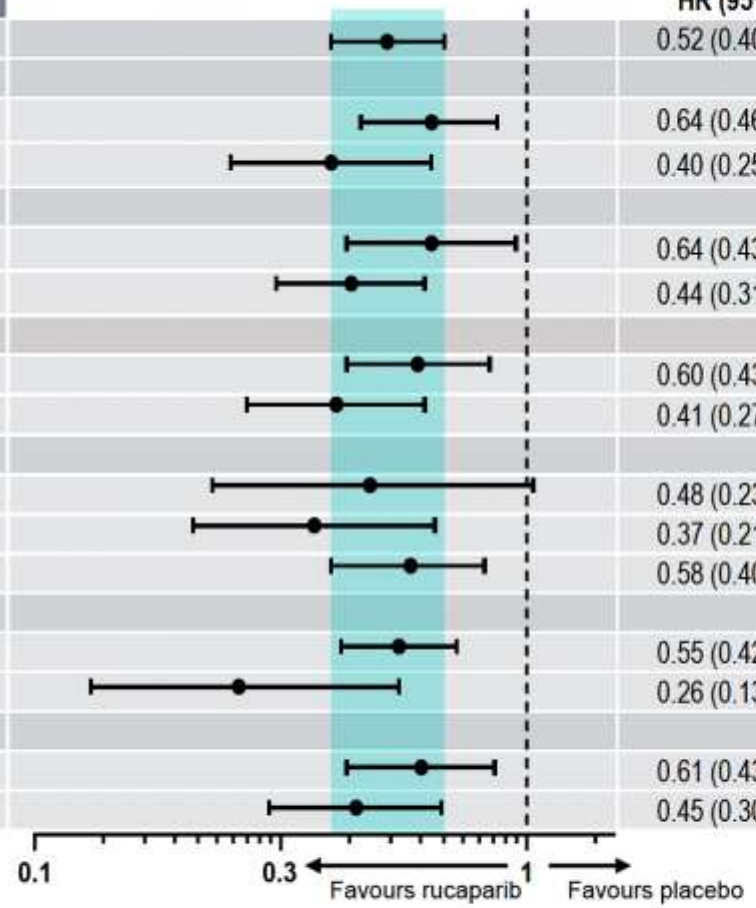
- Rucaparib demonstrated treatment benefit vs placebo regardless of BRCA mutation and HRD status

Data cutoff date: March 23, 2022.
BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; mut, mutant; NR, not reached; PFS, progression-free survival; wt, wild type.

Monk B., ASCO 2022

PFS in the ITT Population by Subgroup

	Rucaparib (n/N)	Placebo (n/N)	HR (95% CI)	Median (95% CI) Rucaparib	Median (95% CI) Placebo
ITT Population	230/427	78/111	0.52 (0.40–0.68)	20.2 (15.2–24.7)	9.2 (8.3–12.2)
FIGO stage, n (%)					
III	170/323	51/78	0.64 (0.46–0.87)	20.3 (15.6–25.6)	10.4 (9.1–20.1)
IV	59/104	27/33	0.40 (0.25–0.64)	17.5 (11.9–25.8)	6.4 (3.8–11.3)
Timing of surgery					
Primary surgery	94/209	33/54	0.64 (0.43–0.95)	28.8 (20.2–NR)	18.4 (9.3–25.8)
Interval debulking	136/218	45/57	0.44 (0.31–0.62)	14.5 (11.9–19.7)	8.3 (4.1–9.2)
Cytoreductive surgery outcome					
R0	127/263	47/73	0.60 (0.43–0.84)	25.1 (18.6–31.3)	12.0 (9.1–20.1)
Non-R0*	103/164	31/38	0.41 (0.27–0.62)	13.9 (10.3–17.8)	6.4 (3.7–9.2)
First-line chemotherapy response					
Complete response	44/73	8/11	0.48 (0.23–1.03)	15.6 (10.2–25.8)	6.4 (2.7–NR)
Partial response	51/76	18/22	0.37 (0.21–0.65)	12.2 (9.2–19.7)	6.4 (3.7–9.2)
No disease after surgery†	107/224	42/64	0.58 (0.40–0.82)	25.4 (18.1–31.5)	12.0 (9.1–20.1)
CA-125 at baseline					
Normal	187/371	68/100	0.55 (0.42–0.72)	23.2 (18.1–26.8)	10.4 (9.1–17.1)
Above normal	43/56	10/11	0.26 (0.13–0.55)	9.3 (6.3–12.1)	3.6 (2.1–6.1)
Disease free with normal CA-125					
Yes	132/270	44/69	0.61 (0.43–0.86)	25.1 (18.6–31.1)	16.0 (9.2–20.3)
No	98/157	34/42	0.45 (0.30–0.67)	12.2 (9.3–18.4)	6.4 (4.0–9.2)

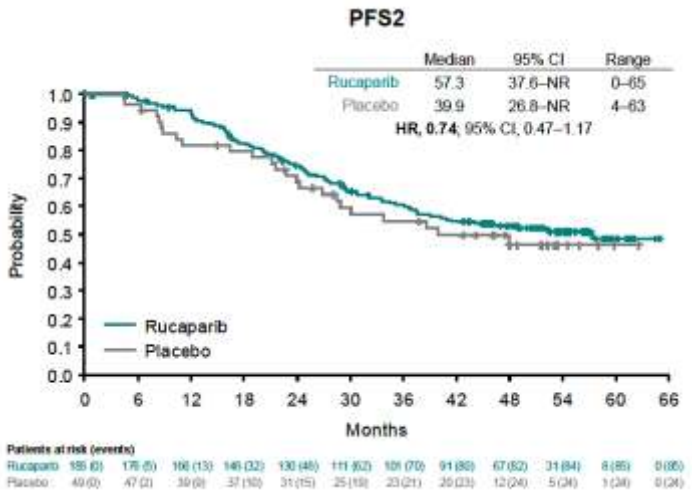


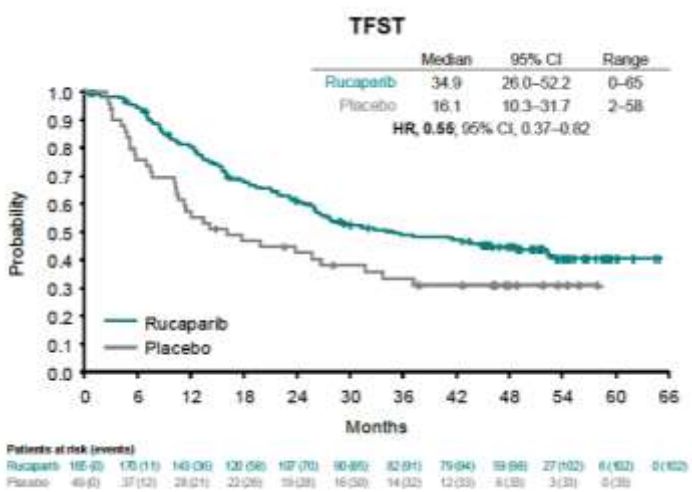
- Safety was similar between subgroups analysed

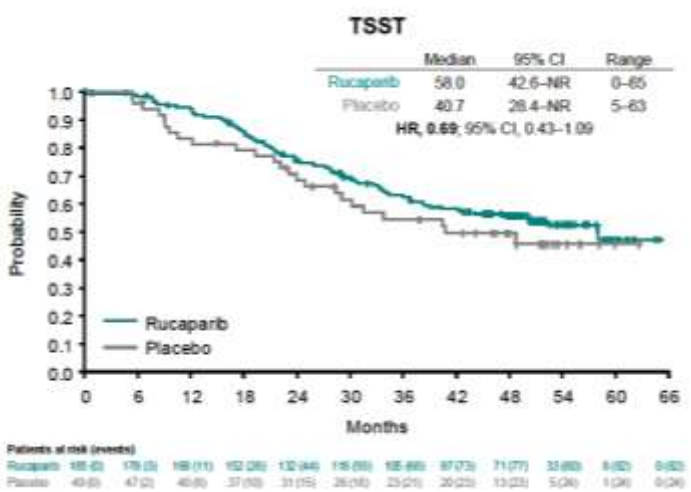
Data cutoff: 23 March 2022.
*Includes microscopic residual (<1 cm) and macroscopic residual (≥1 cm) disease.
†Surgical outcome of R0 and no disease on the screening scan.
CA-125, cancer antigen 125; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.

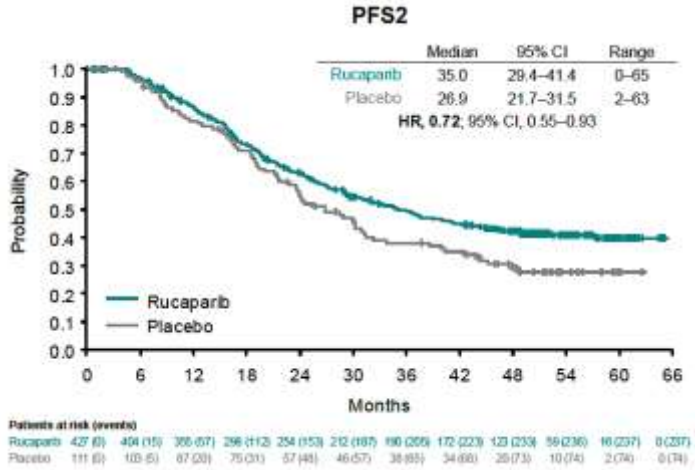
ATHENA-MONO Post-Progression Survival Data Update

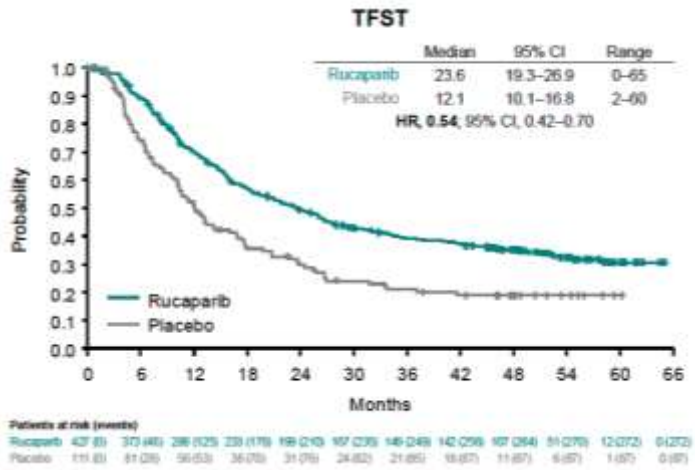
Kaplan-Meier Plots of PFS2, TFST, and TSST in the HRD and ITT Population

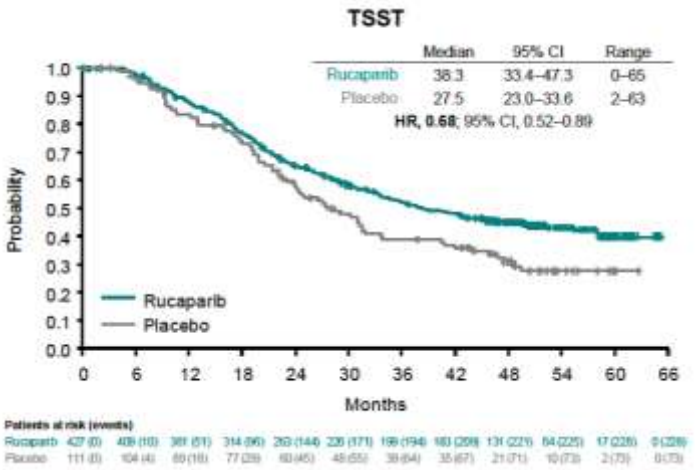












Ghamande, ESGO 2025

Rucaparib as 1L maintenance therapy: 3 clinical cases

pharma &

BRCAm

BRCAwt / HRD+

HRD-

FRANCESCA, 70 yrs

1L treatment | Maintenance | Toxicity

Family Cancer History
• None

Comorbidities
• Hypertension • Recurrent epistaxis

Jan 2025

- Diagnosis of HGSOC, FIGO stage IIIBr, BRCAwt/HRD-
- No ascites or pleural effusion
- CA125 = 688 KU/L
- Primary cytoreductive surgery (open) – **RT = 0**

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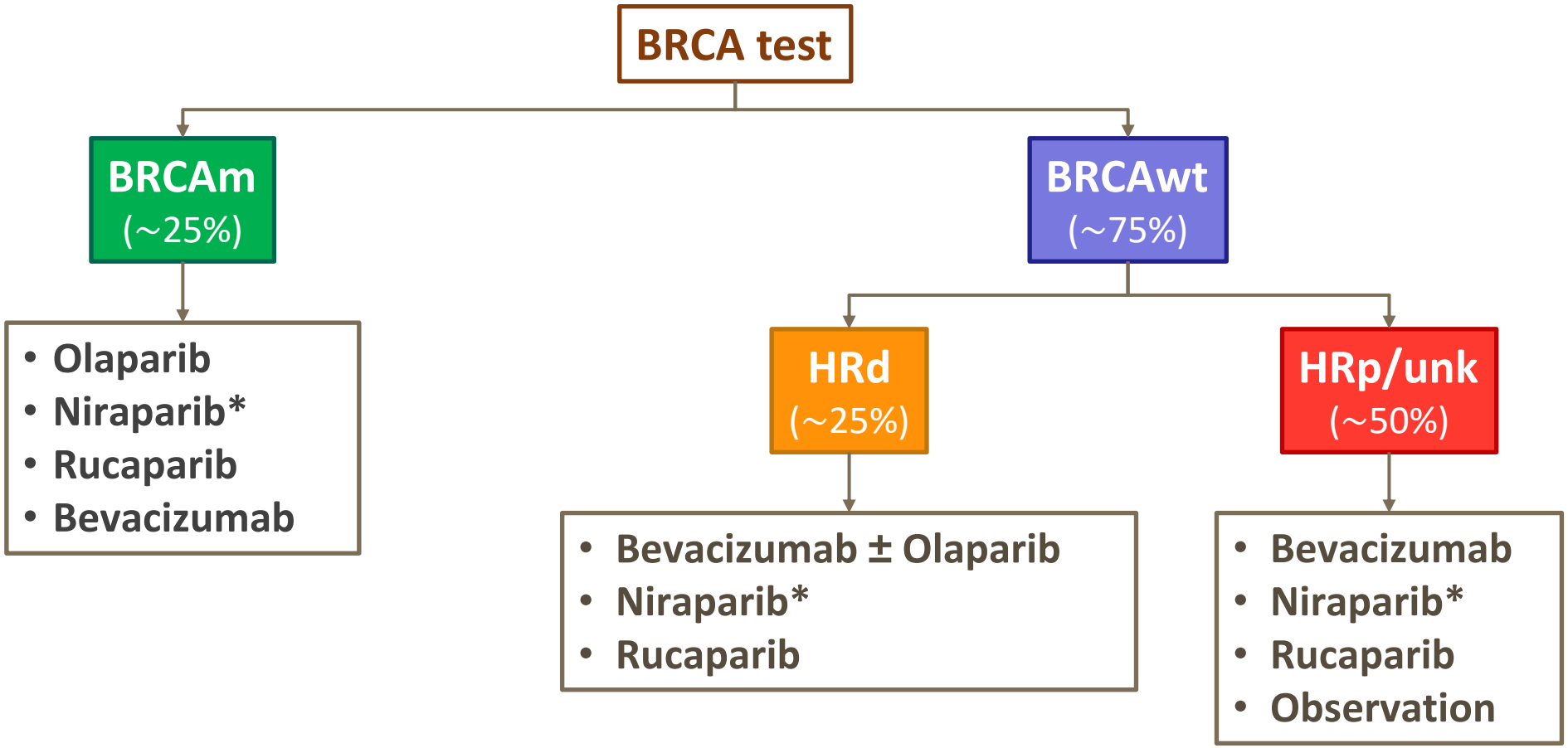
FIRST-LINE MAINTENANCE THERAPY: STATE OF THE ART



*Niraparib is not reimbursed for stage III disease with RT=0 after PDS

Adapted from *Caruso et al. IJGC 2023*

Question n. 1

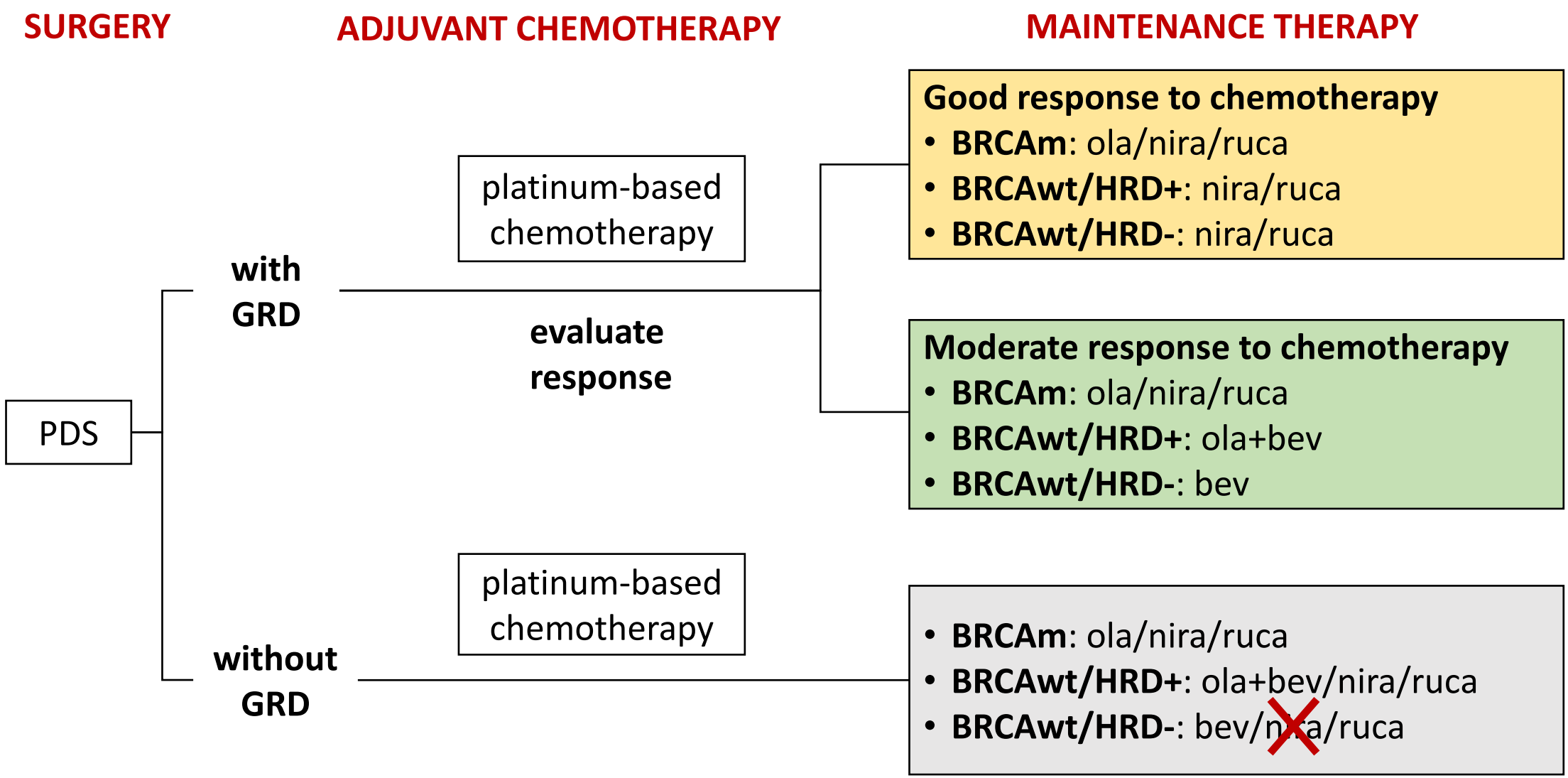
Which maintenance therapy option would you choose for this patient?

1. **Bevacizumab**
2. **Niraparib**
3. **Rucaparib**
4. **Observation**

RECAP

- 70 yr, hypertension, recurrent epistaxis
- HGSOC, BRCAwt/HRD-
- Stage IIIB (no ascites or pleural effusion)
- RT=0 after PDS

THERAPEUTIC ALGORITHM

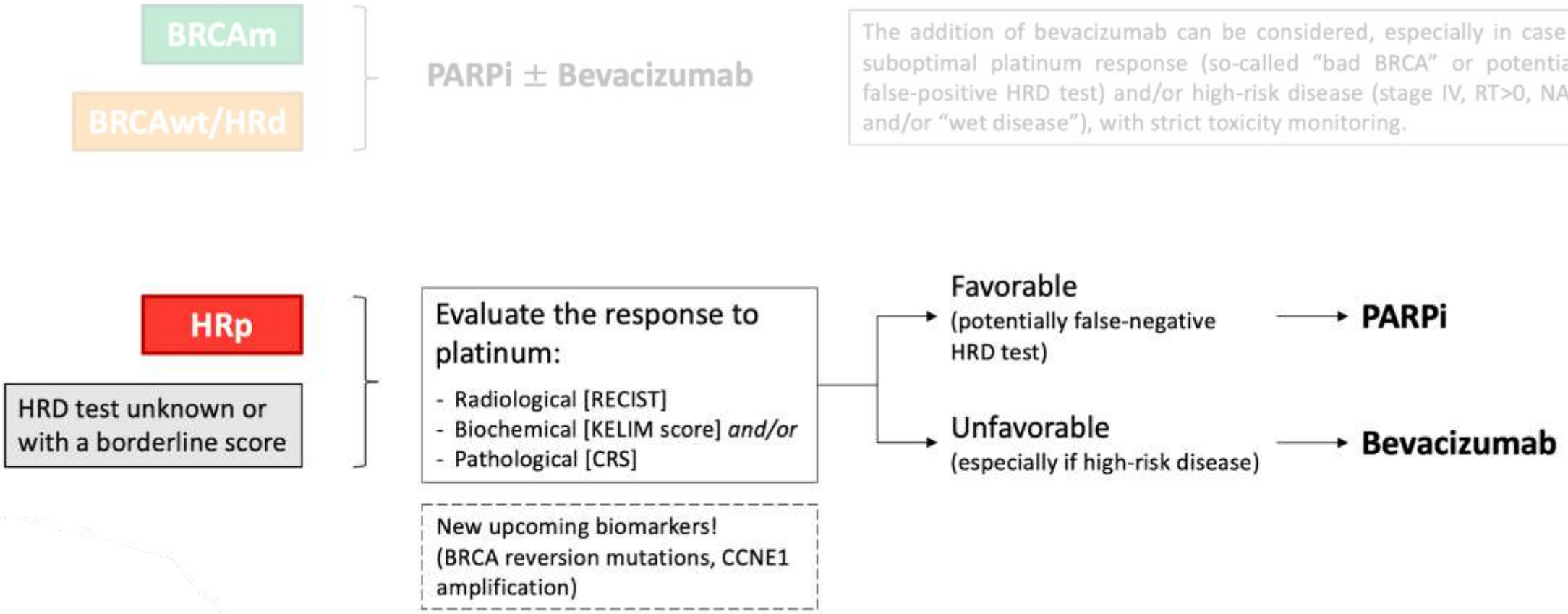


Note: Niraparib is not reimbursed for stage III disease with RT=0 after PDS.

Adapted from *Colombo N, Gyn Oncol 2023*

How to choose the best first-line maintenance option

Mutational status



Caruso et al. IJGC 2023

How to choose the best first-line maintenance option

PARPi or bevacizumab?

- **Platinum sensitivity? Not evaluable after PDS with RT=0**
- **Bevacizumab? PFS benefit, but not OS in the low-risk subpopulation**
- **PARPi benefit? PFS benefit regardless of *BRCA*/HRD status, but not OS**
- **PARPi: The earlier, the better...**

Why should PARPi be preferred upfront?

1. Updated PFS data of pivotal trials showed long-term benefit for all-comers

2. HRD test are not perfect

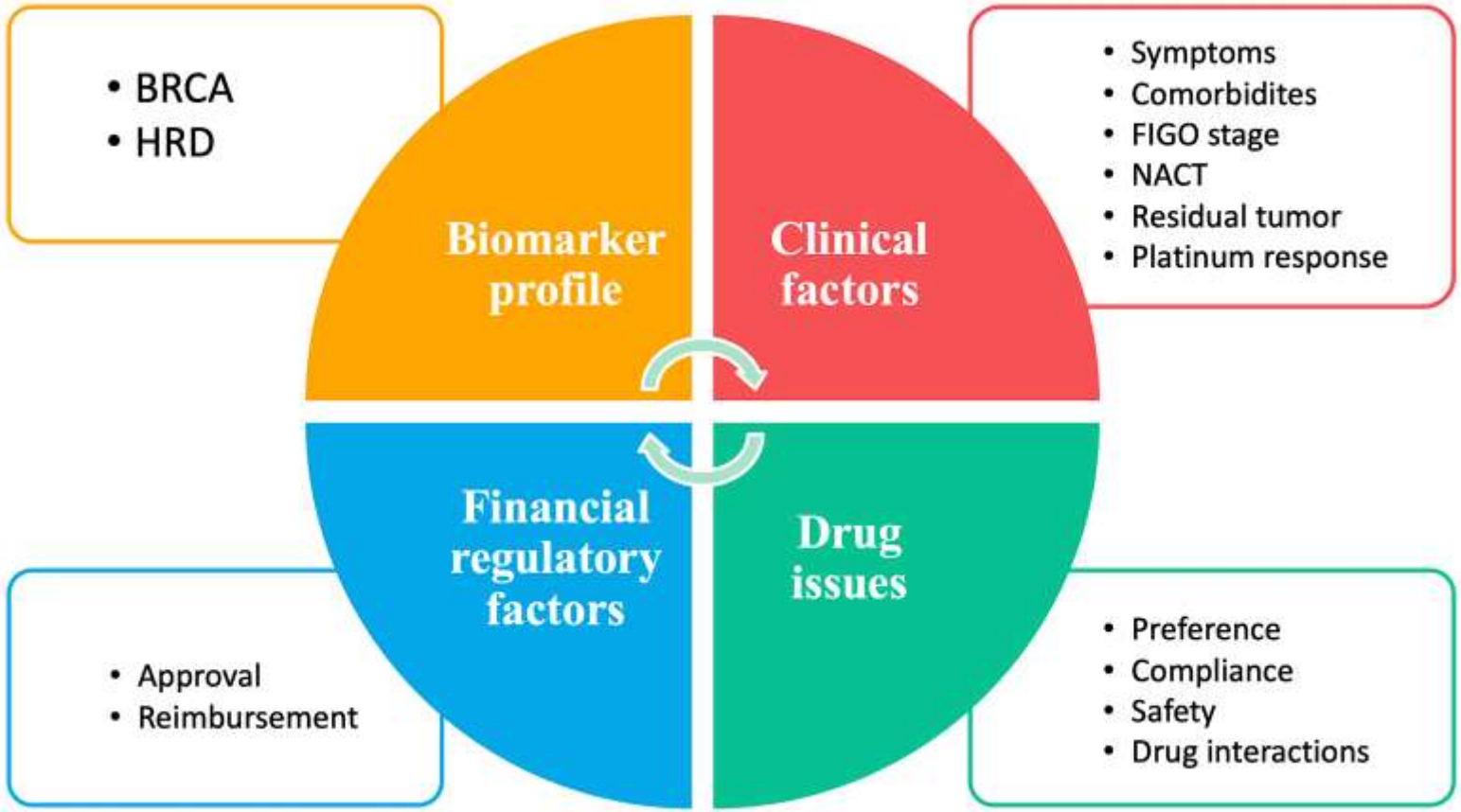
3. For up to 40% of patients, first line may represent the only opportunity to receive a PARPi

4. New OS data warranted caution in using PARPi in 2nd line for unselected (*BRCAwt*) patients

5. Reduced risk of developing secondary myeloid neoplasms

6. Advantages of oral administration route

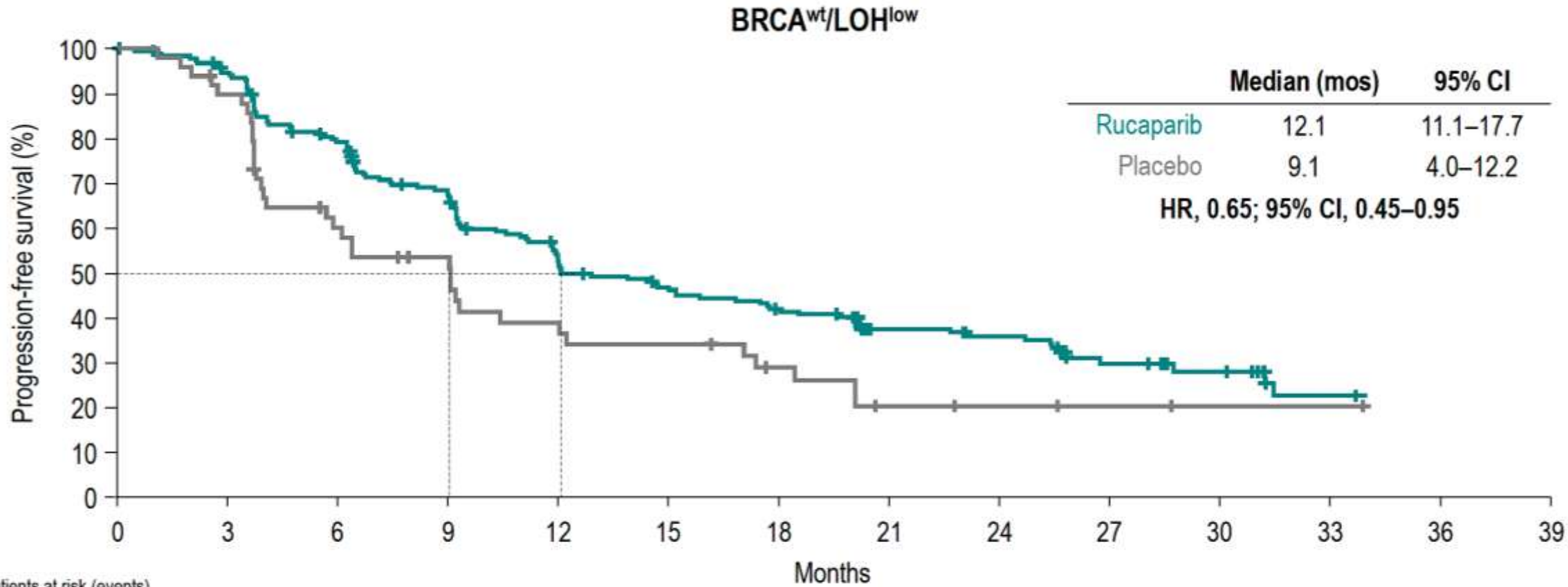
How to choose the best first-line maintenance option



Caruso et al. IJGC 2023

INVESTIGATOR-ASSESSED PFS[1]

ATHENA-MONO HRD-negative population



	Median (mos)	95% CI
Rucaparib	12.1	11.1–17.7
Placebo	9.1	4.0–12.2

HR, 0.65; 95% CI, 0.45–0.95

Patients at risk (events)

Rucaparib	189 (0)	142 (38)	89 (84)	68 (102)	42 (111)	15 (118)	8 (120)
Placebo	49 (0)	27 (19)	16 (28)	10 (32)	5 (35)	3 (35)	3 (35)

Data cutoff: 23 March 2022.
HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; BRCA^wt, wild-type *BRCA*; PFS, progression-free survival.

1. Monk BJ, et al. *J Clin Oncol*. 2022;40:3952-3964

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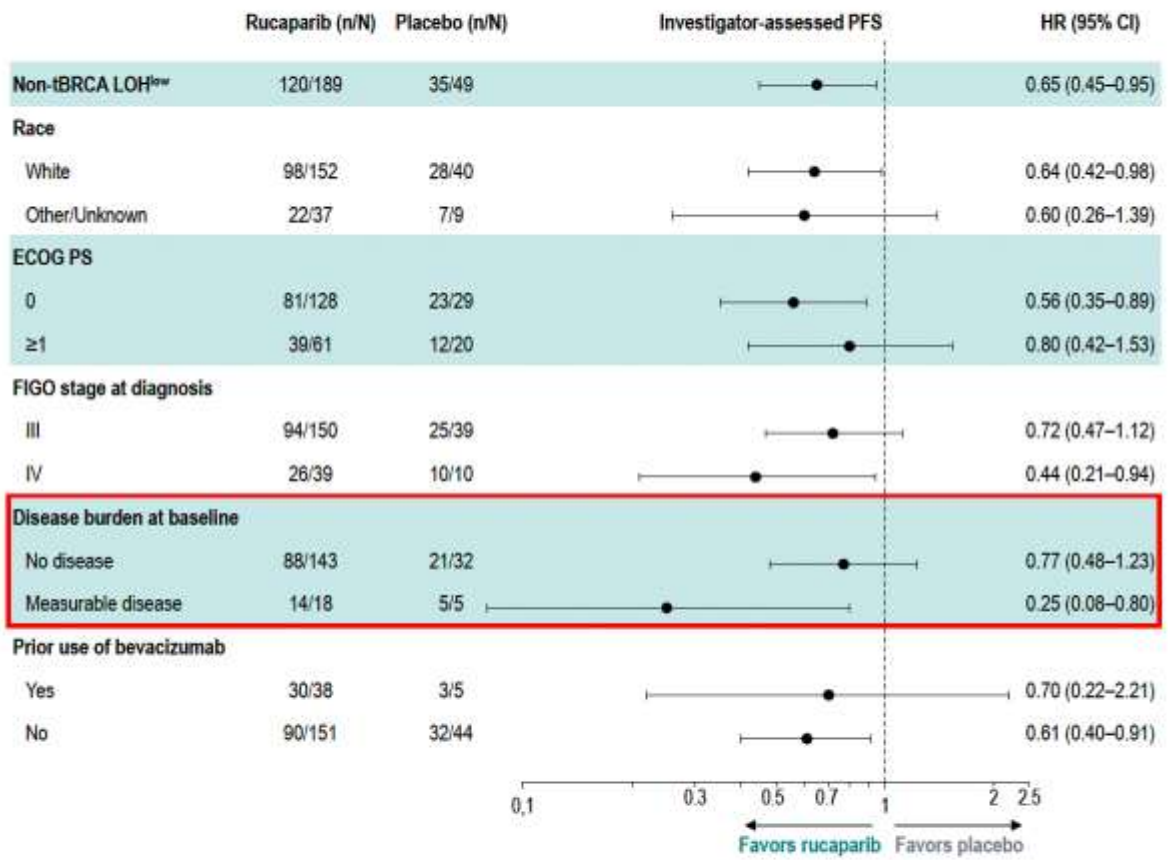
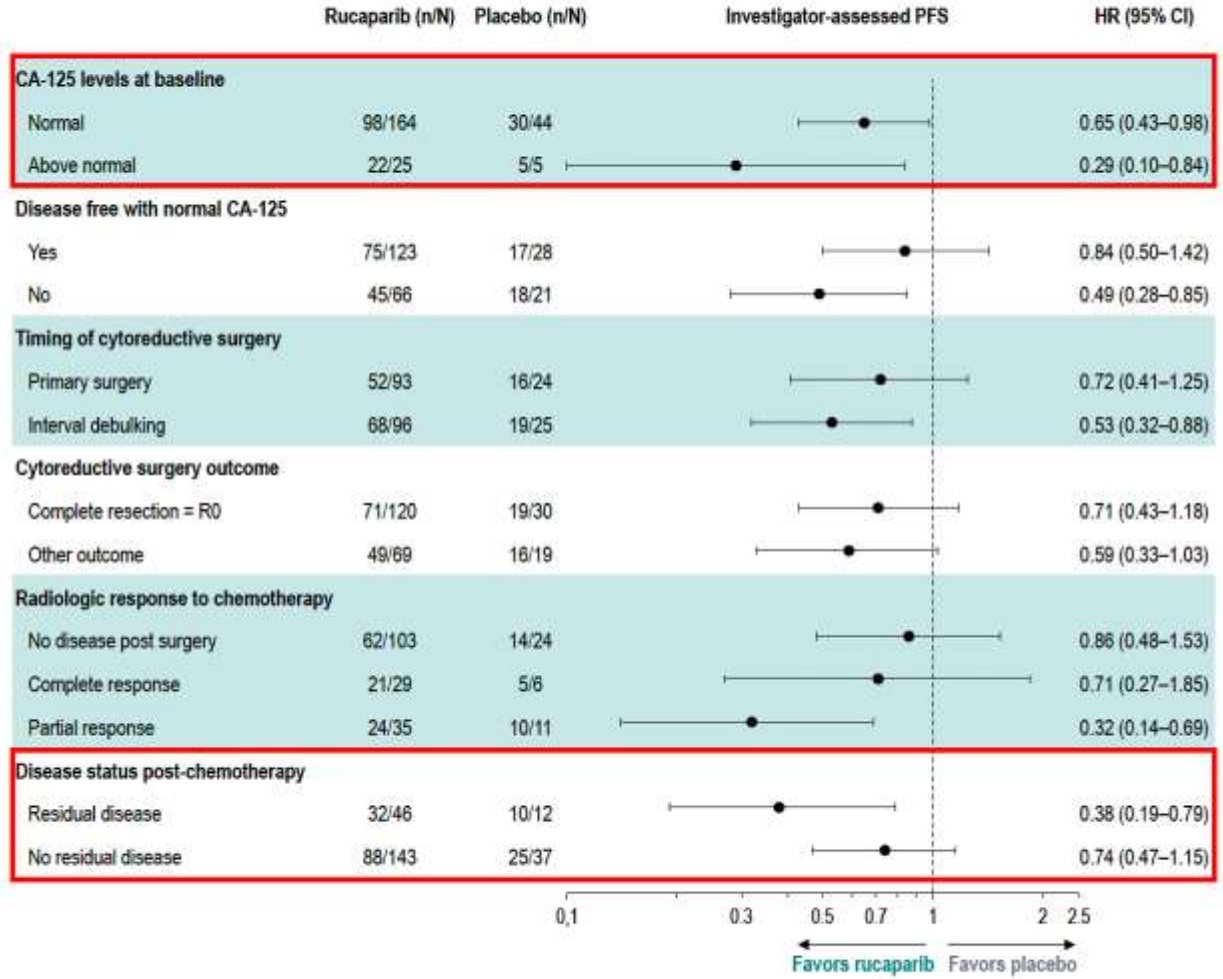
SUBGROUP ANALYSIS OF INVESTIGATOR-ASSESSED PFS

ATHENA-MONO HRD-negative population





Data cutoff: 23 March 2022.
CA-125, cancer antigen 125; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; non-tBRCA, wild-type *BRCA*; PFS, progression-free survival.

1. Monk BJ, et al. *J Clin Oncol*. 2022;40:3952-3964

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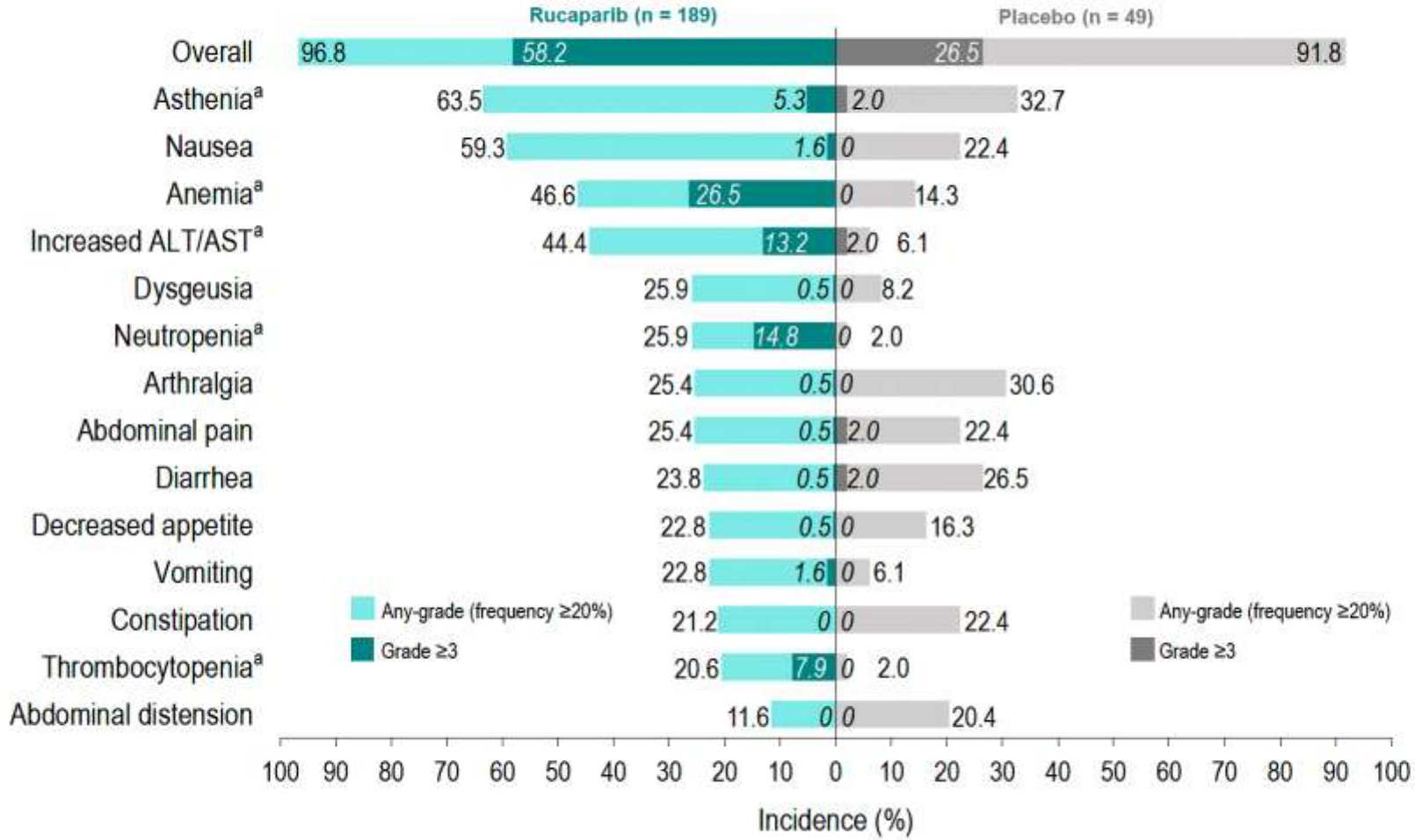
MOST COMMON TEAEs
ATHENA-MONO HRD-negative population



Data cutoff: 23 March 2022.
[a]Combined terms: asthenia or fatigue, anemia or hemoglobin decreased, ALT or AST, neutropenia or neutrophil count decreased, thrombocytopenia or platelet count decreased.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse events.

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