UPDATE SUGLI ALGORITMI DI TRATTAMENTO IN SEGUITO ALLE NUOVE INDICAZIONI EMA/FDA SULL'USO DEI PARPi

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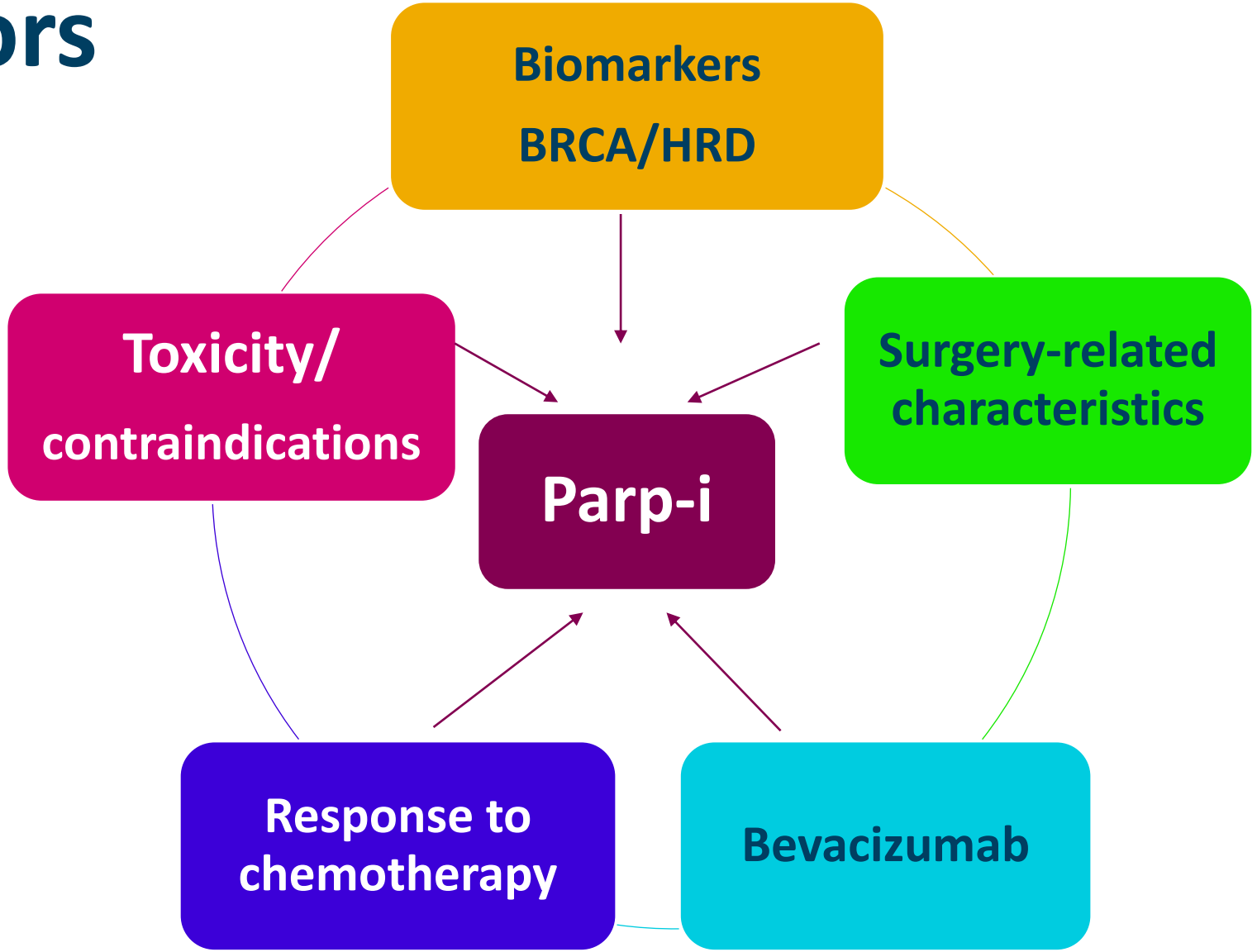
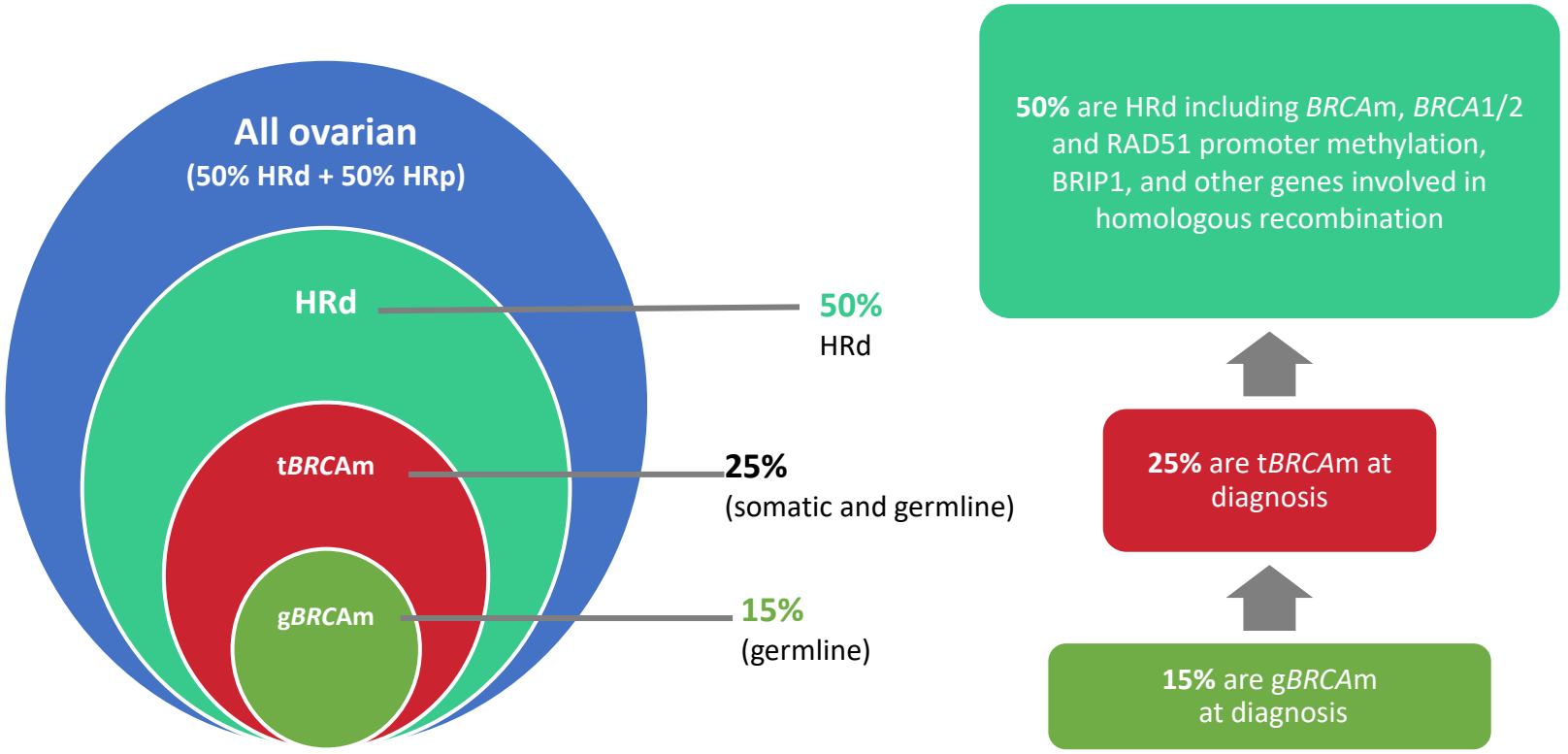
Key factors


Biomarkers
BRCA/HRD
Toxicity/
contraindications
Parp-i
Surgery-related
characteristics
Response to
chemotherapy
Bevacizumab

Exploiting Biomarker subgroups in high-grade serous ovarian cancer to optimise treatment

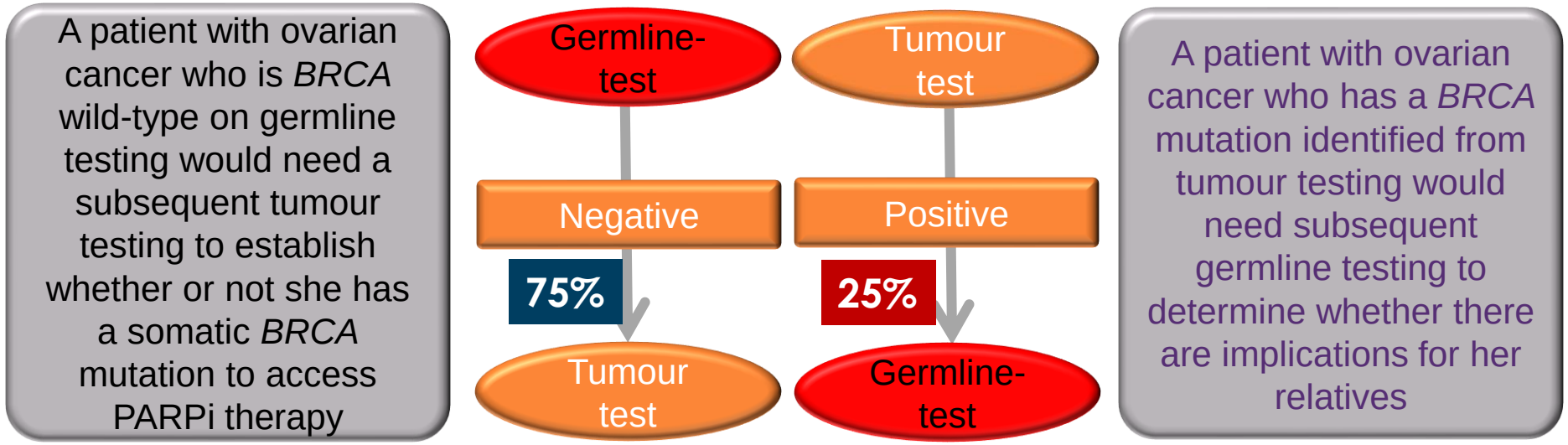
Half of high-grade serous ovarian cancer exhibit a high degree of genomic instability due to deficiencies in homologous recombination



BRCA, breast cancer gene; BRIP1, *BRCA*1-interacting protein; g*BRCA*, germline *BRCA* mutant; HR, homologous recombination deficient; OC, ovarian cancer; t*BRCA*m, tumour *BRCA* mutant.

The Cancer Genome Atlas Research Network, Nature 2011;474:609–15; Konstantinopoulos PA, et al. Cancer Discov 2015;11:1137–54.

Germline or Tumor *BRCA* testing?



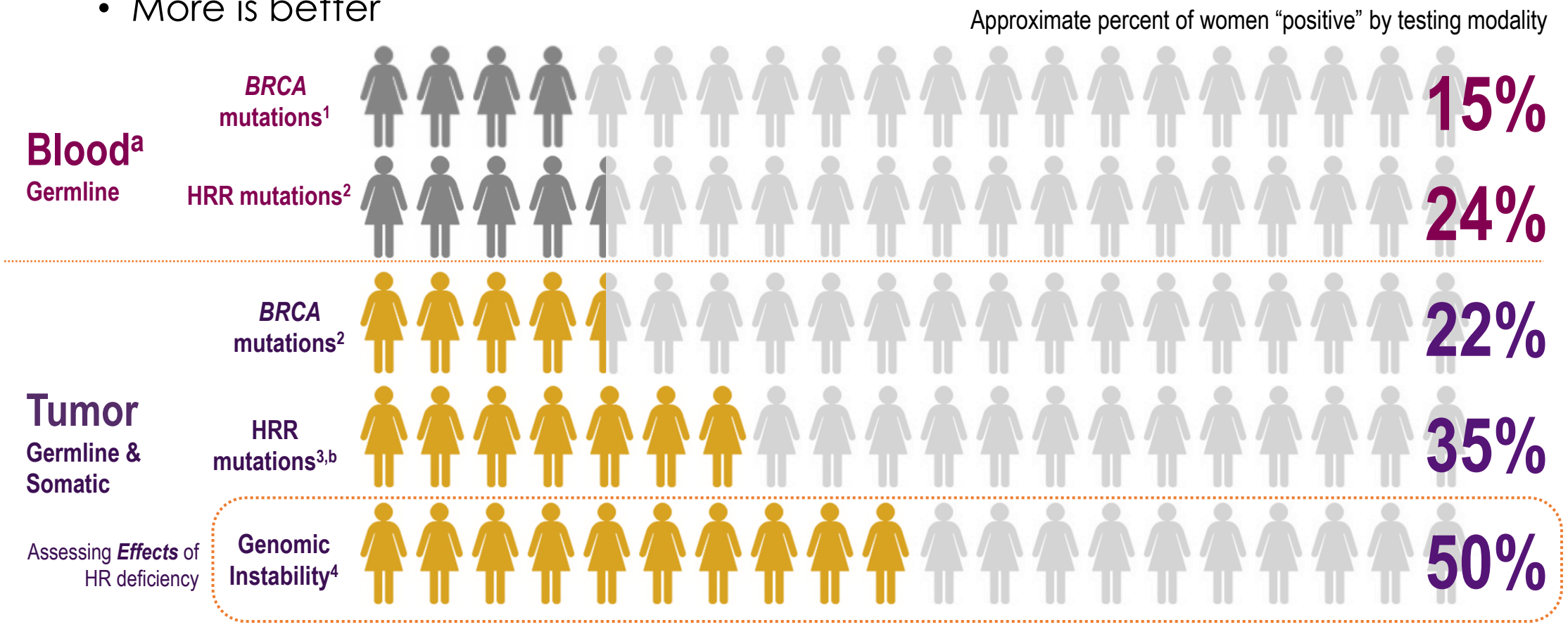
Beginning with a tumour test rather than a germline test:

- Fewer patients will require two rounds of *BRCA* testing (a greater number of women with ovarian cancer will test negative on germline testing than will test positive on tumour testing). ?more cost-effective
- Consent may be perceived as more straight forward
- **Potential risk of not obtaining an accurate results : reflex test MLPA on peripheral blood to detect large rearrangements**

Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients. Vergote, Banerjee, Gerdes, van Asperen, Marth, Vaz, Ray- Coquard, Stoppa-Lyonnet, Gonzalez-Martin, Sehouli and Colombo. EJC 2016 in press.
Germline BRCA testing first.

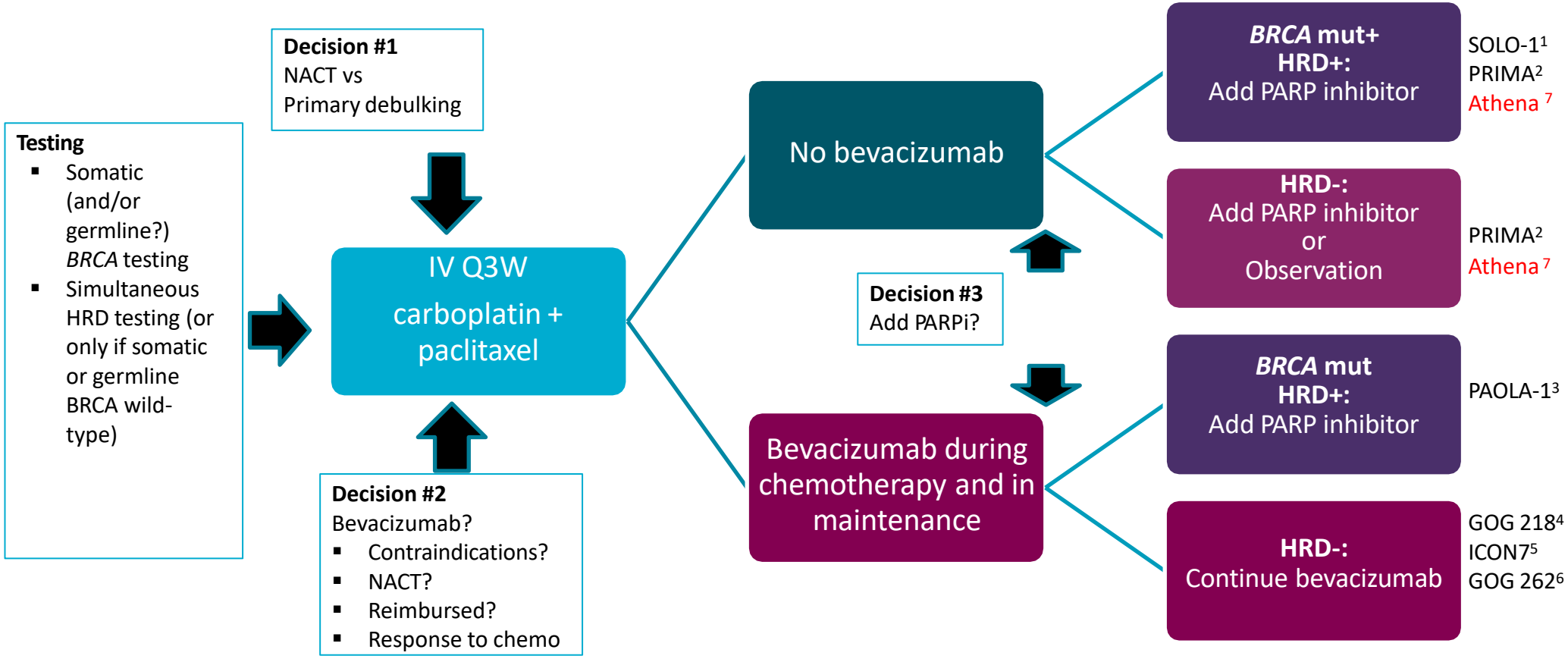
Patient identification and testing modalities

- More is better



1. Neff RT *et al. Ther Adv Med Oncol*. 2017;9(8):519-31. 2. Pennington KP, *et al. Clin Cancer Res*. 2014;20(3):764-75. 3. Konstantinopoulos PA, *et al. Cancer Discov*. 2015;5(11):1137-54. 4. Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-15.

Integrated Maintenance Treatment Paradigm for First-line Ovarian Cancer (2023)



Comparisons across trials should not be made as trials were not head-to-head

1. Moore. NEJM. 2018;379:2495. 2. González-Martin. NEJM. 2019;381:2391. 3. Ray-Coquard. NEJM. 2019;381:2416.
4. Burger. NEJM. 2011;365:2473. 5. Perren. NEJM. 2011;365:2484. 6. Chan. NEJM. 2016;374:738 7. Monk et al. JCO Published online June 06, 2022.

How these factors alone or in combination can help us deciding whether to use PARP-I alone or in combination with bevacizumab?

Biomarkers and PARP-i

	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

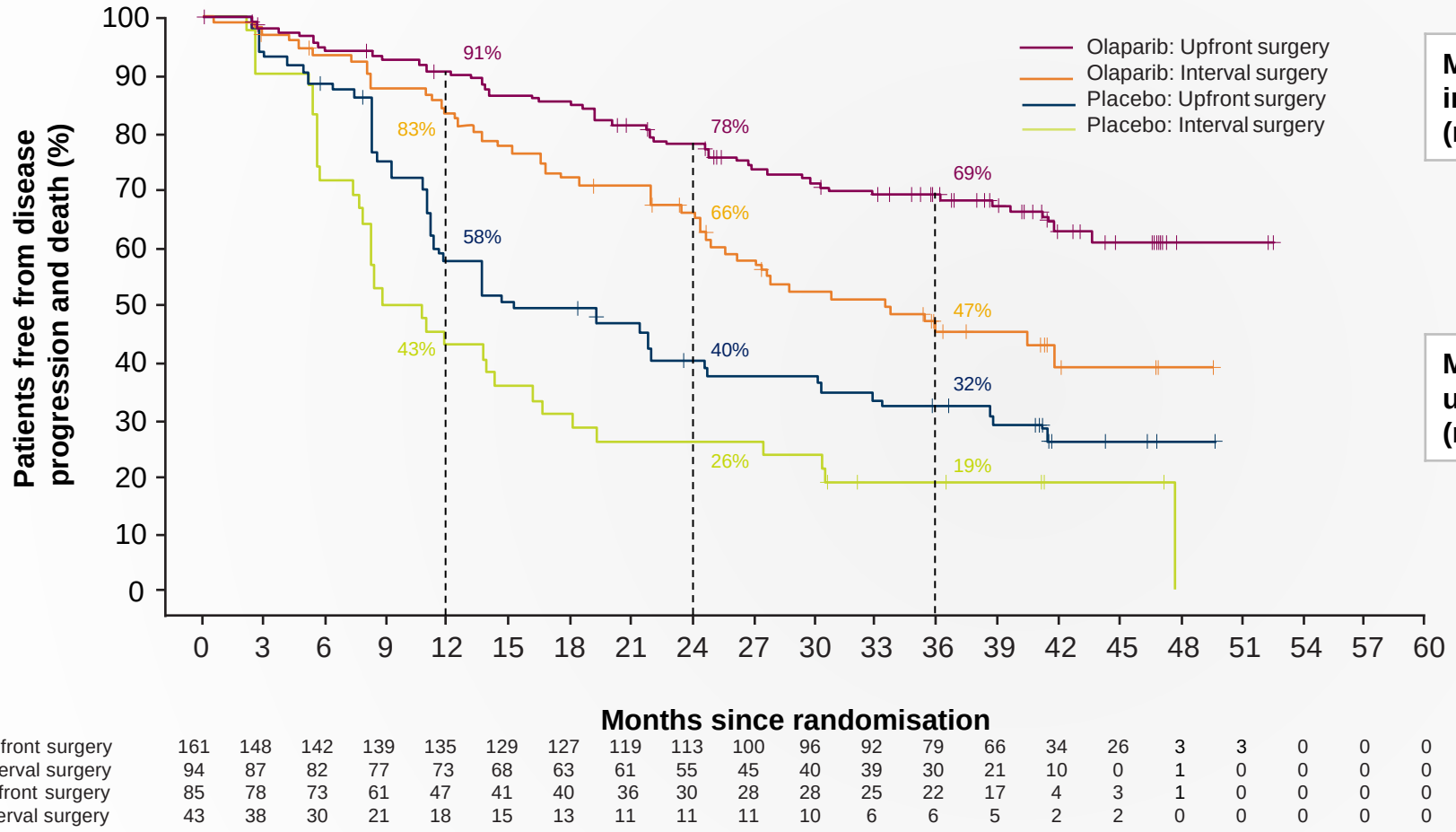
Surgery-related characteristics and PARP-i

HR (95% CI)	SOLO-1[1]	PRIMA	PAOLA-1
PDS	**0.31** (0.21 - 0.46)	**0.67** (0.46 - 0.96)	**0.52** (0.40 - 0.69)
IDS	**0.37** (0.24 - 0.58)	**0.57** (0.44 - 0.73)	**0.66** (0.50 - 0.87)
No-GRD	**0.33** (0.23 - 0.46)		**0.47** (0.20 - 0.75)*
		0.65 (0.46 - 0.91)**	**0.61** (0.41– 0.91)**
GRD	**0.44** (0.25 - 0.77)	**0.58** (0.39 - 0.86)*	**0.74** (0.48–1.15)*
		0.41 (0.26 - 0.62)**	**0.70** (0.41 - 1.20)**

PDS: primary debulking surgery; IDS: Interval debulking surgery; GRD: Gross residual disease;
*after PDS; ** after IDS

1. Paul DiSilvestro et al. J Clin Oncol 2020 Oct 20;38(30):3528-3537
2. Roisin O'Cearbhaill et al. SGO 2021
3. Grimm et al. SGO 2020

SOLO-1: PFS by timing of surgery



No. at risk:

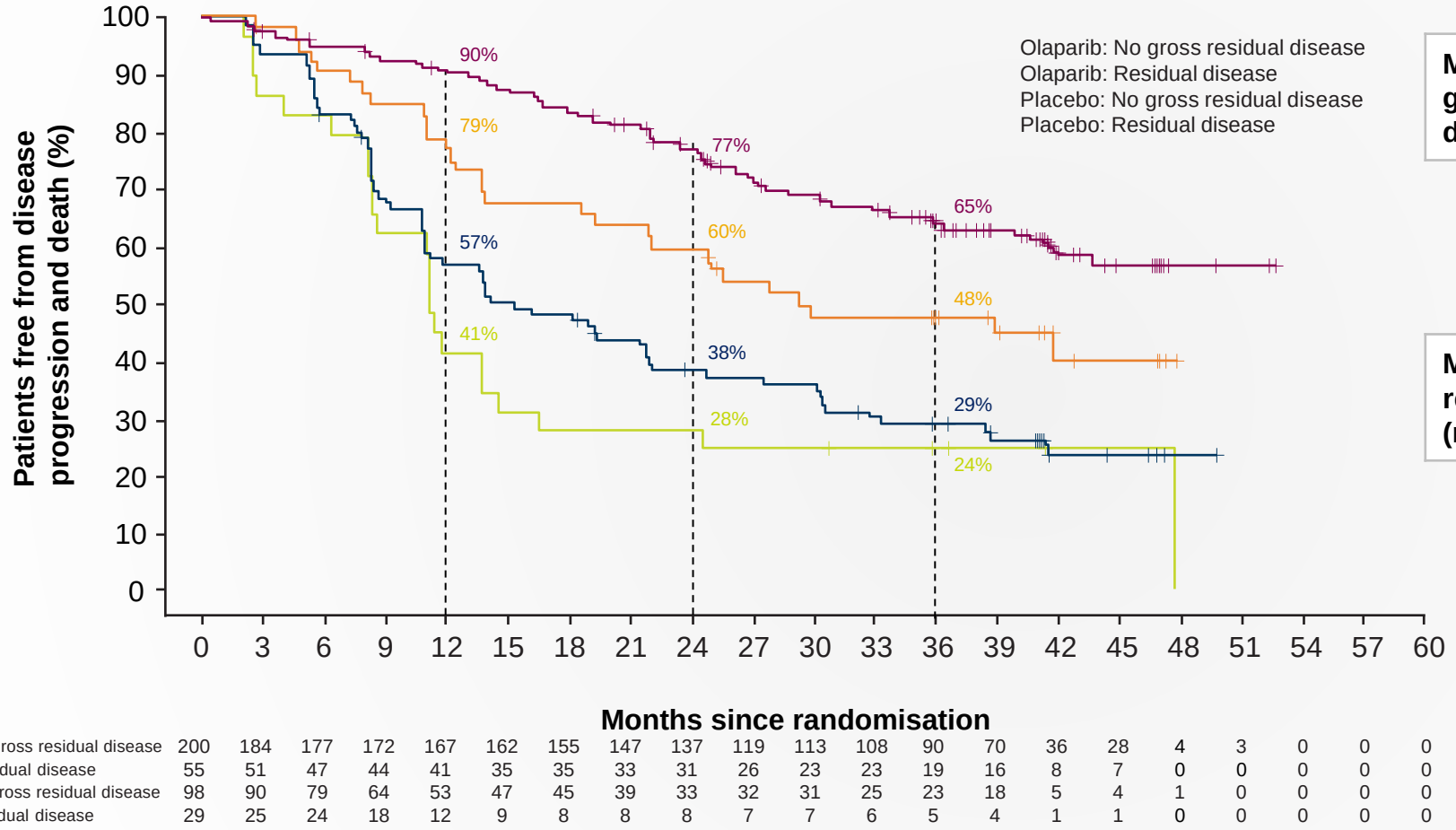
Olaparib: Upfront surgery	161	148	142	139	135	129	127	119	113	100	96	92	79	66	34	26	3	3	0	0	0
Olaparib: Interval surgery	94	87	82	77	73	68	63	61	55	45	40	39	30	21	10	0	1	0	0	0	0
Placebo: Upfront surgery	85	78	73	61	47	41	40	36	30	28	28	25	22	17	4	3	1	0	0	0	0
Placebo: Interval surgery	43	38	30	21	18	15	13	11	11	11	10	6	6	5	2	2	0	0	0	0	0

	Olaparib	Placebo
Median PFS with interval surgery (months)	33.6	9.8
	HR 0.37 95% CI 0.24–0.58	

	Olaparib	Placebo
Median PFS with upfront surgery (months)	NR	15.3
	HR 0.31 95% CI 0.21–0.46	

Investigator-assessed PFS. Primary DCO: May 2018
CI=confidence interval; HR=hazard ratio; NR=not reached; PFS=progression-free survival
DiSilvestro P et al. *J Clin Oncol*. Epub 4 Aug 2020; doi: 10.1200/JCO.20.00799

SOLO-1: PFS by surgical outcome



No. at risk:

Olaparib: No gross residual disease	200	184	177	172	167	162	155	147	137	119	113	108	90	70	36	28	4	3	0	0	0
Olaparib: Residual disease	55	51	47	44	41	35	35	33	31	26	23	23	19	16	8	7	0	0	0	0	0
Placebo: No gross residual disease	98	90	79	64	53	47	45	39	33	32	31	25	23	18	5	4	1	0	0	0	0
Placebo: Residual disease	29	25	24	18	12	9	8	8	8	7	7	6	5	4	1	1	0	0	0	0	0

	Olaparib	Placebo
Median PFS with no gross residual disease (months)	NR	15.3
	HR 0.33 95% CI 0.23–0.46	

	Olaparib	Placebo
Median PFS with residual disease (months)	29.4	11.3
	HR 0.44 95% CI 0.25–0.77	

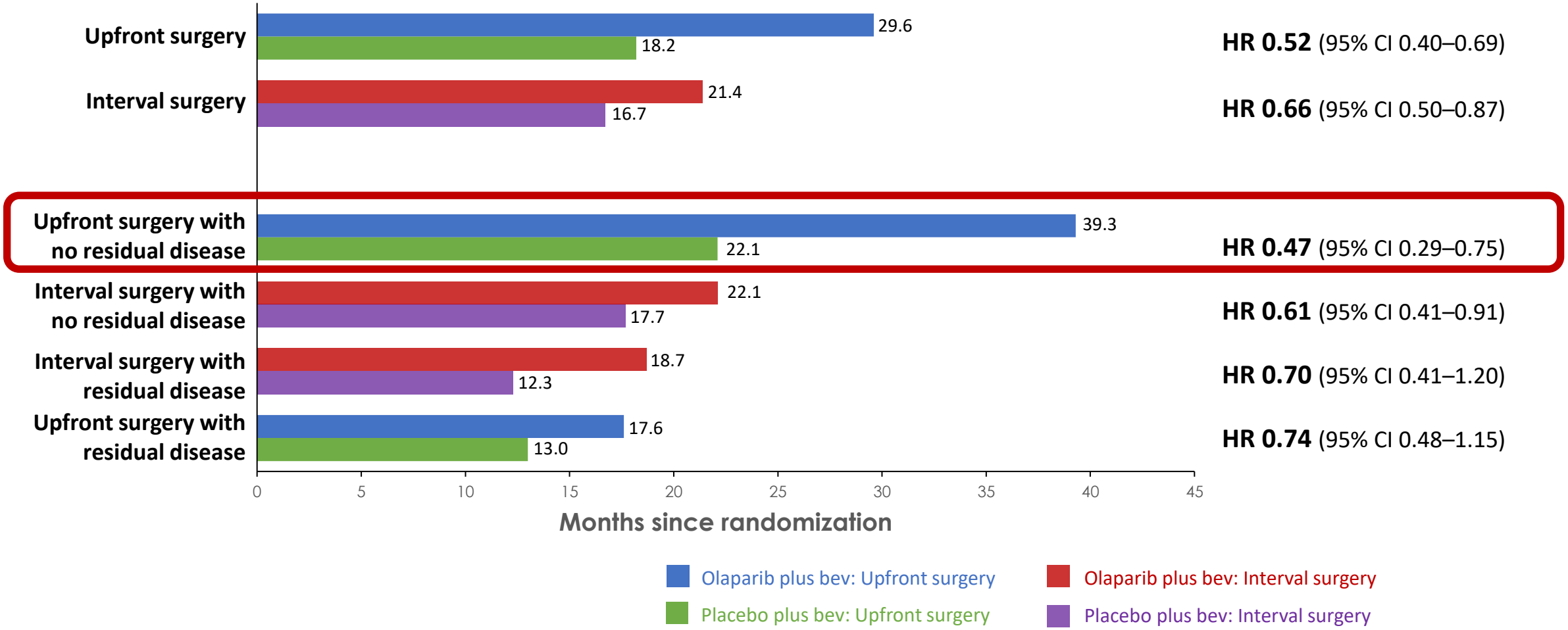
Investigator-assessed PFS. Primary DCO: May 2018

*Pre-selected subgroup analyses defined as clinically relevant for study patients. Surgical outcome was reported by the treating physician

CI=confidence interval; HR=hazard ratio; NR=not reached; PFS=progression-free survival

DiSilvestro P et al. *J Clin Oncol*. Epub 4 Aug 2020; doi: 10.1200/JCO.20.00799

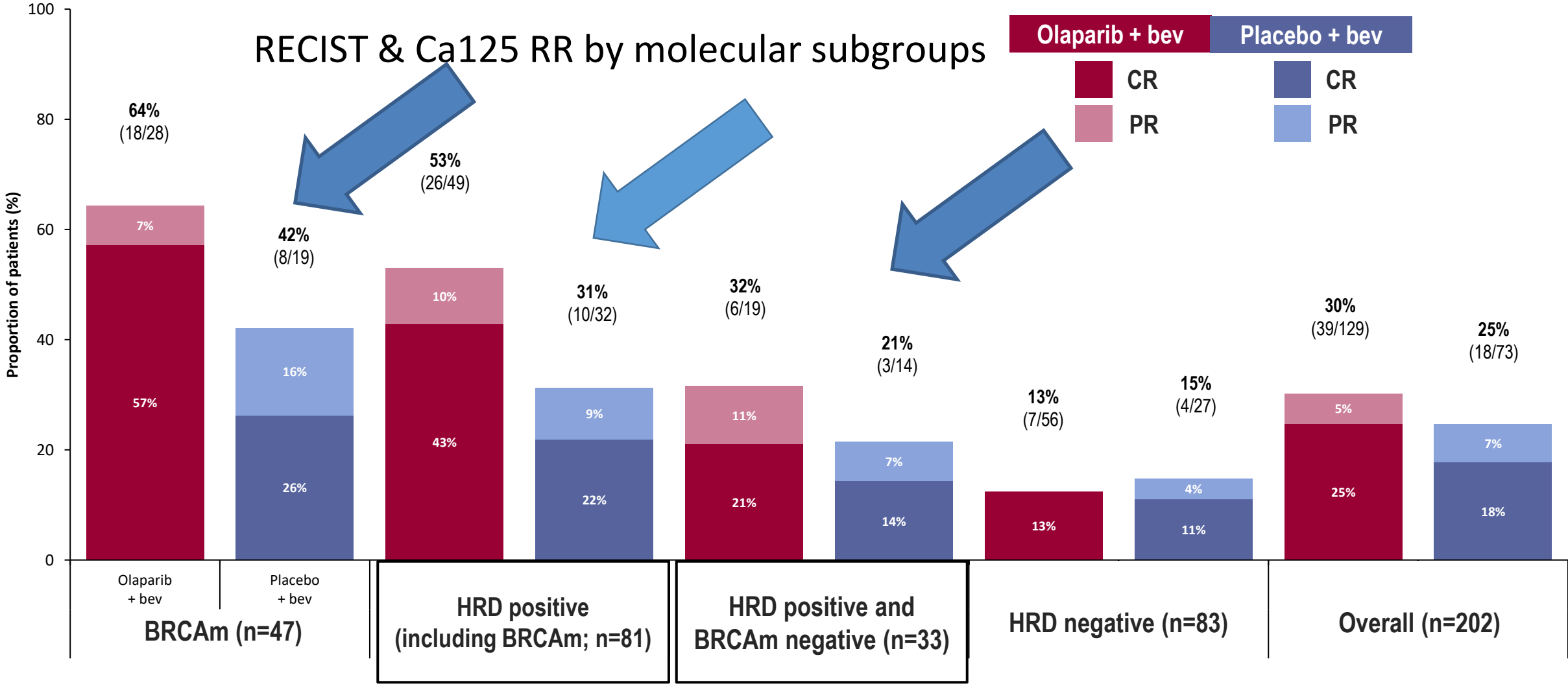
PAOLA-1
Summary of PFS: Timing of surgery and residual disease status



Can we predict response to bevacizumab?

Biomarkers and Bevacizumab

Impact of maintenance therapy for patients in partial response after 1st line CT+Bev regimen from PAOLA-1



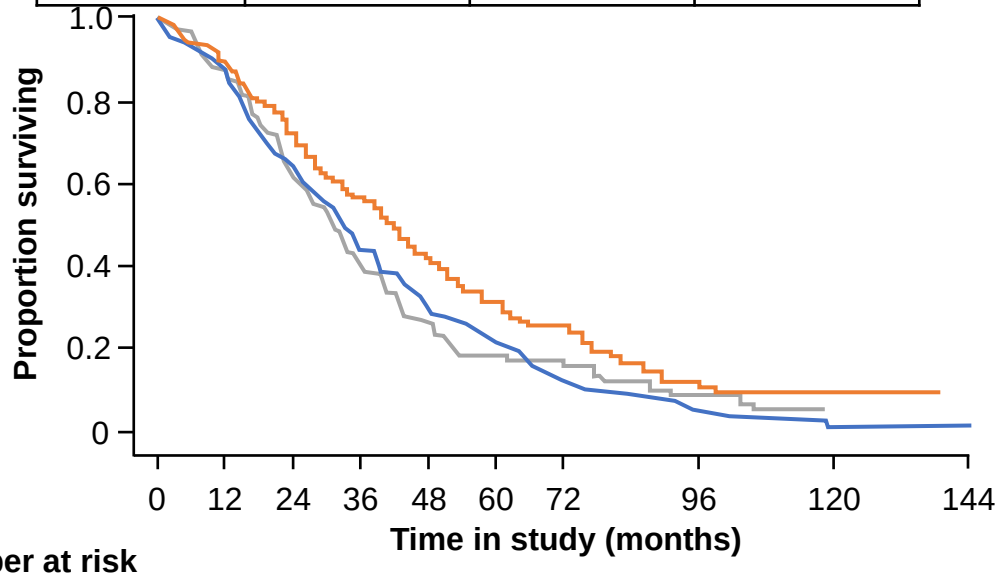
Among patients with an HRD status of unknown, RECIST ORR was 25% (6/24) in the olaparib arm and 29% (4/14) in the placebo arm. Data are n (%) unless otherwise indicated. Patients had evidence of disease by RECIST and/or CA-125 ≥2 x ULN at baseline. Percentages may not sum to total because of rounding. *Score ≥42 by Myriad HRD test; †One patient in the olaparib arm and four patients in the placebo arm discontinued because of non-RECIST disease progression.

Colombo N, et *al. ESMO 2020,* Abstract 812MO

Surgery related characteristics and Bevacizumab

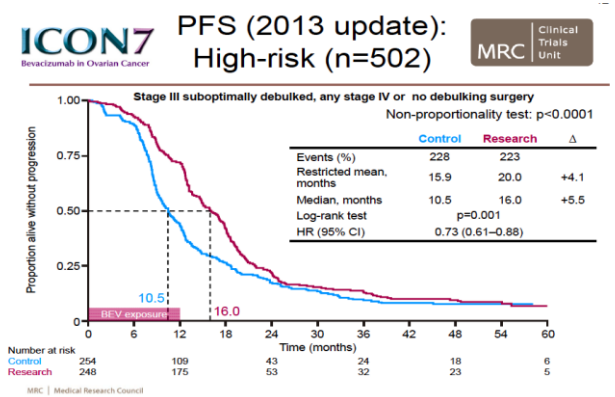
GOG-0218[1] OS, Stage IV subgroup

	CP + Bev → Bev	CP + Bev → Pla	CP + Pla → Pla
No of events	131	145	130
Total	163	164	154
Median	42.8	34.5	32.6

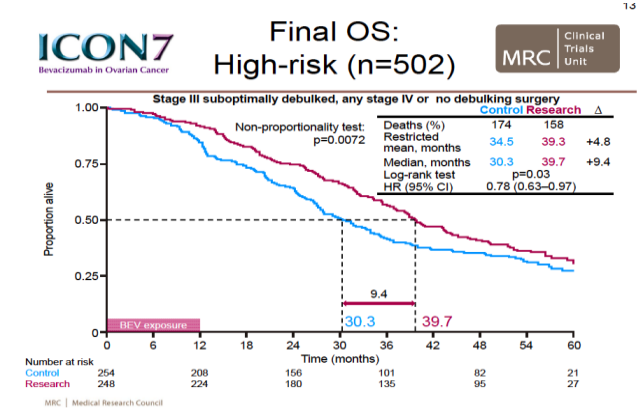


Number at risk

CP+Bev → Bev	163	142	115	92	70	53	43	17	1	0
CP+Bev → Pla	164	139	104	74	51	40	25	14	3	1
CP+Pla → Pla	154	130	96	64	44	31	26	14	0	



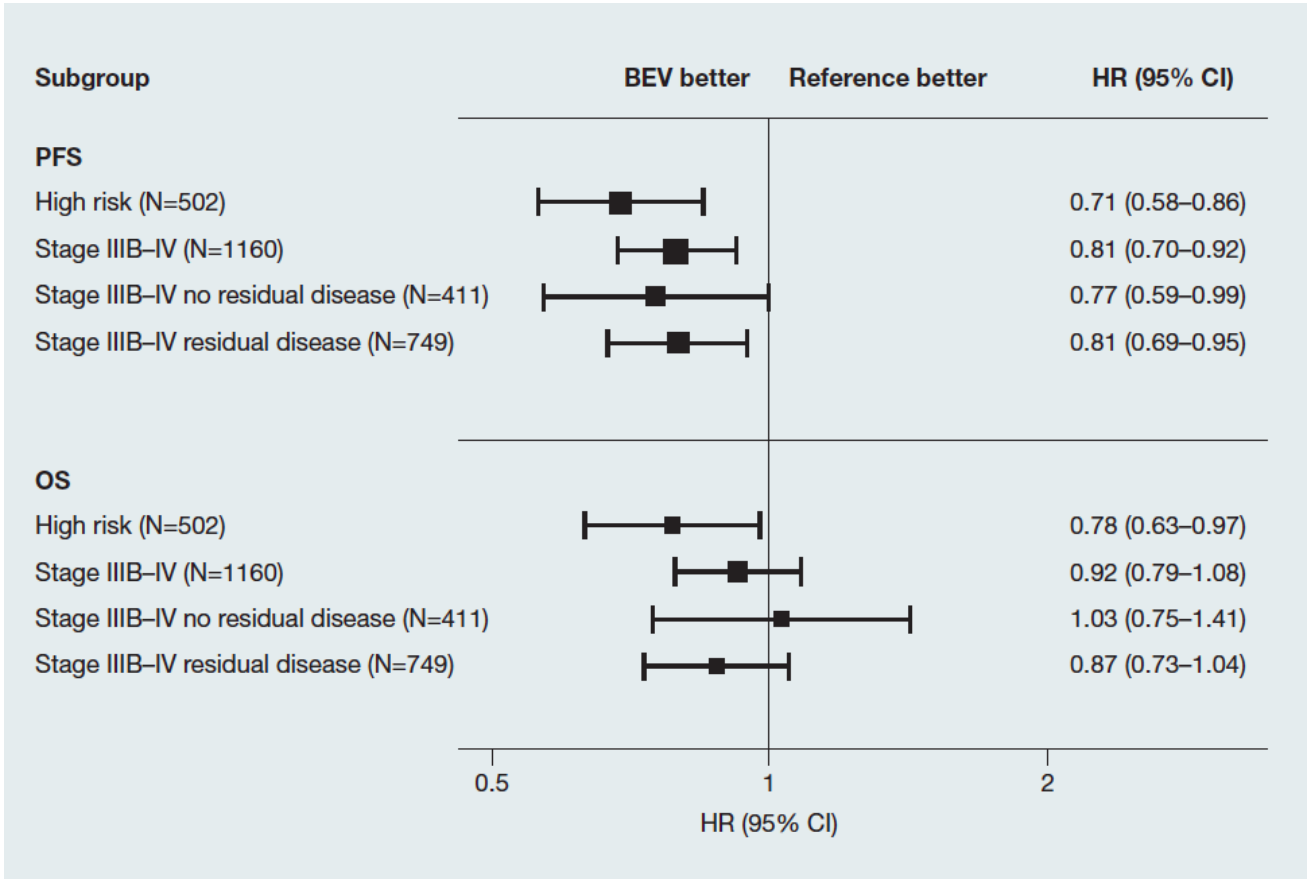
Final PFS analysis HR 0.73 (0.61-0.88)
Oza. ESMO 2013

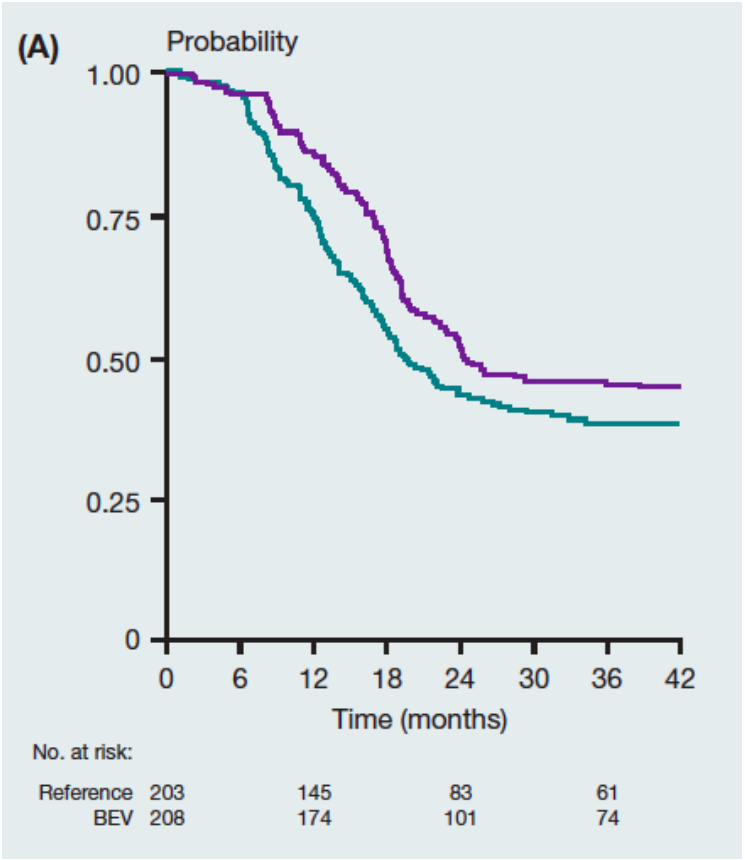


Final OS analysis HR 0.78 (0.63-0.97)
Oza. ESMO 2013

1. Tewari et al J Clin Oncol 2019; 2. Oza A et al. Lancet Oncol 2015; 16: 928–36

Bevacizumab in “Low-risk” patients (ICON-7 exploratory analysis)





González-Martín et al. Gynecol Oncol 2019

Can we predict response to Bevacizumab ?

Bevacizumab

1. CD31 (MVD) & tVEGF
2. IL6 in plasma
3. Visceral fat density (VFD)
4. high c-MET/VEGFR-2 co-localisation
5. Low VEGF-A165b expression
6. TCGA proliferative and mesenchymal molecular subtypes

1. Bais C et al. J Natl Cancer Inst. 2017 Nov 1;109(11):djx066. doi: 10.1093/jnci/djx066 (GOG-218)
2. Alvarez Secord et al. Clin Cancer Res. 2020 Mar 15;26(6):1288-1296. doi: 10.1158/1078-0432.CCR-19-0226. (GOG-218)
3. Buechel et al. Gynecol Oncol. 2021 May;161(2):382-388. doi: 10.1016/j.ygyno.2021.02.032. (GOG-218)
4. Morgan R et al. BMC Med. 2022 Feb 11;20(1):59. doi: 10.1186/s12916-022-02270-y. (ICON-7)
5. Wimberger et al. Clin Cancer Res. 2022 Aug 24:CCR-22-1326. doi: 10.1158/1078-0432.CCR-22-1326. (ICON-7)
6. Kommos et al. Clin Cancer Res. 2017 Jul 15;23(14):3794-3801. doi: 10.1158/1078-0432.CCR-16-2196 (ICON-7)

Modeled CA-125 ELIMination rate constant K (KELIM) & bevacizumab benefit in GOG-218

FIGO stage IV and Stage III with VRD > 1 cm after PCS

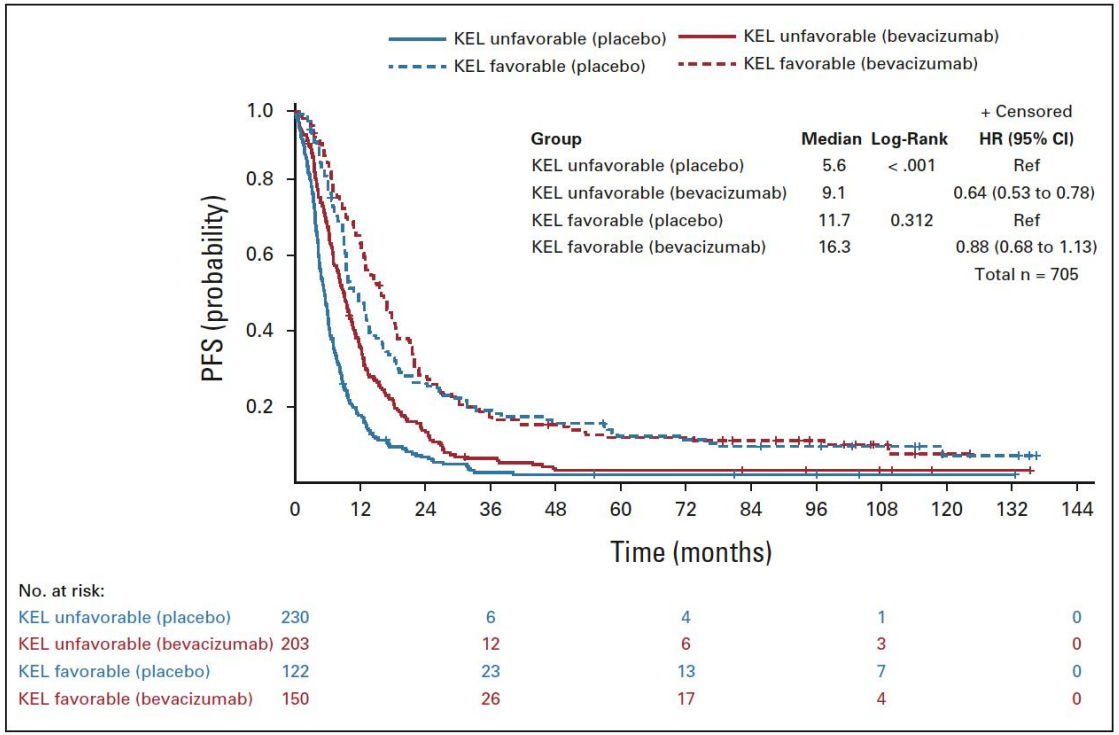


FIG 3. Kaplan-Meier curves of the PFS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with favorable or unfavorable KELIM (KEL) score, in the population of patients with a high-risk disease (stage IV + stage III operated with suboptimal surgery). HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); PFS, progression-free survival; Ref, reference.

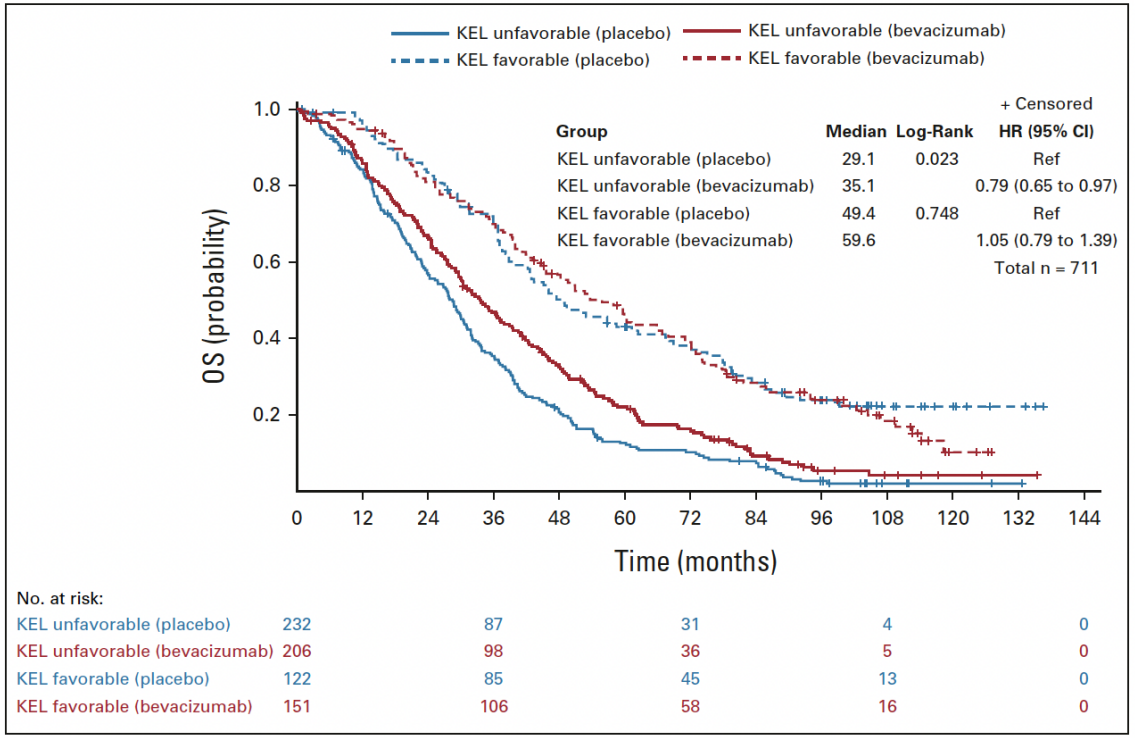


FIG 4. Kaplan-Meier curves of the OS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with favorable or unfavorable KELIM (KEL) score, in the population of patients with a high-risk disease (stage IV + stage III operated with suboptimal surgery). HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); OS, overall survival; PFS, progression-free survival; Ref, reference.

You et al. J Clin Oncol 2022 , Oct 17:JCO2201207. doi: 10.1200/JCO.22.01207

Predictive factors for PARP-i or bevacizumab

- Biomarkers and PARP-i

- Biomarkers and Bevacizumab

- Surgery-related characteristics and PARP-i

- Surgery-related characteristics and Bevacizumab

What about ….

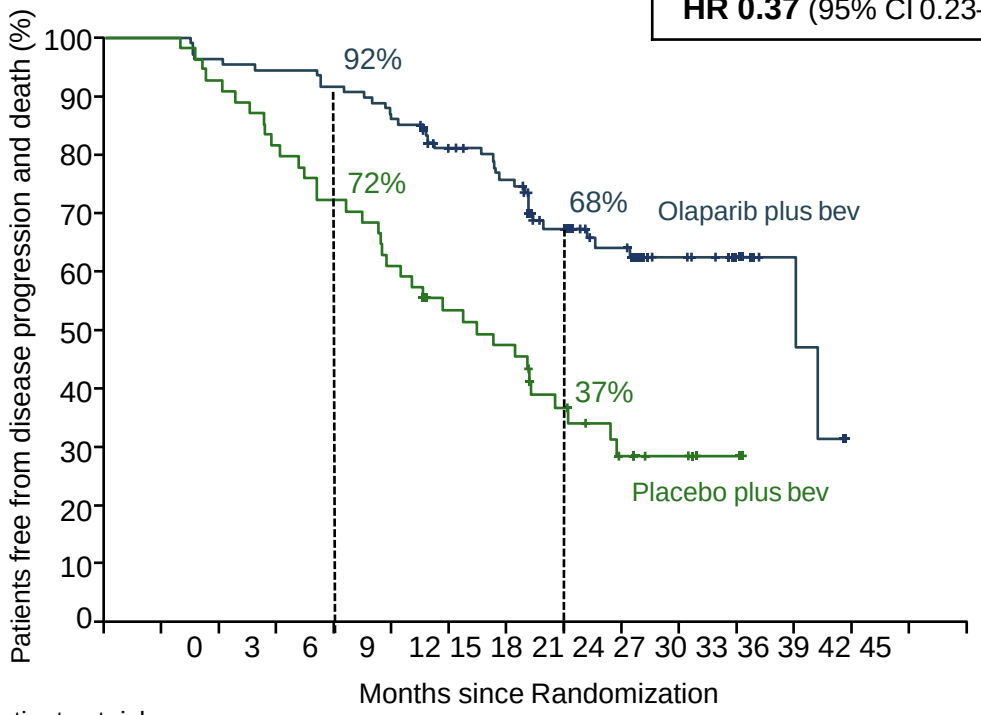
Biomarkers , surgery related characteristics and PARP-i+ Bevacizumab

Biomarkers, surgery-related characteristics , PARP-i+Bev
PAOLA1: PFS by clinical risk in tumour BRCAm patients

Higher risk, tumour BRCAm

	Olaparib + bev (n=109)	Placebo + bev (n=55)
Events, n (%)	37 (34)	36 (65)
Median PFS, months	**36.0***	**19.4**

HR 0.37 (95% CI 0.23–0.59)



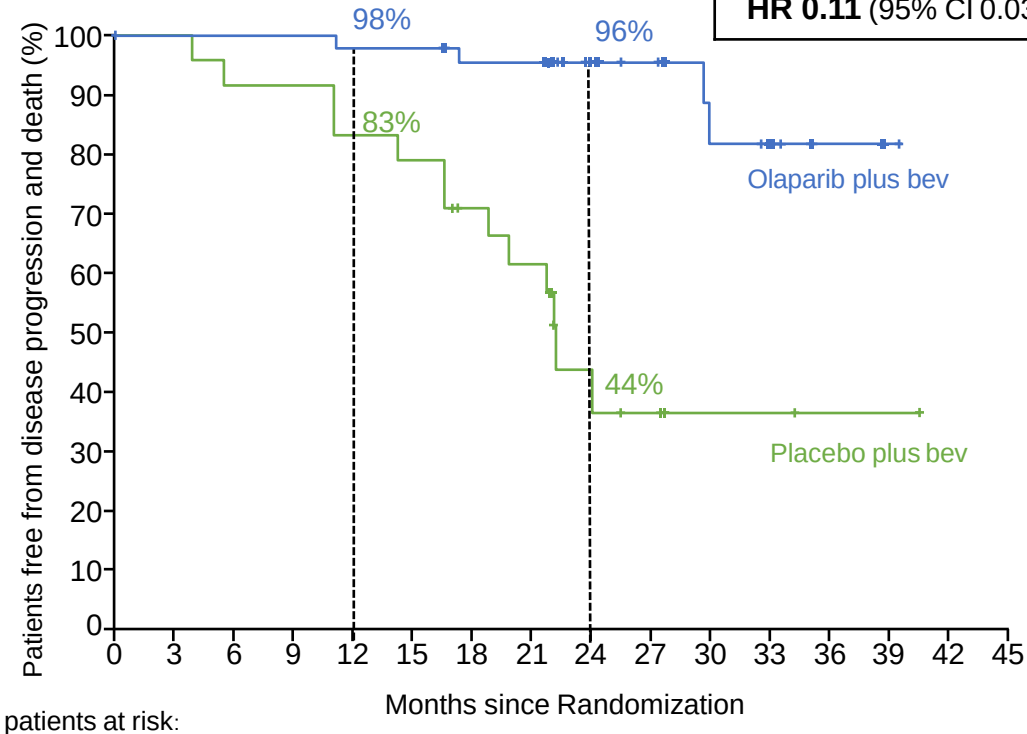
Number of patients at risk:

Olaparib plus bev	109	107	103	101	98	92	77	70	51	38	19	11	4	0
Placebo plus bev	55	54	50	44	39	33	26	23	16	9	5	2	0	

Lower risk, tumour BRCAm

	Olaparib + bev (n=48)	Placebo + bev (n=25)
Events, n (%)	4 (8)	13 (52)
Median PFS, months	**NR**	**22.2**

HR 0.11 (95% CI 0.03–0.31)



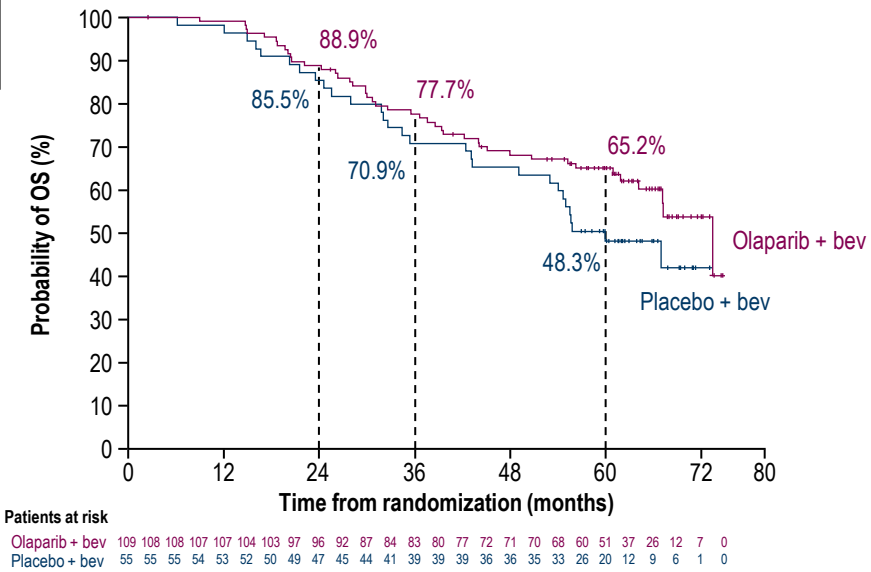
Number of patients at risk:

Olaparib plus bev	48	47	47	47	46	46	40	40	25	20	12	8	3	1	0
Placebo plus bev	25	24	22	22	20	19	15	13	6	4	2	2	1	1	0

Harter P, et al. *Gynecologic Oncology* https://doi.org/10.1016/j.ygyno.2021.12.016

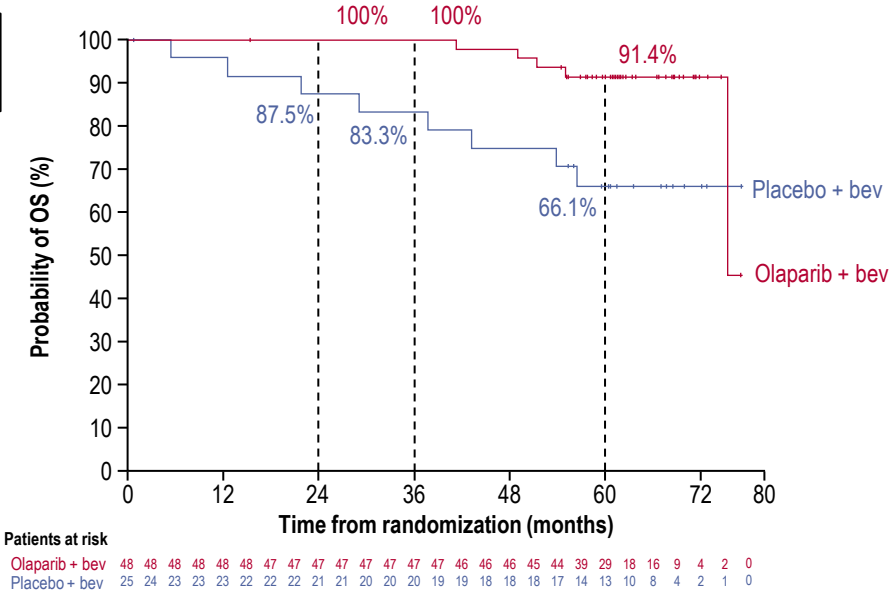
5-year OS by clinical risk in tBRCAm patients

Higher risk



	Olaparib + bevacizumab (n=109)	Placebo + bevacizumab (n=55)
Events, n (%)	43 (39.4)	29 (52.7)
Median OS, months	73.3*	59.8
5-year OS rate, %	65.2	48.3
	HR 0.69 (95% CI 0.43–1.12)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	25.7	63.6

Lower risk



	Olaparib + bevacizumab (n=48)	Placebo + bevacizumab (n=25)
Events, n (%)	5 (10.4)	8 (32.0)
Median OS, months	75.2*	NE
5-year OS rate, %	91.4	66.1
	HR 0.27 (95% CI 0.08–0.80)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	20.8	36.0

tBRCAm determined by central labs.
*Median unstable because of a lack of events.

Domenica Lorusso, ESMO Gynecological Cancer 2023

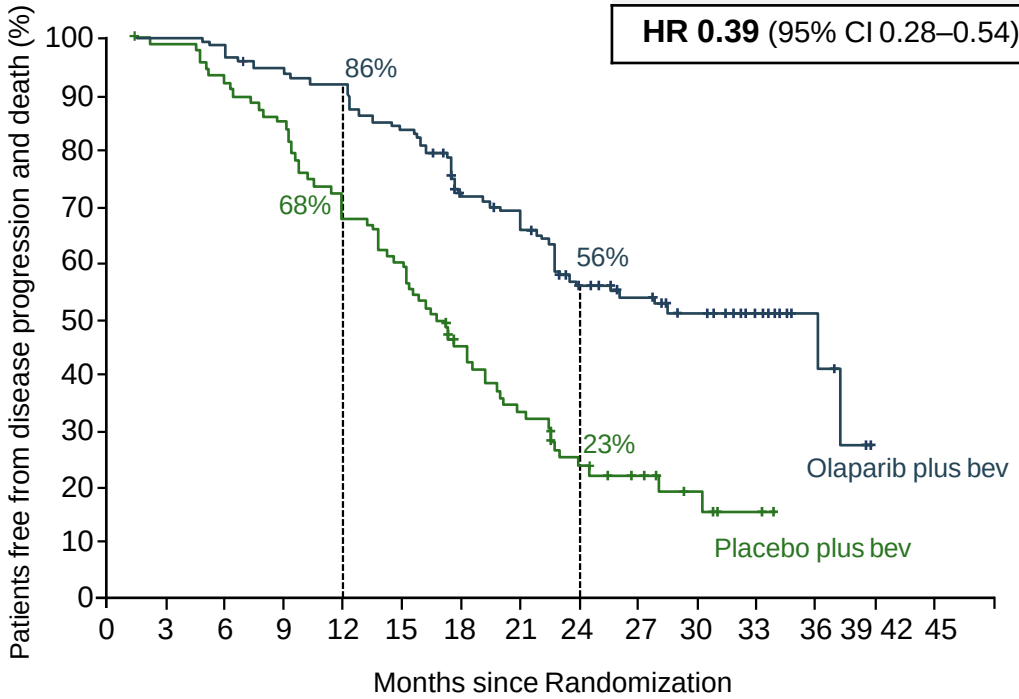
This study was supported by AstraZeneca

Biomarkers, surgery-related characteristics , PARP-i+Bev
Paola 1: PFS by clinical risk in HRD-positive patients

Higher risk, HRD positive

	Olaparib + bev (n=177)	Placebo + bev (n=89)
Events, n (%)	77 (44)	67 (75)
Median PFS, months	**36.0***	**16.0**

HR 0.39 (95% CI 0.28–0.54)



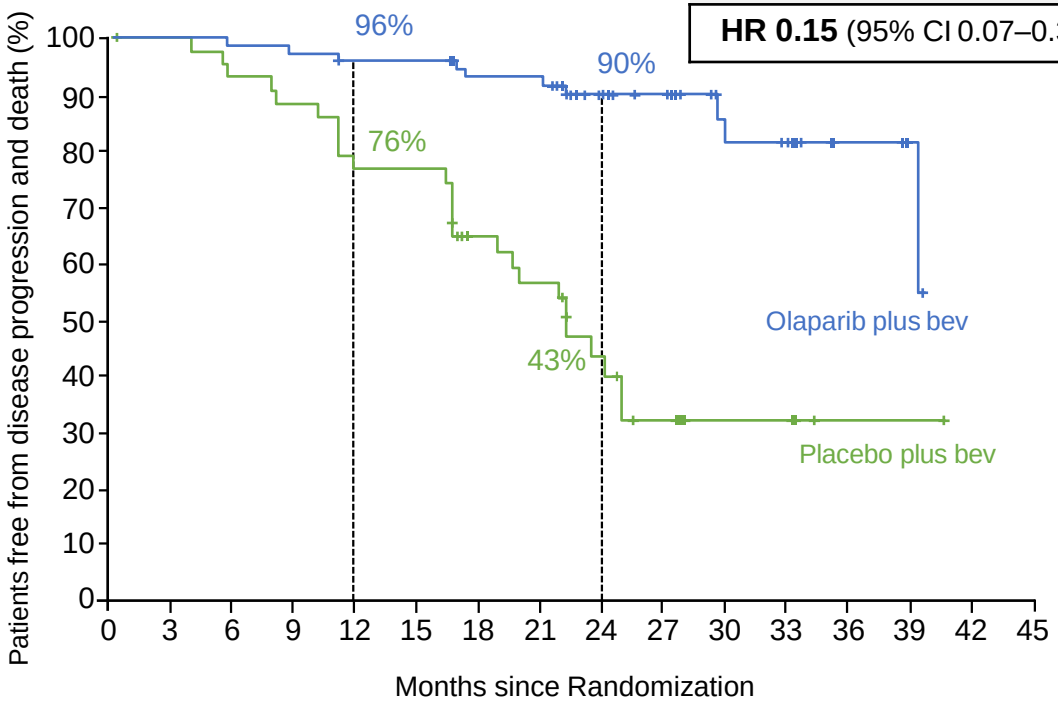
Number of patients at risk:

Olaparib plus bev	177	175	166	161	150	140	109	95	63	50	27	15	5	0	0
Placebo plus bev	89	86	78	66	59	47	31	24	16	11	5	2	0	0	0

Lower risk, HRD positive

	Olaparib + bev (n=78)	Placebo + bev (n=43)
Events, n (%)	10 (13)	25 (58)
Median PFS, months	**NR**	**22.1**

HR 0.15 (95% CI 0.07–0.30)



Number of patients at risk:

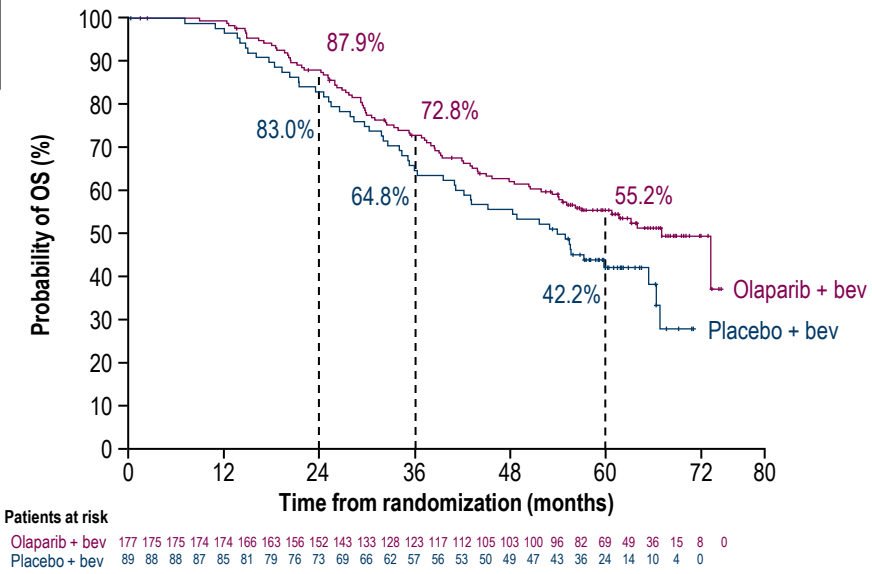
Olaparib plus bev	78	77	76	75	73	73	60	60	40	35	19	14	6	3	0
Placebo plus bev	43	42	39	37	32	32	23	20	12	7	3	3	1	1	0

Harter P, et al. *Gynecologic Oncology* https://doi.org/10.1016/j.ygyno.2021.12.016

*Unstable median due to lack of events

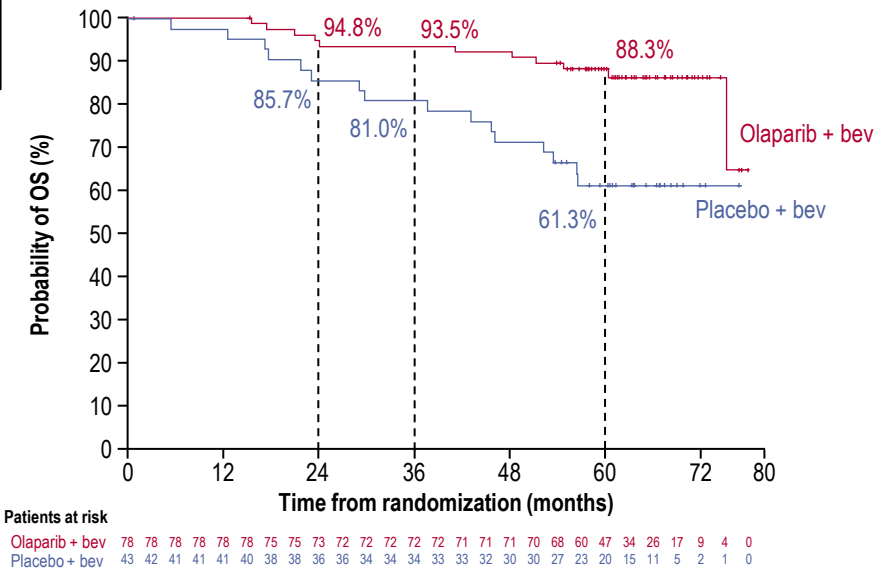
5-year OS by clinical risk in HRD-positive patients

Higher risk



	Olaparib + bevacizumab (n=177)	Placebo + bevacizumab (n=89)
Events, n (%)	82 (46.3)	53 (59.6)
Median OS, months	67.0*	54.0
5-year OS rate, %	55.2	42.2
	HR 0.70 (95% CI 0.50–1.00)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	18.6	56.2

Lower risk



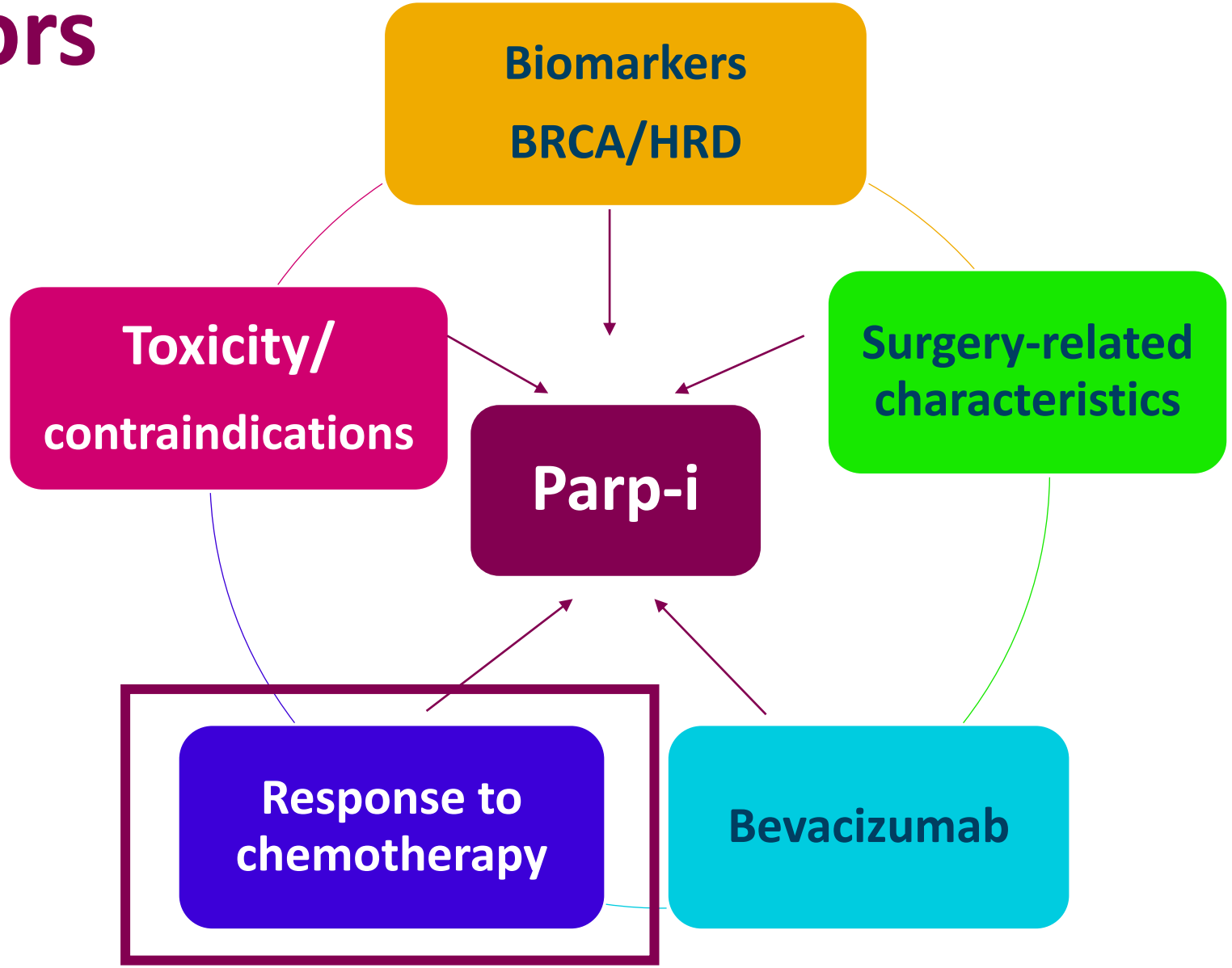
	Olaparib + bevacizumab (n=78)	Placebo + bevacizumab (n=43)
Events, n (%)	11 (14.1)	16 (37.2)
Median OS, months	NE	NE
5-year OS rate, %	88.3	61.3
	HR 0.31 (95% CI 0.14–0.66)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	14.1	39.5

HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.
*Median unstable because of a lack of events.

Domenica Lorusso, ESMO GYNaecological Cancer, Febraruary 2023

This study was supported by AstraZeneca

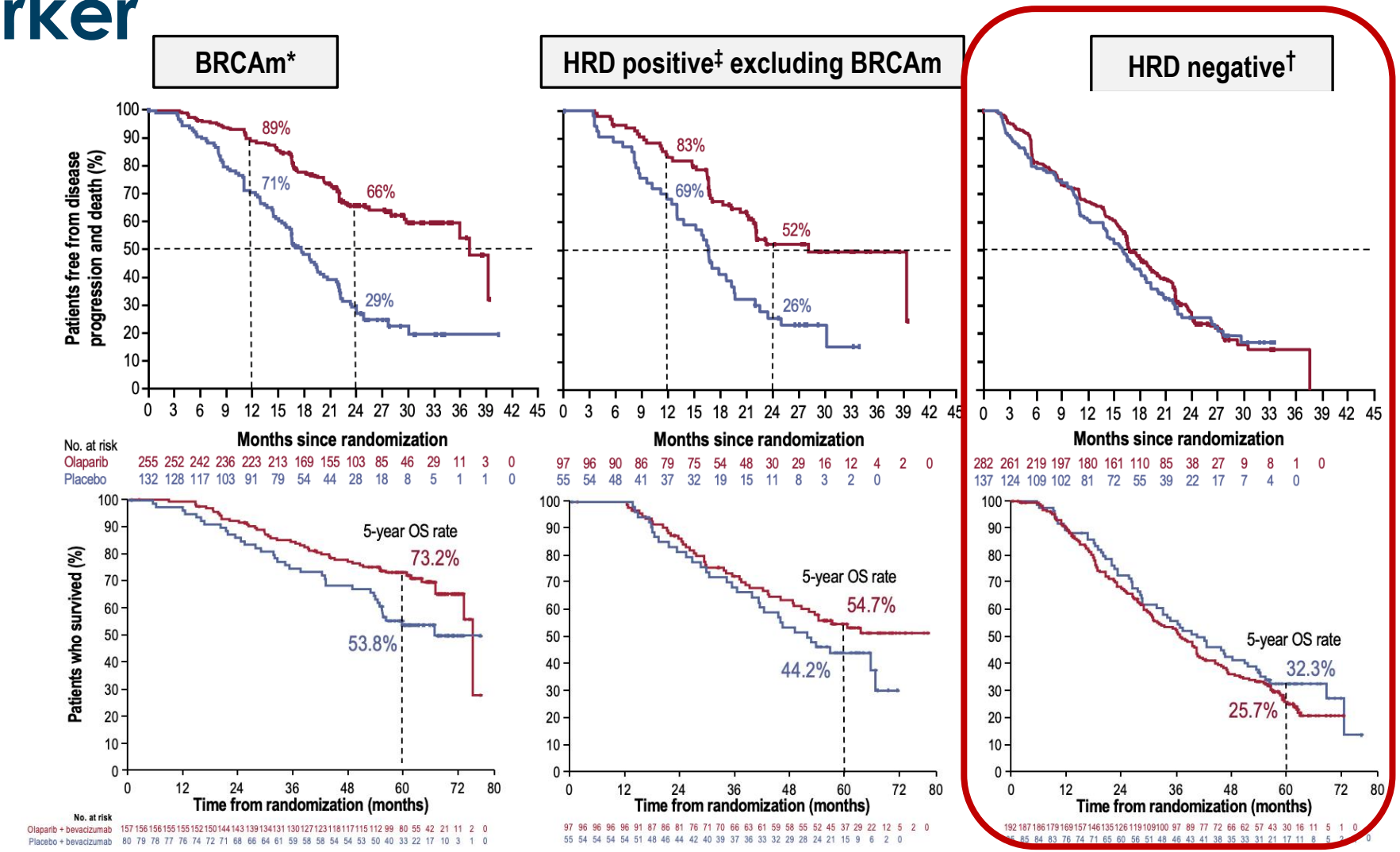
Key factors


Biomarkers
BRCA/HRD
Toxicity/
contraindications
Surgery-related
characteristics
Parp-i
Response to
chemotherapy
Bevacizumab

PAOLA-1: HRD (MyChoice) is a perfect predictive biomarker

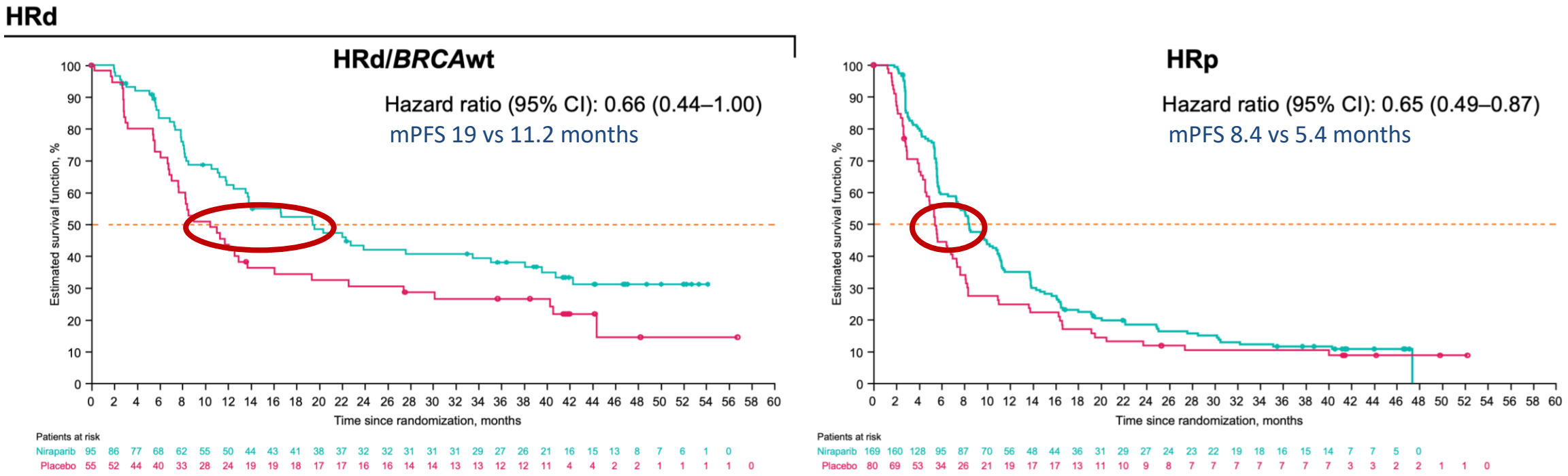
PFS

OS



Ray-Coquard et al. ESMO 2019 & 2022

PRIMA
HRD is predictive of magnitude of iPARP benefit



Gonzalez-Martin et al. ESMO & IGCS 2022

Response to chemotherapy predict outcome with PARP-i

• PRIMA and PAOLA-1: Clinical Context of Trial Populations

	PRIMA[a] Niraparib	PAOLA-1[b] Olaparib + Bevacizumab
Prior surgical status	▪ Stage III PDS with residual disease ▪ Stage III IDS / stage IV	▪ No limitation
Response criteria	▪ CR/PR (investigator) AND ▪ All Stage III PDS patients **had measurable disease** to assess platinum response ▪ PR > 2 cm excluded ▪ **Normal or > 90% ↓ CA-125** ▪ CR rate after chemotherapy:	▪ CR/PR (investigator) ▪ CR rate after chemotherapy: 20% ▪ **Response partially based on bevacizumab** ▪ **50% PDS & 60% RD = 0 mm**
Control arm	▪ Placebo	▪ Placebo + bevacizumab
Duration of PARP inhibitor maintenance	▪ 3 years	▪ 2 years
Primary endpoint	▪ PFS by BICR ▪ Stratification factors: HRD positive (including *BRCA* mutated) vs other; CR/PR; NACT	▪ Investigator-assessed PFS (ITT) ▪ Stratification factors: *BRCA* mutated vs negative/unknown; NED/CR/PR
Follow-up duration	▪ 13.8 months	▪ 24.0 months
Scanning schedule	▪ Every 12 weeks	▪ Every 24 weeks (every 12 weeks if CA-125 elevated)

STRONG selection for evaluable response to platinum

Response to platinum less certain

- a. Gonzalez-Martin A, et al. N Engl J Med 2019;381:2391–2402; b. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–2428.

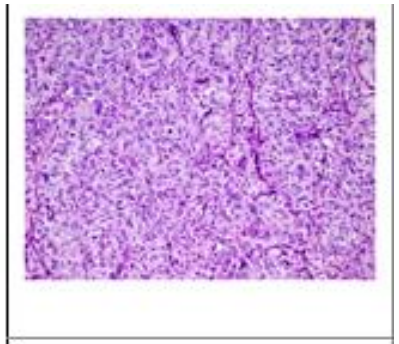
How to define response to chemotherapy?

How to define response to chemotherapy?

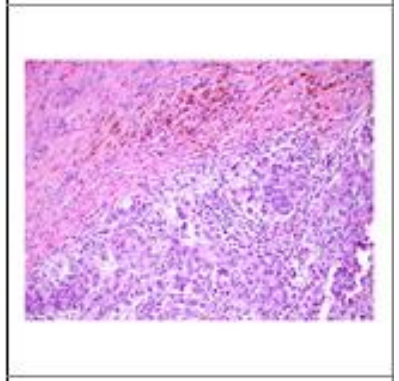
- RECIST (if measurable diseae)
- Kelim score (if elevated CA125)
- Surgical outcome (if IDS)
- Chemotherapy response score (CRS) (if IDS)

HOW MUCH PLATINUM SENSITIVE IS THIS TUMOR?

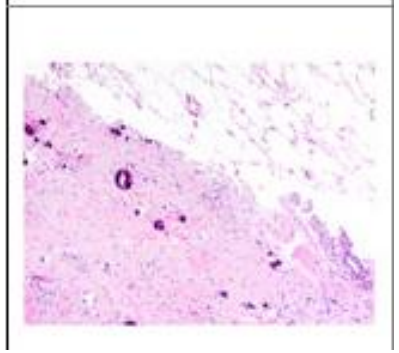
The chemotherapy response score (CRS)



CRS score 1: No or minimal tumour response (mainly viable tumour with no or minimal regression-associated fibro-inflammatory changes, limited to a few foci)



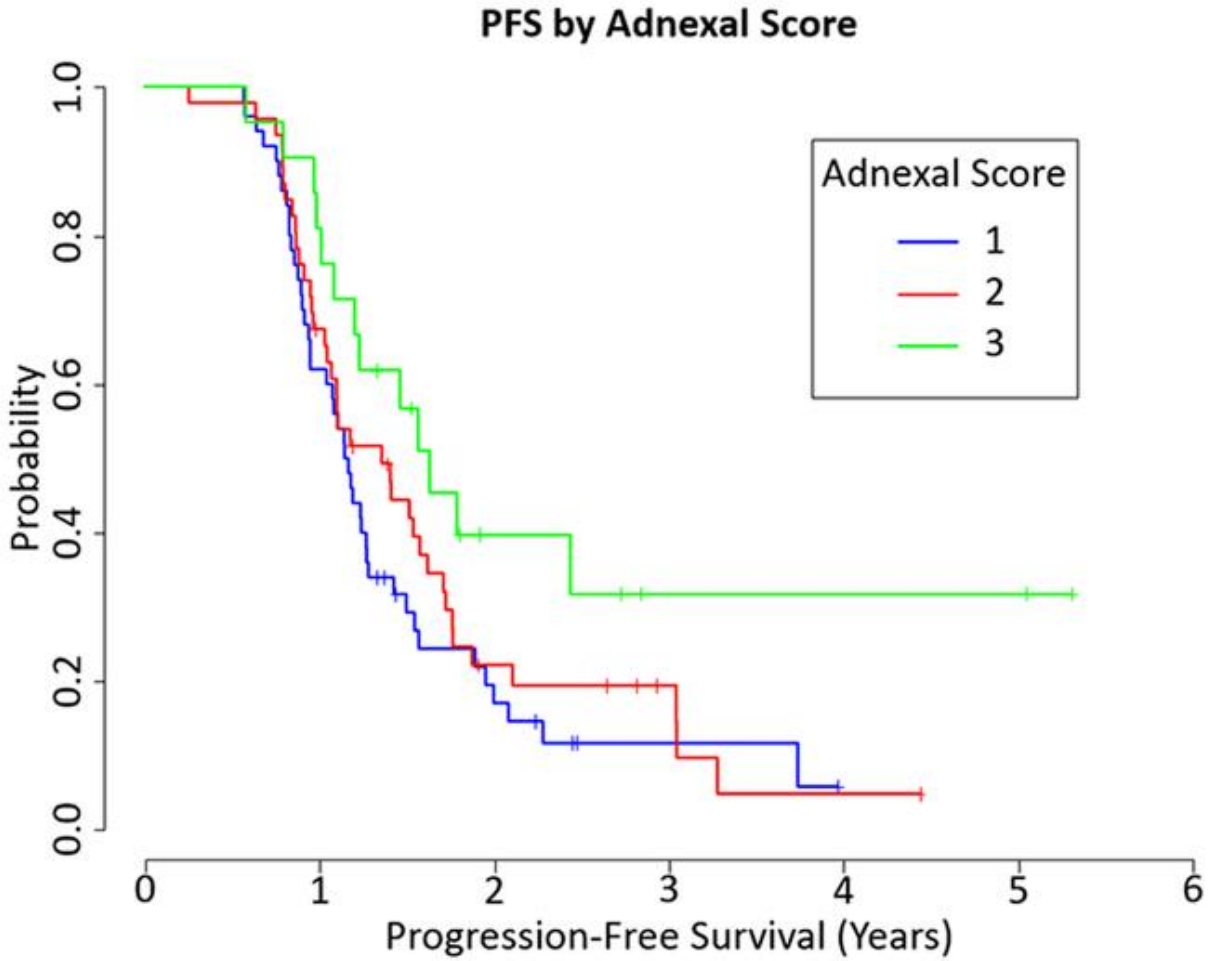
CRS score 2: Appreciable tumour response with residual tumour, (ranging from multifocal or diffuse fibro-inflammatory regressive changes, with tumour in sheets, streaks or nodules, to extensive regression associated fibro-inflammatory changes with multifocal residual tumour which is **regularly** distributed and easily identifiable)



CRS score 3: Complete or near-complete response (mainly regression associated fibro-inflammatory changes with minimal i.e. very few, **irregularly** scattered individual tumour cells or cell groups or nodules up to 2mm OR no residual tumour identified)

Steffen Böhm 2015 Aug 1;33(22):2457-63

CRS 1-2 MAY BE ASSOCIATED WITH PLATINUM RESISTANCE



Barrett C. Lawson et al Am J Surg Pathol. 2020 Feb; 44(2): 206–213.

How to define response to chemotherapy?

Patients with gross residual disease after primary debulking surgery		
RECIST	**CA125 value**	
1 = Partial response 2 = Complete response	0 = Abnormal CA125 1 = CA125 normalization	
Patients treated with internal debulking therapy		
Pathology	**KELIM**	**Surgical outcome**
1 = Minimal 2 = Partial[a] 3 = Near-complete Complete[b]	1 = KELIM < 1 2 = KELIM ≥ 1	0 = Residual tumor 2 = No residual tumor

[a] Chemotherapy Response Score 2

[b] Chemotherapy Response Score 3

How to define response to chemotherapy?

Patients with gross residual disease after primary debulking surgery	
Total score	**Response definition**
<2 ≥ 2	Moderate Good
Patients treated with internal debulking therapy	
Total score	**Response definition**
<4 ≥ 4	Moderate Good

Predictive factors for PARP-i, Bevacizumab, or combination

- HRD+, optimal response , and PARP-i

- HRD -, optimal response and PARP-i

- HRD +, suboptimal response , Bev and PARP-i

- HRD-, suboptimal response , bevacizumab

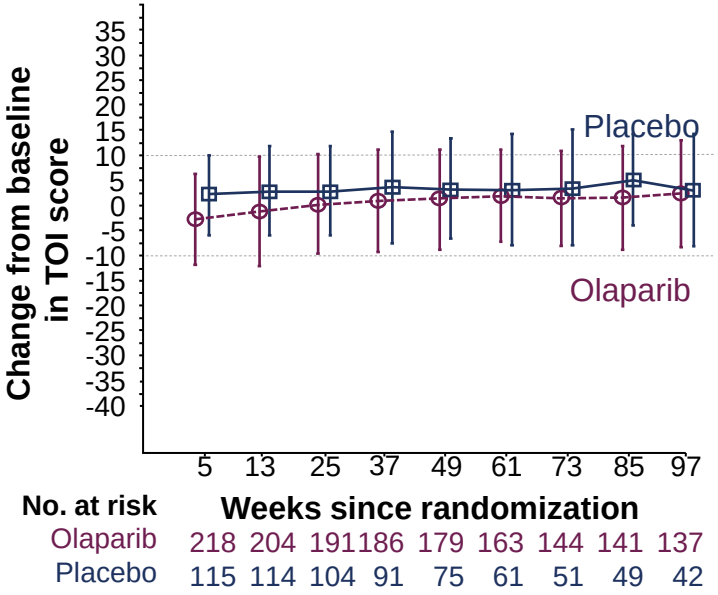
PRIMA, PAOLA-1 & SOLO1 Safety Overview

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

	PRIMA[1]	SOLO1	PAOLA-1
Adverse Event, no. (%)	Niraparib (n=484)	Olaparib (n=260)	Olaparib + bevacizumab (n=535)
Any TEAE	478 (98.8)	256 (98.5)	531 (99)
Grade ≥3	341 (70.5)	102 (39.2)	303 (57)
Led to treatment discontinuation	58 (12.0)	30 (11.5)	109 (20)
Led to dose reduction	343 (70.9)	74 (28.5)	220 (41)
Led to dose interruption	385 (79.5)	135 (51.9)	291 (54)
TEAEs leading to death	2 (0.4)	0 (0)	1 (<1)

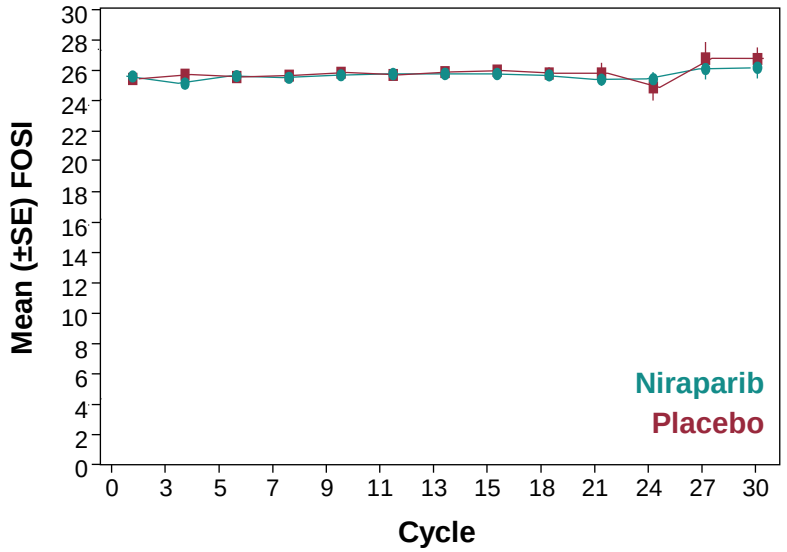
SOLO-1

FACT-O TOI score*



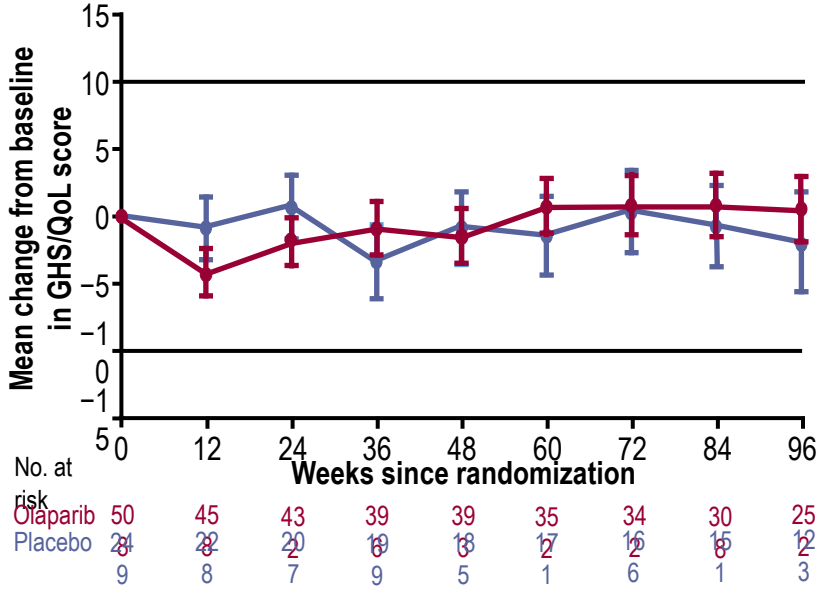
PRIMA/ENGOT-ov26

FOSI Adjusted Health Utility Index Score



PAOLA-1/ENGOT-ov25

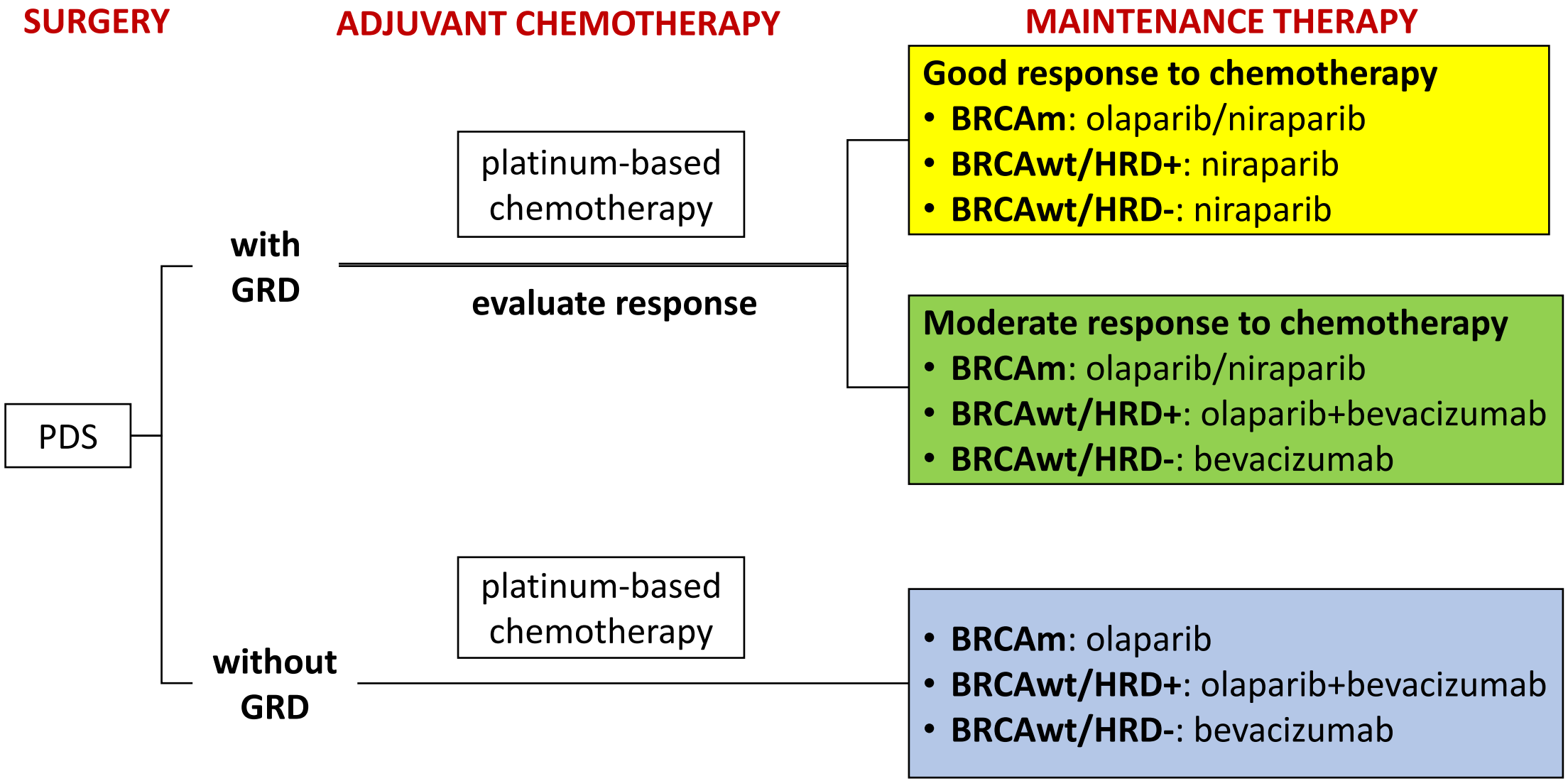
GHS/QoL score



	SOLO-1[1]	PRIMA[2]	PAOLA-1[3]
Discontinuation	11.5%	12%	**20%**
AML/MDS	3 (1%)	1 (< 1%)	6 (1.1%)

1. Barnejee et al. ESMO 2020; 2. Gonzalez-Martin. NEJM 20193; 3. Ray-Coquard. NEJM 2019

L'algoritmo terapeutico



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