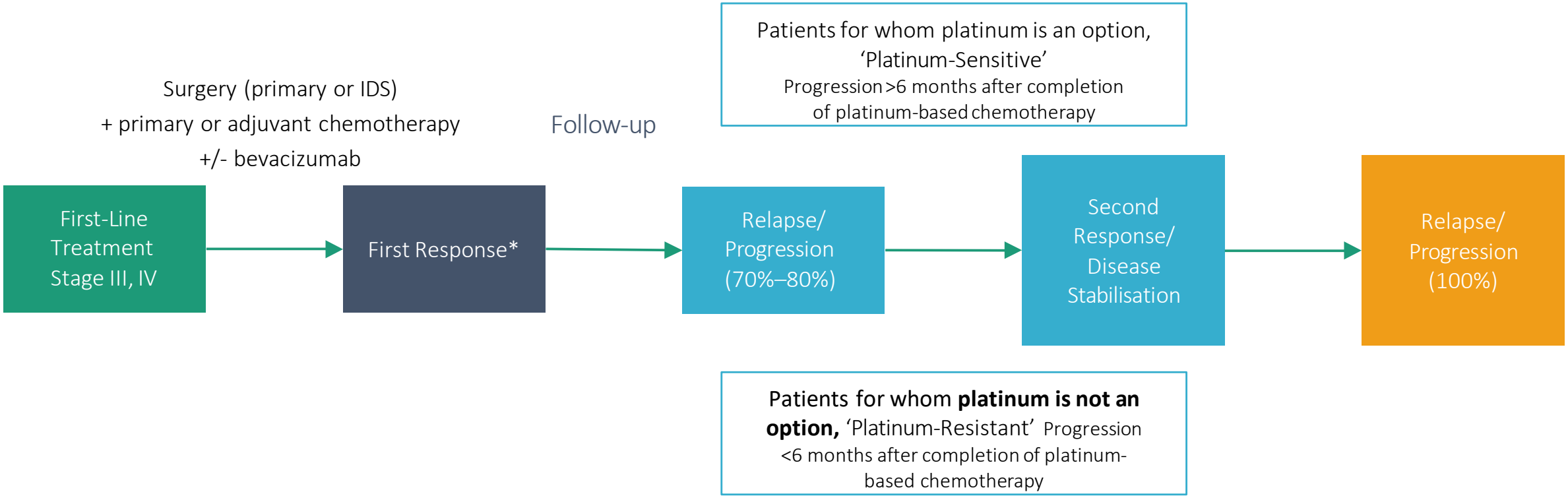
Ovarian Cancer in the Era of Precision Medicine: Update 2023

Tanja Pejovic, MD, PhD

March 3, 2023

The Typical Course of Advanced Ovarian Cancer

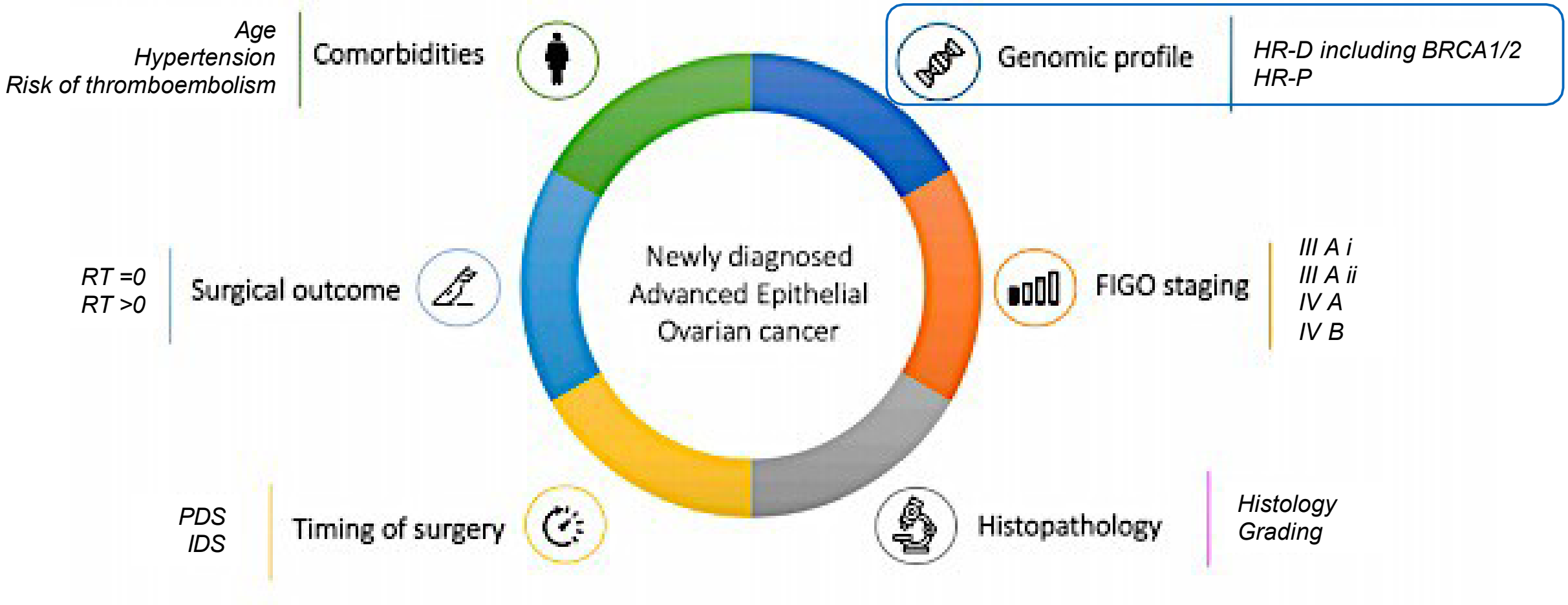


*Around 5% of patients are primary treatment-refractory, meaning disease progressed during therapy or within 4 weeks after the last dose.

IDS=interval debulking surgery.

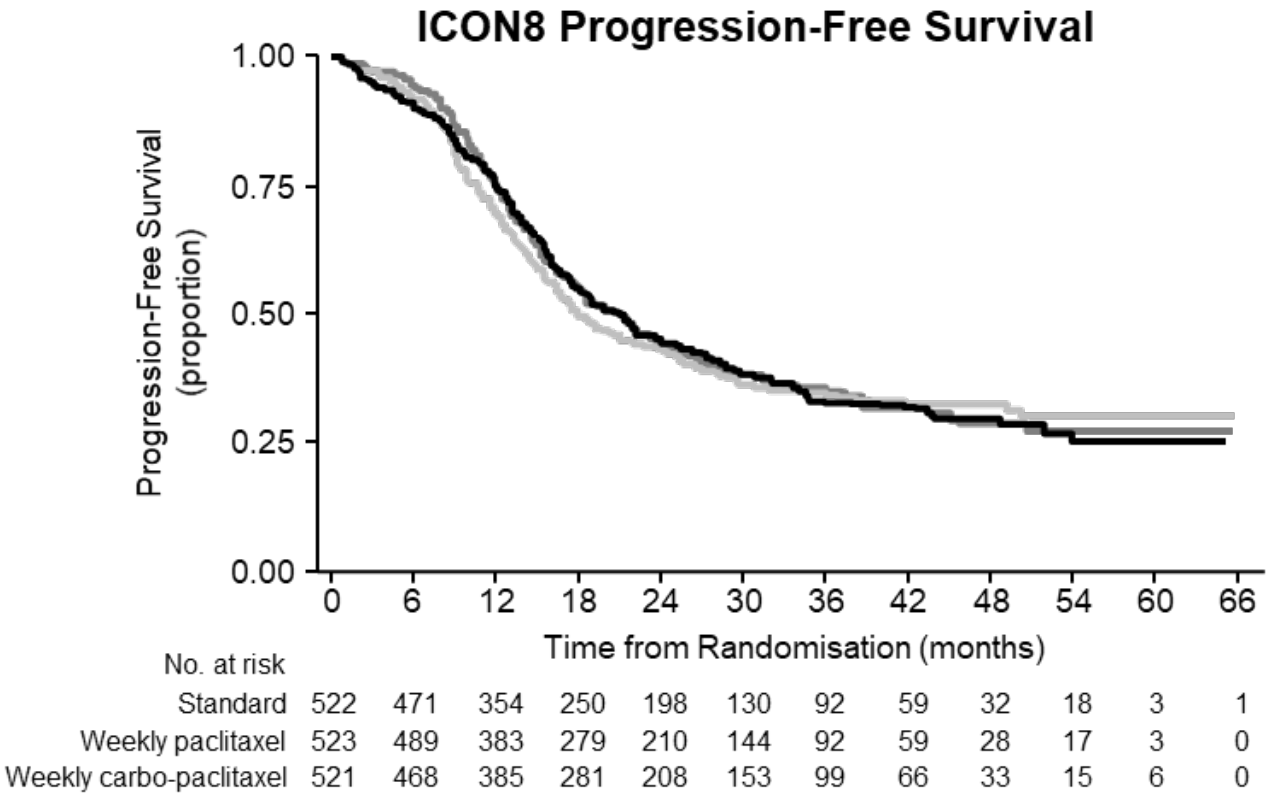
1. Ledermann JA et al. *Ann Oncol.* 2013;24(Suppl 6):vi24-vi32. 2. Giornelli GH. *Springerplus*. 2016;5(1):1197. 3. Pignata S et al. *Ann Oncol.* 2017;28(suppl_8):viii51-viii56. 4. du Bois A et al. *Cancer*. 2009;115(6):1234-1244. 5. Wilson MK et al. *Ann Oncol*. 2017;28(4):727-732.

Decision Making in Front Line Ovarian Cancer



Nero et al. Cancers 2021, 13; 1298

What Can We Expect with Platinum Based Chemo Alone?



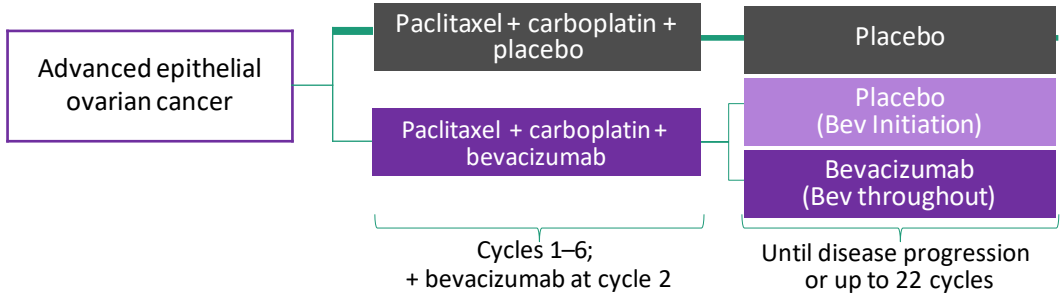
	Standard (n=522)	Weekly paclitaxel (n=523)	Weekly carbo-paclitaxel (n=521)
Progressions	330 (63%)	335 (64%)	338 (65%)
Median PFS, mo	17.9	20.6	21.1
Log rank (vs standard)		P=0.45	P=0.56
HR vs Standard (97.5% CI)		0.92 (0.77–1.09)	0.94 (0.79–1.12)
Restricted means	24.4 mos	24.9 mo	25.3 mo

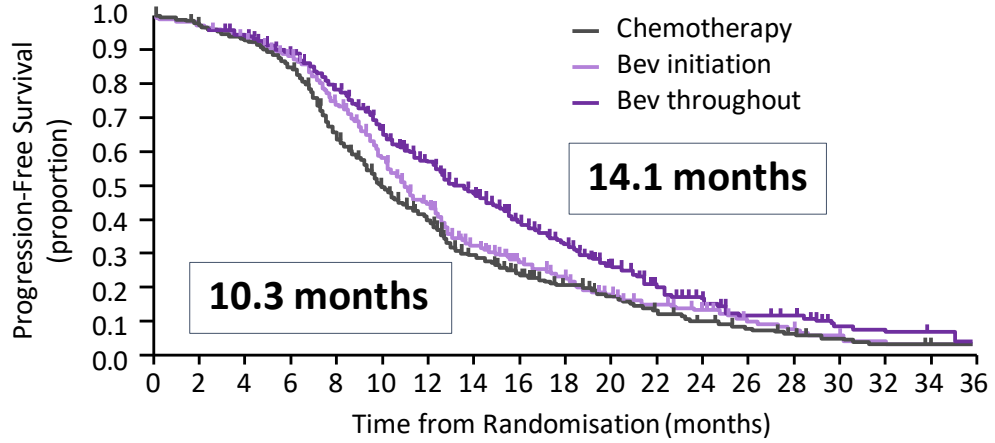
Weekly dose-dense chemotherapy can be delivered successfully as first-line epithelial ovarian cancer treatment without substantial toxicity increase; it does not significantly improve PFS compared to standard 3-weekly chemotherapy

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Clamp AR, et al. ESMO 2017. Abstract 4427.

Platinum Based Chemotherapy + Bevacizumab and Bevacizumab Maintenance Improved PFS

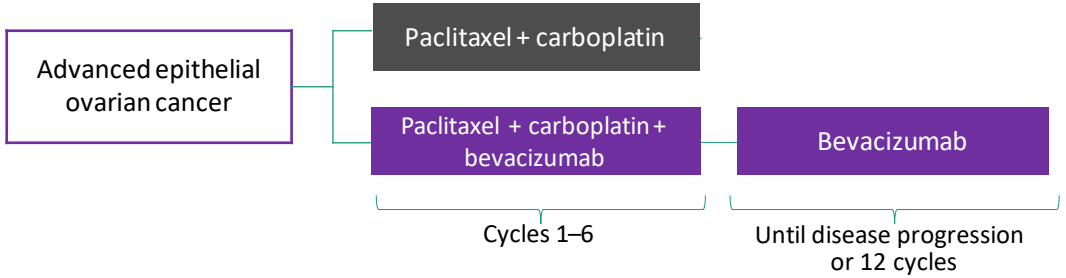
GOG 218[1]

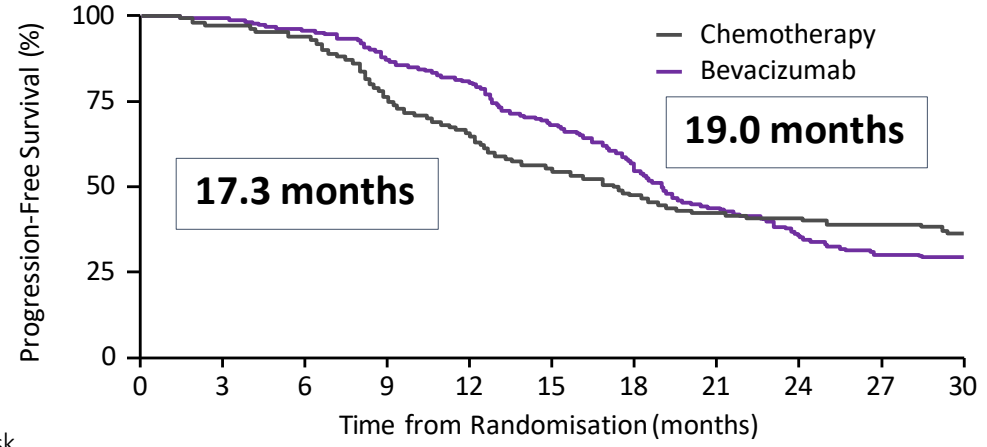




No. at risk				
Chemotherapy	625	199	33	8
Bev initiation	625	219	29	6
Bev throughout	623	254	38	8

ICON7[2]



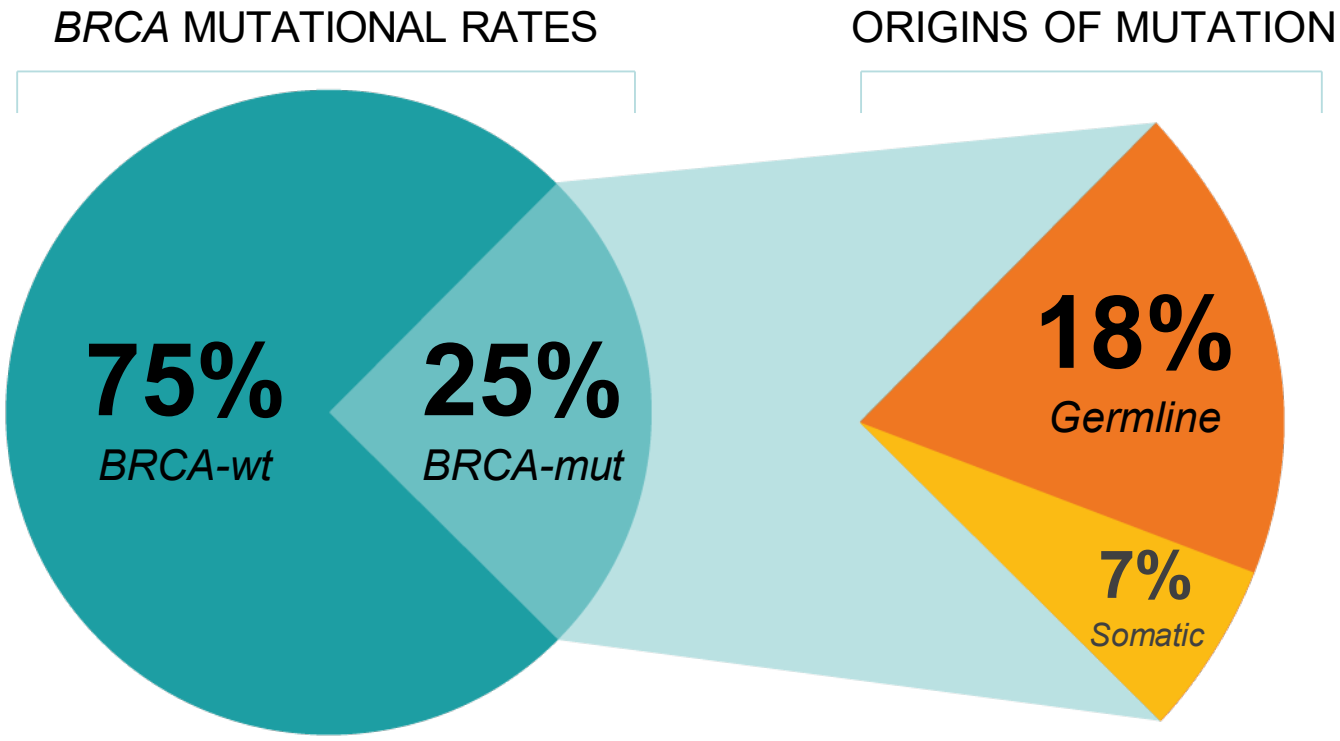


No. at risk						
Chemotherapy	764	693	464	216	91	25
Bevacizumab	764	715	585	263	73	19

Bev=bevacizumab.

1. Burger RA et al. *N Engl J Med.* 2011;365(26):2473-2483. 2. Perren TJ et al. *N Engl J Med.* 2011;365(26):2484-2496.

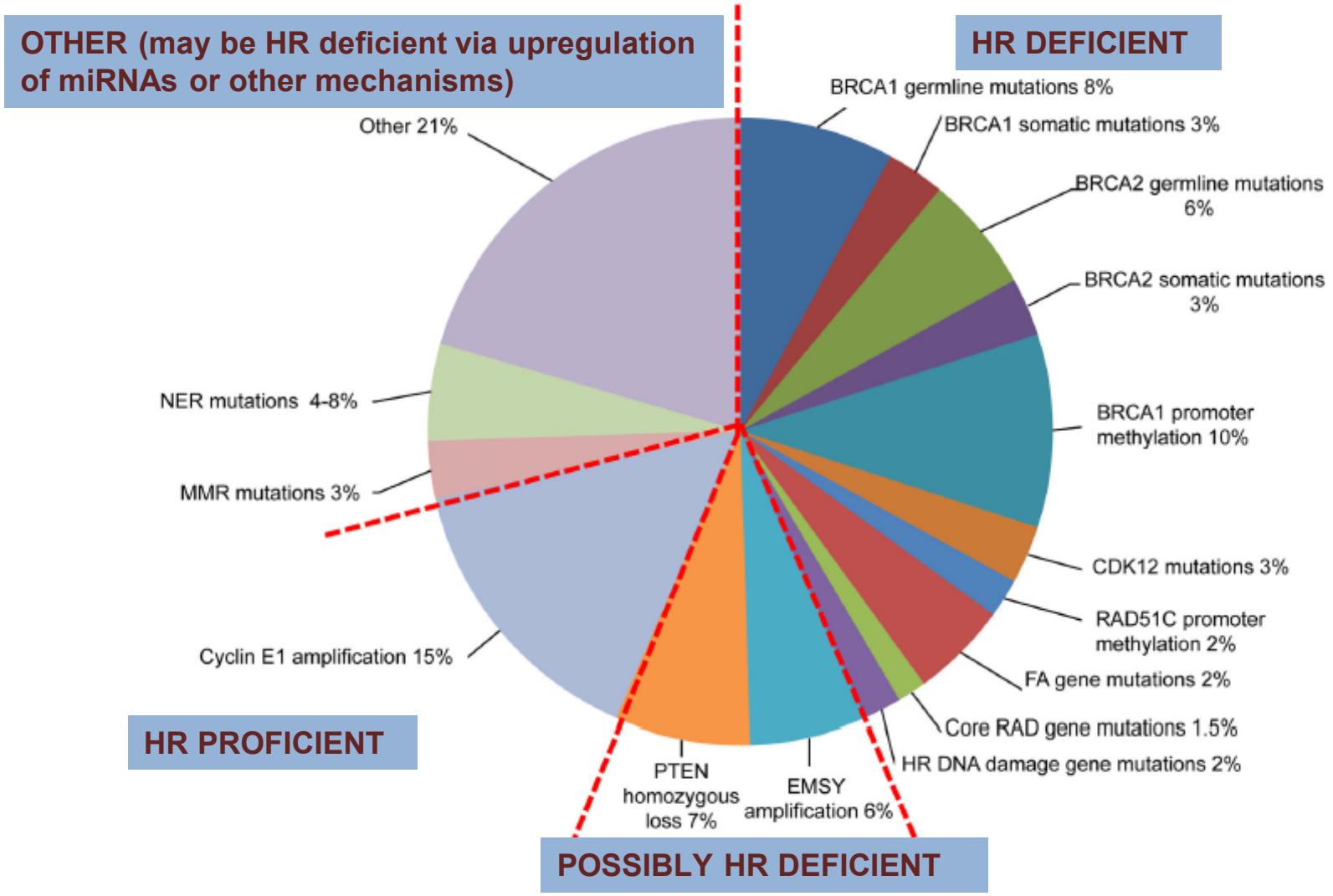
An estimated 25% of Newly Diagnosed Ovarian Cancers Harbor *BRCA 1/2* Mutations



An estimated 1 in 4 women with EOC will have a *BRCA*-positive tumor result
Tumor testing detects more patients with *BRCA* mutations than blood/saliva tests that do not look at tumor DNA

EOC, epithelial ovarian cancer; mut, mutation; wt, wild type
Pennington et al. Clin Cancer Res. 2014;20(3):764-75.

Genetic Mutations Beyond *BRCA* Mutations May Lead to Homologous Recombination Deficiency (HRd)

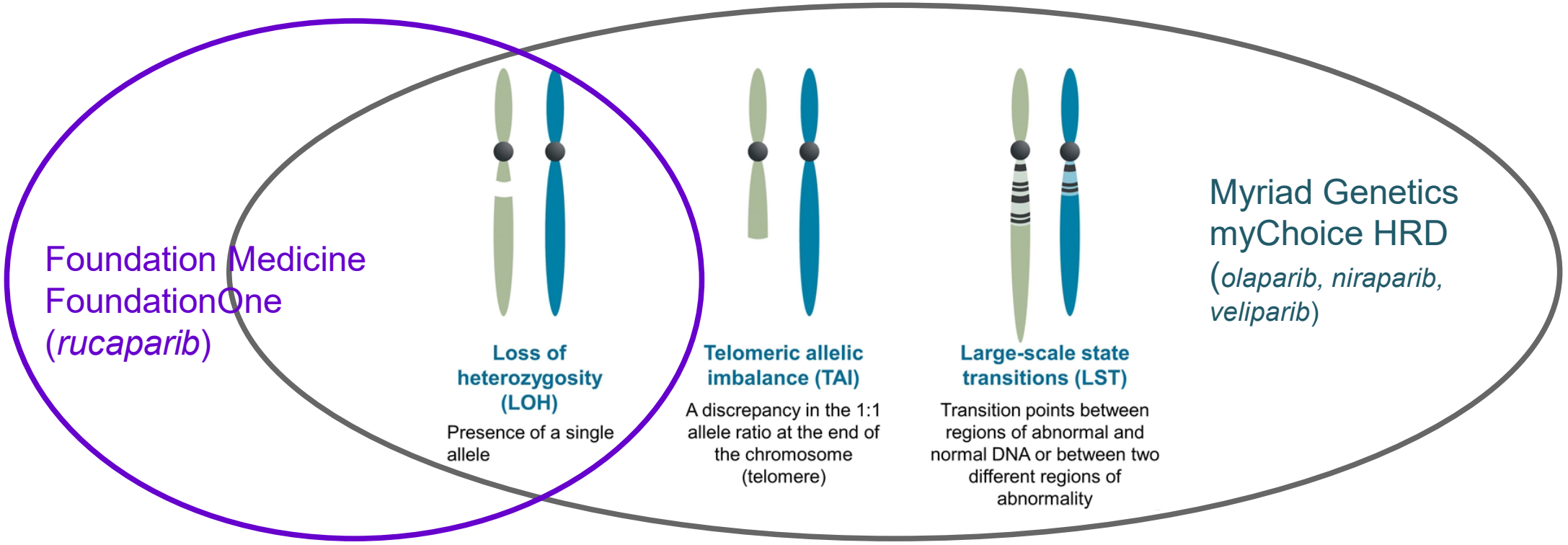


HR=homologous recombination; NER=nucleotide excision repair; MMR=mismatch repair; PTEN=phosphatase and tensin homolog.

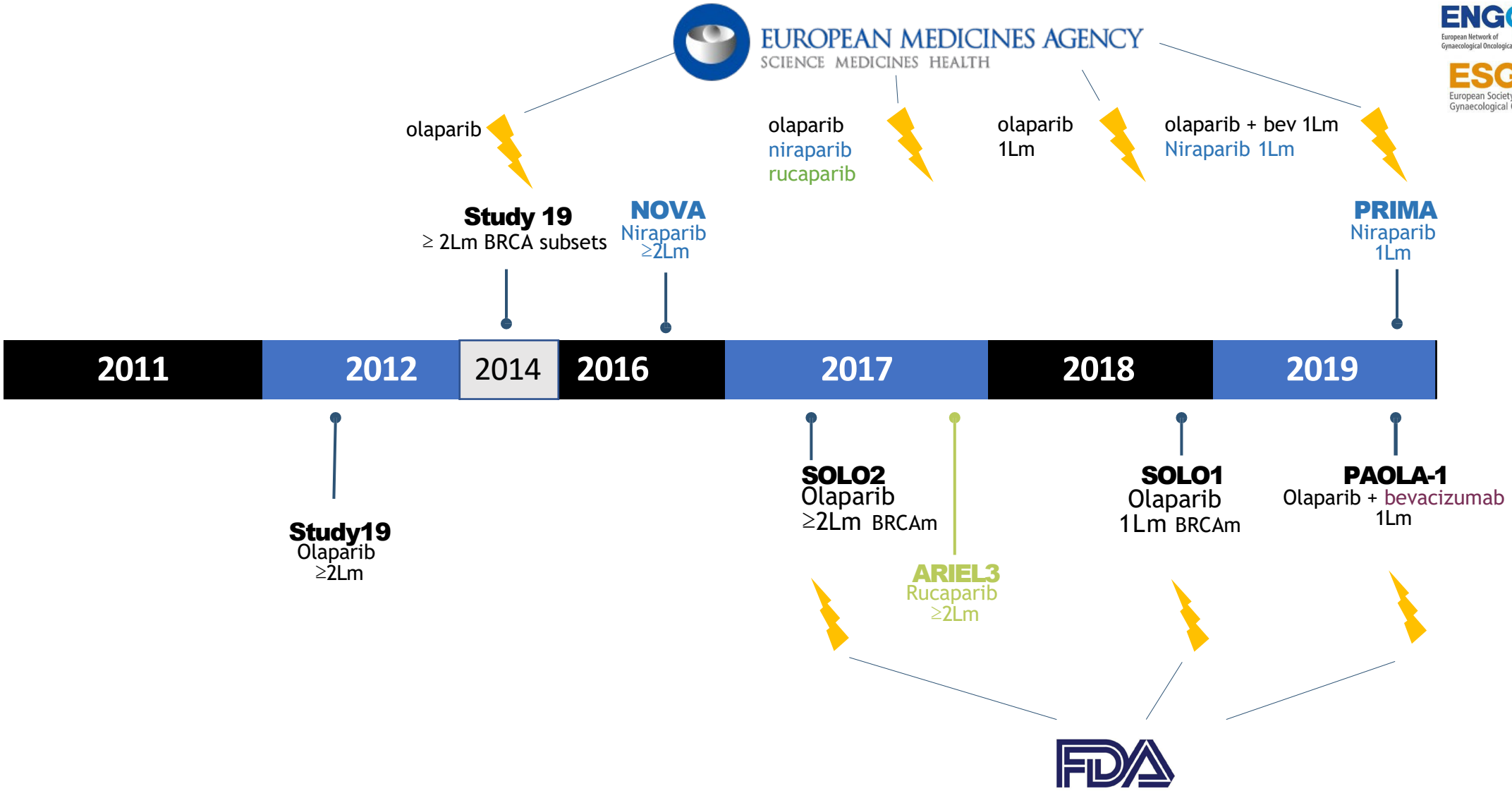
Konstantinopoulos PA et al. *Cancer Discov*. 2015;5:1137-54; Liu JF et al. *Gynecol Oncol*. 2014;133:362-369; Antoniou A et al. *Am J Hum Genet*. 2003;72:1117-1130; Chen S, Parmigiani G. *J Clin Oncol*. 2007;25:1329-1333.

Commercial “HRD” assays

- Based on Allelic imbalance
- An indirect marker of HR DNA repair capacity
- Not functional assays- represent downstream impact of HRD on genomic stability- genomic scar
- If cancers acquire resistance , i.e., restore HR proficiency, genomic scar persists.

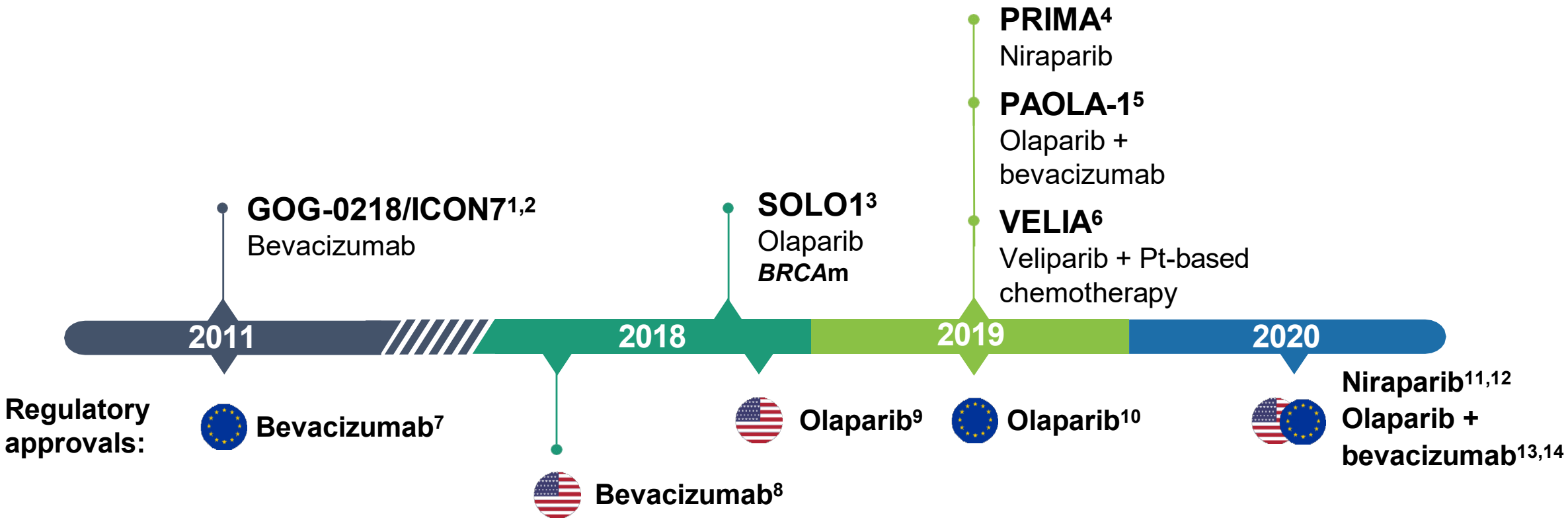


PARP Inhibitor therapy in advanced ovarian cancer



Pivotal trials and regulatory milestones in **1L maintenance therapy** of advanced ovarian cancer

Pivotal trials:



Dates shown indicate the year of the publication of the pivotal studies and regulatory approvals for these compounds.

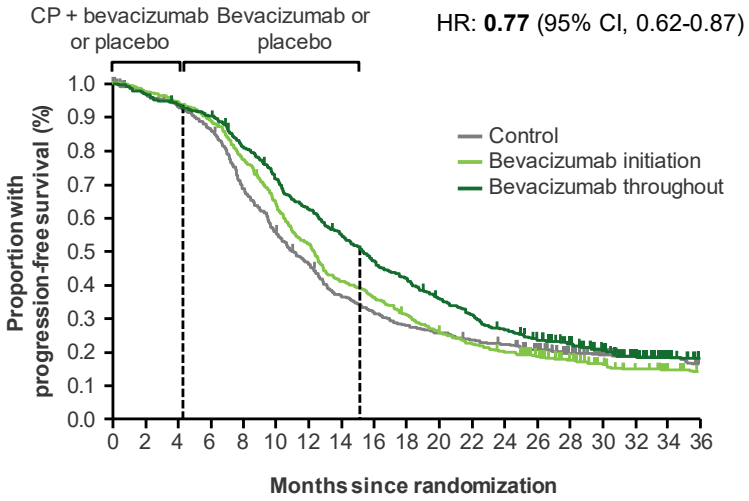
1L, first line; *BRCA*m, breast cancer gene mutant; GOG, Gynecologic Oncology Group; Pt, platinum.

1. Burger RA et al. *N Engl J Med*. 2011;365(26):2473-2483. **2.** Perren TJ et al. *N Engl J Med*. 2011;365(26):2484-2496. **3.** Moore K et al. *N Engl J Med*. 2018;379(26):2495-2505. **4.** González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **5.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428. **6.** Coleman RL et al. *N Engl J Med*. 2019;381(25):2403-2415. **7.** European Medicines Agency. Published September 22, 2011. Accessed June 7, 2021. **8.** F. Hoffmann-La Roche Ltd. Published June 13, 2018. Accessed June 7, 2021. **9.** US Food and Drug Administration. Published December 26, 2018. Accessed June 7, 2021. **10.** European Medicines Agency. Published April 26, 2019. Accessed June 7, 2021. **11.** GlaxoSmithKline. Published April 29, 2020. Accessed June 7, 2021. **12.** GlaxoSmithKline. Published October 29, 2020. Accessed June 7, 2021. **13.** US Food and Drug Administration. Published May 11, 2020. Accessed June 7, 2021. **14.** European Medicines Agency. Published September 17, 2020. Accessed June 7, 2021.

PARP inhibitors are changing the course of disease progression in patients with advanced ovarian cancer : *BRCA+*

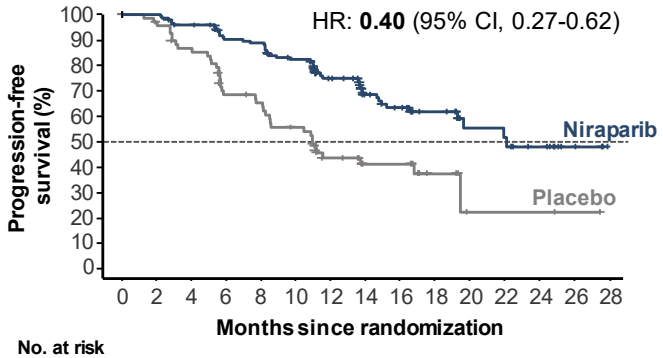
PARP inhibitors

GOG-0218[1]



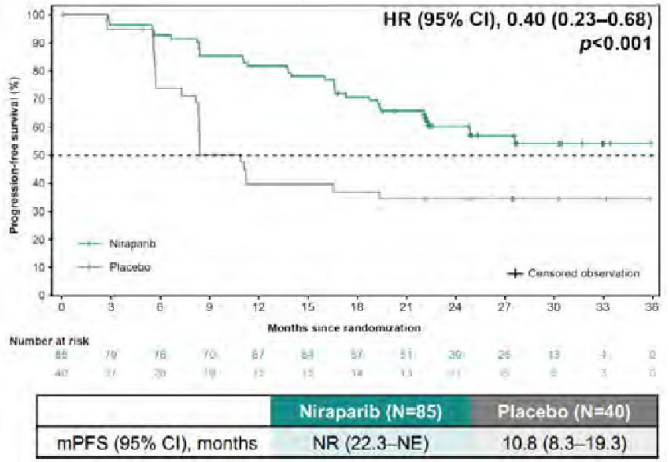
No. at risk							
Control	625	535	283	169	133	78	49
Bevacizumab initiation	625	552	319	190	121	67	40
Bevacizumab throughout	623	559	386	256	162	97	56

PRIMA: HRd *BRCA*m[2]



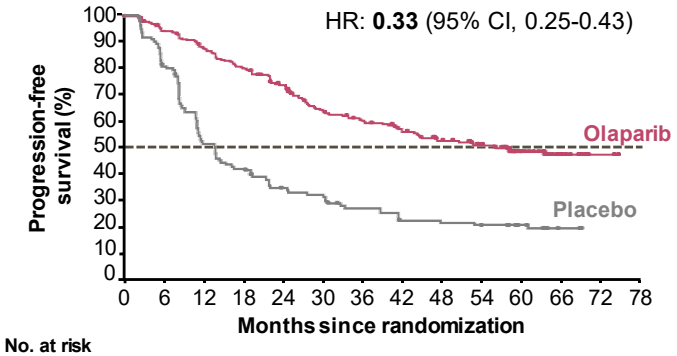
No. at risk													
Niraparib	152	148	140	127	125	113	77	55	48	29	15	14	10	4
Placebo	71	65	57	44	41	34	21	14	14	7	2	2	2	1

PRIME: HRd BRCAm[3]



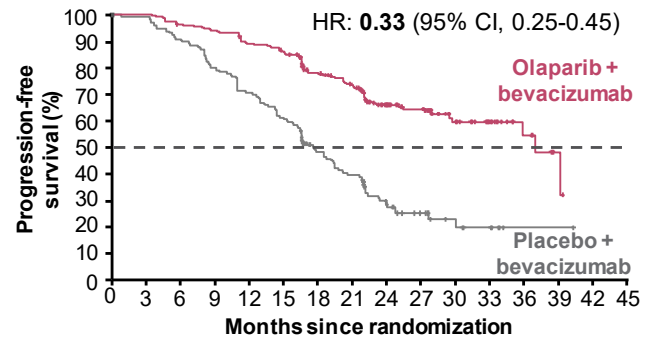
	Niraparib (N=85)	Placebo (N=40)
mPFS (95% CI), months	NR (22.3–NE)	10.8 (8.3–19.3)

SOLO1: *BRCA*m[4]



No. at risk													
Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0	0

PAOLA-1: BRCA[5]



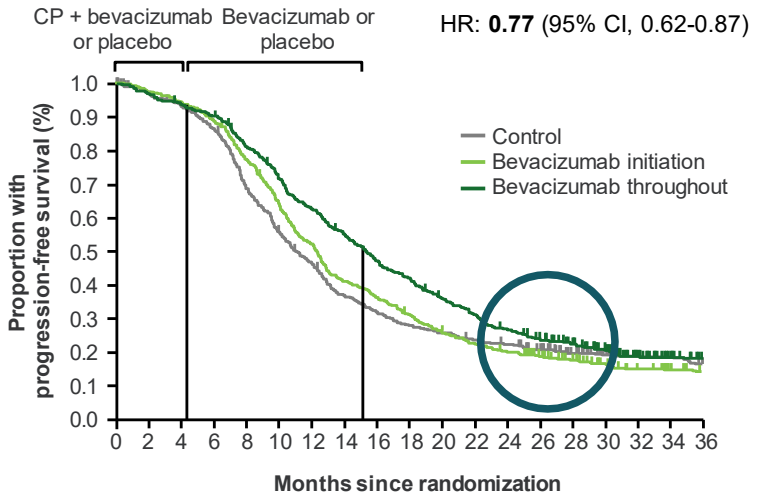
No. at risk														
Olaparib + bevacizumab	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo + bevacizumab	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

1. Burger RA et al. *N Engl J Med*. 2011;365(26):2473-2483. **2.** Monk BJ et al. Presented at: SGO Annual Meeting; March 29, 2020. Presentation 31. **3.** Li et al. SGO Phoenix 2022. **4.** Banerjee S et al. Presented at: ESMO Virtual Congress; September 19-21, 2020. Presentation 811MO. **5.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428.

PARP inhibitors are changing the course of disease progression in patients with advanced ovarian cancer : HRp

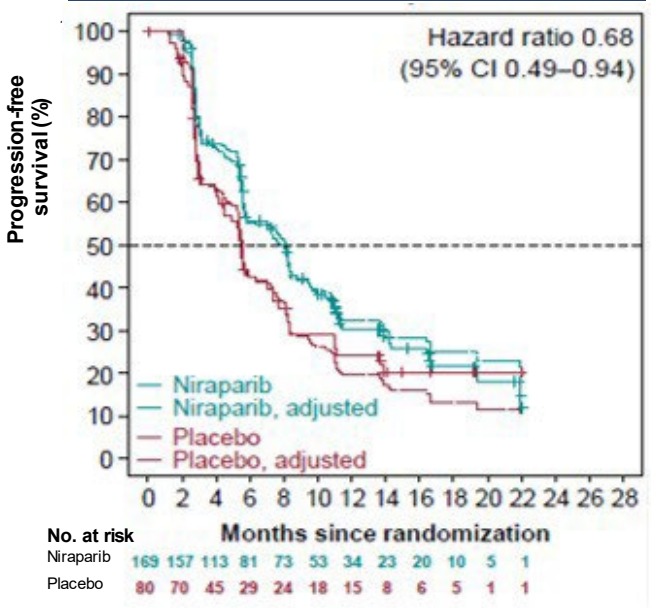
PARP inhibitors

GOG-0218[1]

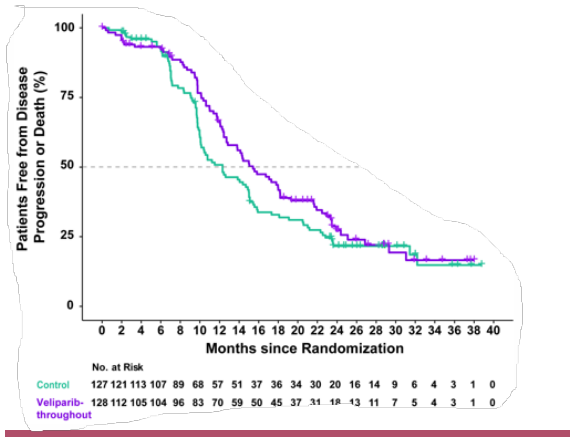


No. at risk							
Control	625	535	283	169	133	78	49
Bevacizumab initiation	625	552	319	190	121	67	40
Bevacizumab throughout	623	559	386	256	162	97	56

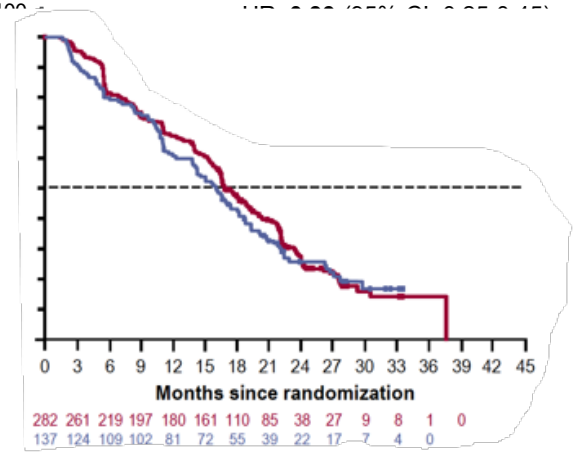
PRIMA: HRp [2]



VELIA: *HRp*[4]

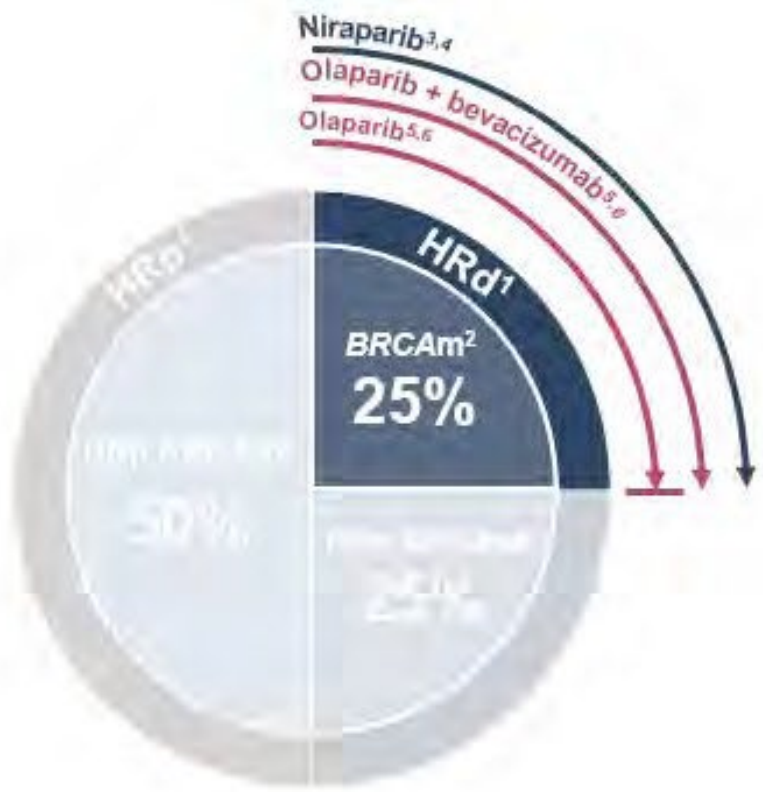


PAOLA-1: HRp[5]



1. Burger RA et al. *N Engl J Med*. 2011;365(26):2473-2483. **2.** Monk BJ et al. Presented at: SGO Annual Meeting; March 29, 2020. Presentation 31. **3.** González Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **4.** Coleman et al. N Engl J Med. 2019: 381(25): 2403. **5.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428.

PARP inhibitors are available for 1L maintenance therapy across biomarker subgroups



BRCAm/HRd

Niraparib (PRIMA)[3,4,7]

HR: 0.40 (95% CI, 0.27-0.62)

Niraparib (PRIME)[3,4,7,10]

HR: 0.40 (95% CI, 0.23-0.68)

Olaparib + bevacizumab (PAOLA-1)[5,6,8]

HR: 0.31 (95% CI, 0.20-0.47)

Olaparib (SOLO1)[5,6,9]

HR: 0.33 (95% CI, 0.25-0.43)

Percentages denote proportion of patients with genomic mutations in ovarian cancer.[2]

1L, first line; *BRCA*m, breast cancer gene mutant; *BRCA*wt, breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PARP, poly (ADP-ribose) polymerase.

1. The Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615. **2.** Pennington KP et al. *Clin Cancer Res*. 2014;20(3):764-775. **3.** ZEJULA. Summary of Product Characteristics. GlaxoSmithKline (Ireland) Ltd; 2021. **4.** ZEJULA. Prescribing Information. GlaxoSmithKline; 2021. **5.** Lynparza. Prescribing Information. AstraZeneca Pharmaceuticals LP; 2021. **6.** Lynparza. Summary of Product Characteristics. AstraZeneca AB; 2021. **7.** González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **8.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(5):2416-2428. **9.** Banerjee S et al. Presented at: ESMO Virtual Congress; September 19-21, 2020. Presentation 811MO. 10. Li et al. PRIME SGO 2022 Phoenix

PARP inhibitors are available for 1L maintenance therapy across biomarker subgroups

HRd

Niraparib (PRIMA)[3,4,7]

HR: 0.43 (95% CI, 0.31-0.59; *P*<0.001)

Niraparib (PRIME)[3,4,7,9]

HR: 0.48 (95% CI, 0.37-0.68)

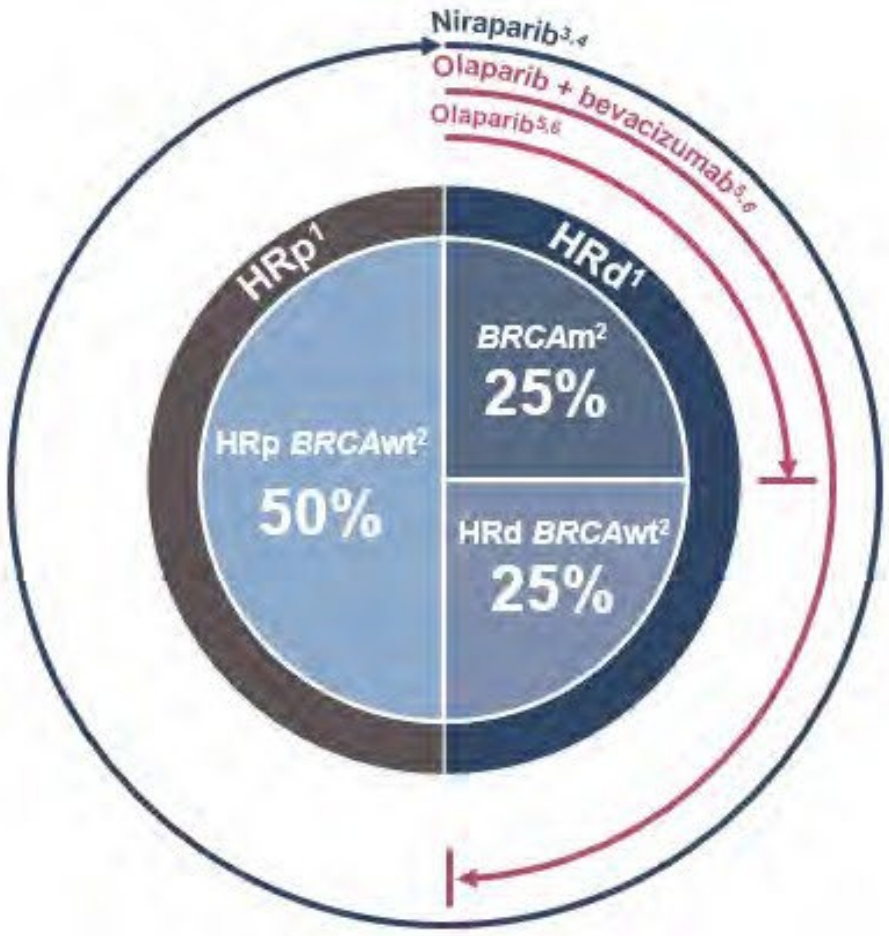
Olaparib + bevacizumab (PAOLA-1)[5,6,8]

HR: 0.33 (95% CI, 0.25-0.45)

1L, first line; *BRCA*m, breast cancer gene mutant; *BRCA*wt, breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PARP, poly (ADP-ribose) polymerase.

1. The Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615. **2.** Pennington KP et al. *Clin Cancer Res*. 2014;20(3):764-775. **3.** ZEJULA. Summary of Product Characteristics. GlaxoSmithKline (Ireland) Ltd; 2021. **4.** ZEJULA. Prescribing Information. GlaxoSmithKline; 2021. **5.** Lynparza. Prescribing Information. AstraZeneca Pharmaceuticals LP; 2021. **6.** Lynparza. Summary of Product Characteristics. AstraZeneca AB; 2021. **7.** González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **8.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(5):2416-2428. 9. Li et la. PRIME SGO 2022 Phoenix AZ

PARP inhibitors are available for 1L maintenance therapy across biomarker subgroups



All biomarker subgroups

Niraparib (PRIMA)[3,4,7]

HR: 0.62 (95% CI, 0.50-0.76; *P*<0.001)

Niraparib (PRIME)[3,4,7,8]

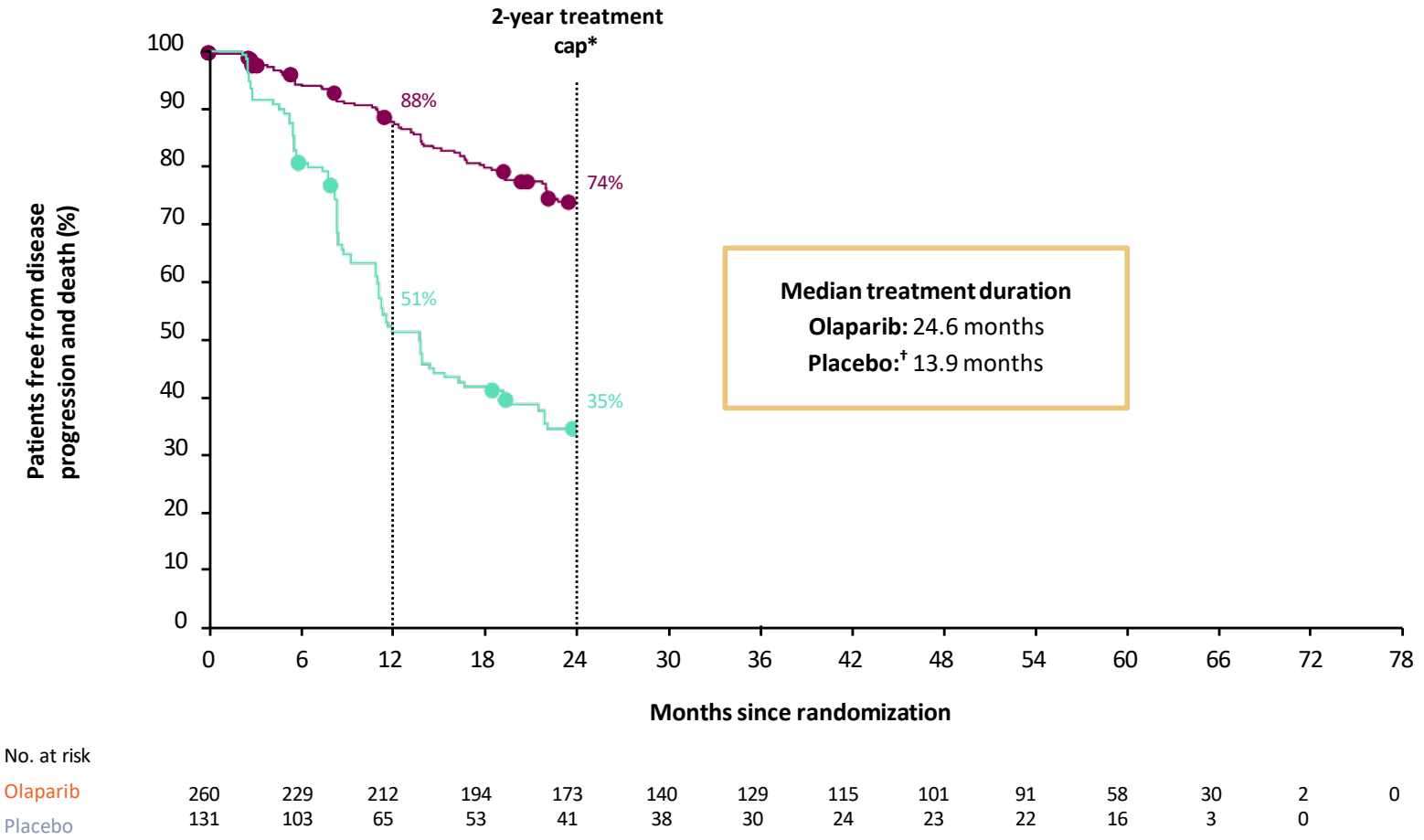
HR: 0.41 (95% CI, 0.25-0.69; *P*<0.001)

2

1L, first line; *BRCA*m, breast cancer gene mutant; *BRCA*wt, breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PARP, poly (ADP-ribose) polymerase.

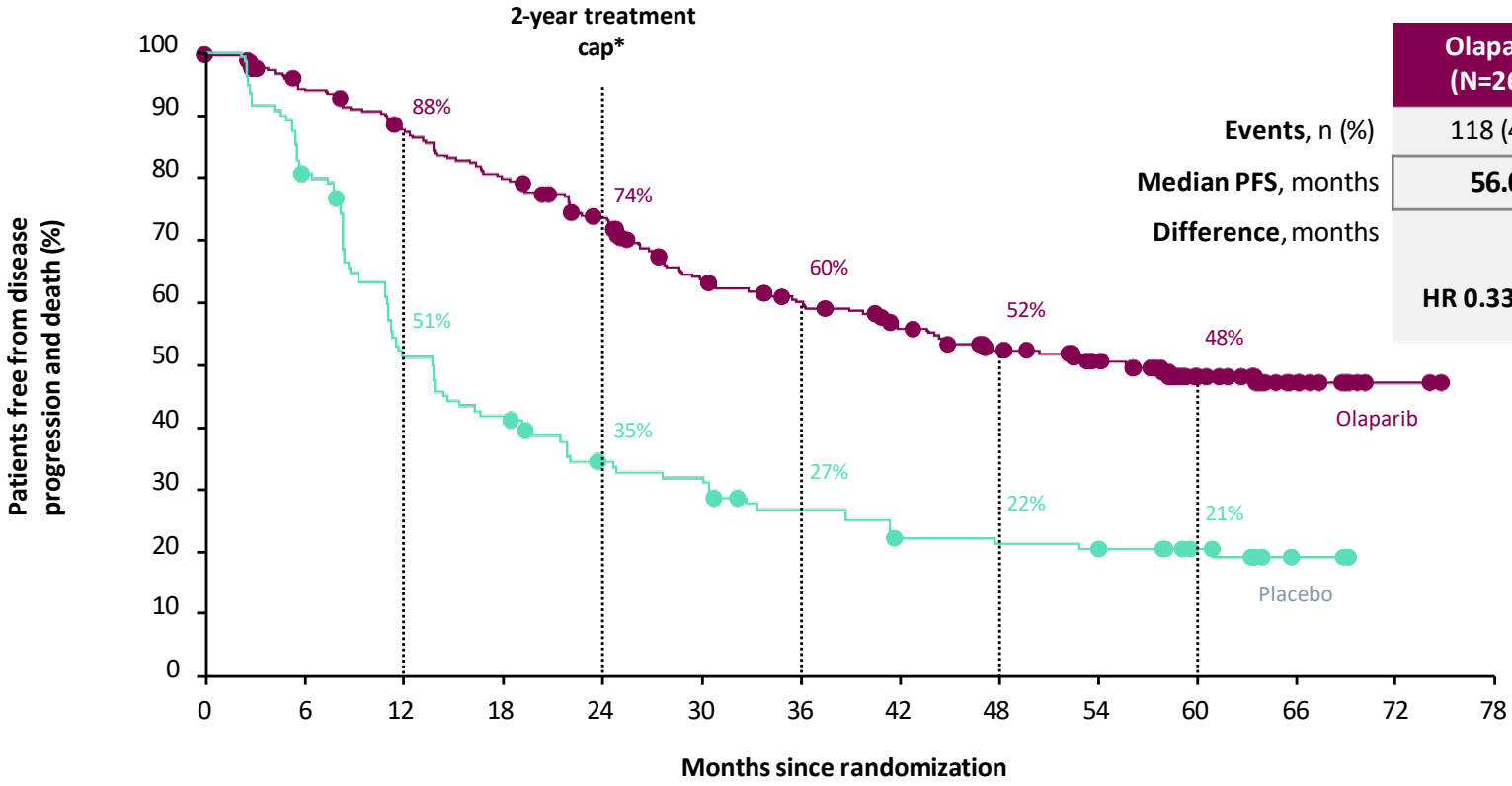
1. The Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615. **2.** Pennington KP et al. *Clin Cancer Res*. 2014;20(3):764-775. **3.** ZEJULA. Summary of Product Characteristics. GlaxoSmithKline (Ireland) Ltd; 2021. **4.** ZEJULA. Prescribing Information. GlaxoSmithKline; 2021. **5.** Lynparza. Prescribing Information. AstraZeneca Pharmaceuticals LP; 2021. **6.** Lynparza. Summary of Product Characteristics. AstraZeneca AB; 2021. **7.** González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402.

Do we have any signal of OS?
No - but we do have 5 year PFS from SOLO-1



*13 patients, all in the olaparib arm, continued study treatment beyond 2 years; †n=130 (safety analysis set).
Investigator-assessed by modified RECIST v1.1. DCO: March 5, 2020.

PFS benefit of maintenance olaparib was sustained beyond the end of treatment



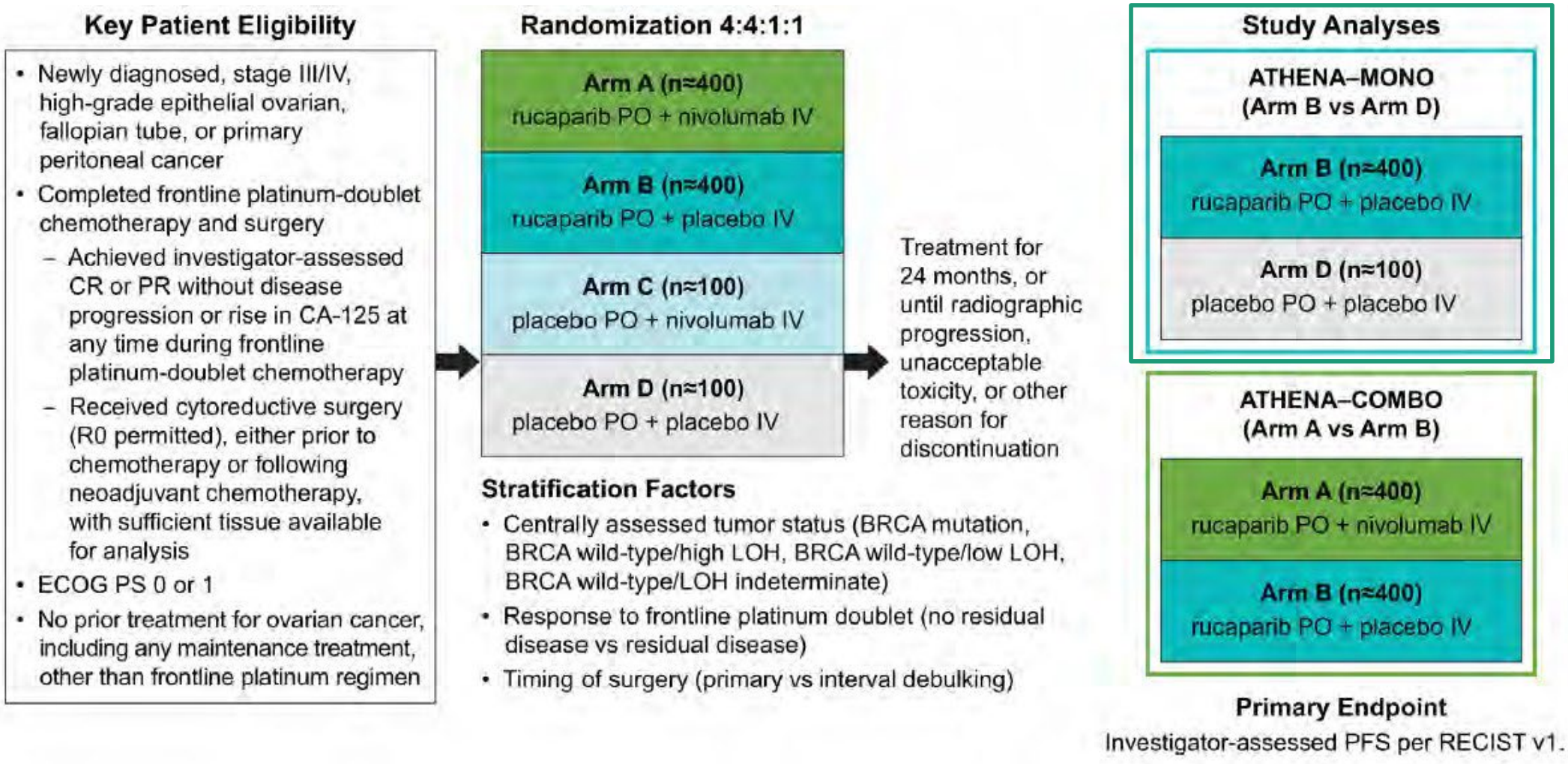
	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	**56.0**	**13.8**
Difference, months	42.2	
	HR 0.33 (95% CI 0.25–0.43)	

No. at risk

Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0	

*13 patients, all in the olaparib arm, continued study treatment beyond 2 years; †n=130 (safety analysis set).
Investigator-assessed by modified RECIST v1.1. DCO: March 5, 2020.

ATHENA-MONO May Add Another Option?

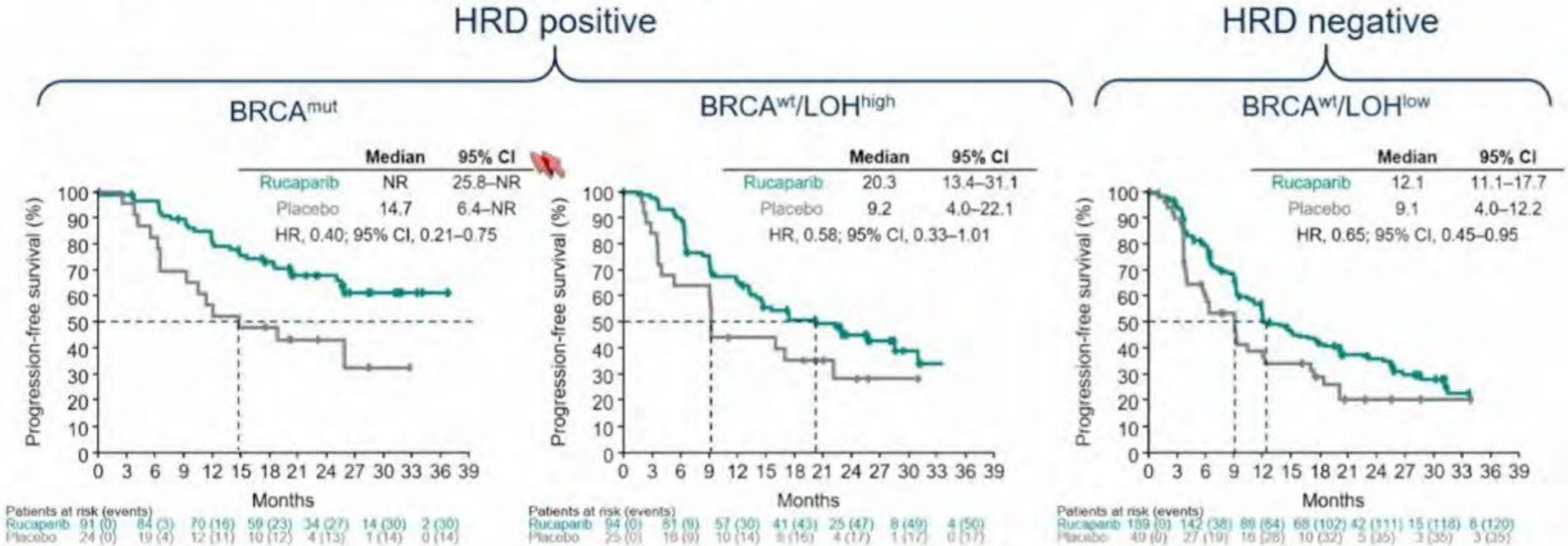


Starting dose of rucaparib is 600mg orally twice a day and nivolumab 480mg IV every 4 weeks.

CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; LOH, loss of heterozygosity; PO, by mouth; PR, partial response; R0, total cytoreduction; RECIST, Response Evaluation Criteria in Solid Tumor.

Monk BJ, et al. *Int J Gynecol Cancer*. 2021;31:1589-1594.

Investigator-Assessed PFS: Exploratory Subgroups



- 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.

Magnitude of Benefit for PARPi Maintenance By Clinical Prognostic Factors

Front Line Ovarian Trials				
Parameter	**SOLO1[3]**	**PAOLA[2]**	**PRIMA**	**VELIA[4]**
Timing of Surgery **pCRS** **iCRS**	HR 0.31 HR 0.37	HR 0.52 HR 0.66	HR 0.66 HR 0.59	HR 0.72 HR 0.64
Residual Disease **NGR** **Residual Dz**	HR 0.33 HR 0.44	HR 0.47-0.61 HR 0.74-0.70	NR	HR 0.60-0.72 HR 0.64-0.77
CR or PR on entry **NED** **CR** **PR**	NR HR 0.34 HR 0.31	HR 0.53 HR 0.44 HR 0.86	NR HR 0.60 HR 0.60	NR
Age **<75** **≥75**		Ref 5 HRD is main independent predictive factor	HR 0.62[1] HR 0.37	HR 0.65 HR 0.77 (< 65)

- Subset analyses from all 4 trials have not shown any subgroups who benefit less from PARPi than others
- Clinical High Risk features (stage, residual disease, timing of surgery) which may identify patients who benefit more from bevacizumab – do not identify patients more likely to benefit from PARPI
- Even patients in the “best” clinical prognostic group (stage III, BRCA, pCRS to NGR) have unprecedented benefit from PARPI.

1. Valabrega et al. ESMO Virtual Congress 2020. Grimm et al. SGO 2020. 3. Mathews et al. ASCO Poster 5541 2019 4. Coleman et al. NEJM 2019 5. Sabatier et al. ESMO 2021 poster 1990

Summary of toxicity of maintenance PARPi trials (first-line)

	GOG-218	SOLO-1	PAOLA-1	PRIMA
Administration	IV q3weeks 15 months	Oral BID 2 years	Oral BID 2y + IV q3w 15m	Oral QD 3 years
% dose reduction	-	28.5	41	70.9
% dose interruption	-	51.9	54	79.5
% discontinuation	**17**	**11.5**	**20**	**12**
Most frequent Grade ≥ 3 AE	Neut G4 (64%) HT G ≥2 (23%)	Anaemia (22%) Neut. (9%) Asthenia (4%)	HT (19%) Anaemia (17%) Lymph (7%)	Anaemia (31%) Plates. (28%) Neut. (12.8%)

Burger. NEJM 2011; Moore. NEJM 2018;Ray-Coquard. NEJM 2019; Gonzalez-Martin. NEJM 2019

Evidence for Optimal duration of maintenance PARPi therapy

	First Line	Relapsed disease
Olaparib	BID for 2 years	BID until progression
Niraparib	OD for 3 years	OD until progression
Rucaparib	-	BID until progression

PARPi for 1LM: Key Efficacy Data

Efficacy	PRIMA[1] (N=733)	PRIME[2] (N=384) (study performed only in China)	SOLO-1[3] (N=391) (5-year follow-up)	ATHENA-MONO[4] (N=538)	PAOLA-1[5] (N=806)	OVARIO[6] (N=105) (updated analysis)
Median PFS, months HR[a] (95% CI)						
ITT	N=733 13.8 vs 8.2 0.62 (0.50-0.76)	N=384 24.8 vs 8.3 0.45 (0.34-0.60)	-	N=538 20.2 vs 9.2 0.52 (0.40-0.68)	N=806 22.1 vs 16.6 0.59 (0.49-0.72)	N=105 19.6
*BRCA*wt/HRp	n=249 8.1 vs 5.4 0.68 (0.49-0.94)	n=127[b] 14.0 vs 5.5 0.41 (0.25-0.65)	-	n=238 12.1 vs 9.1 0.65 (0.45-0.95)	n=211 16.9 vs 16.0 1.00 (0.75-1.35)[b]	n=38 14.2
*BRCA*wt/HRd	n=150 19.6 vs 8.2 0.50 (0.31-0.83)	n=132[c] 24.8 vs 11.1 0.58 (0.36-0.93)	-	N= 119 20.3 vs 9.2 0.58 (0.33-1.01)	n=152 28.1 vs 16.6 0.43 (0.28-0.66)[b]	n=16 28.3
*BRCA*m	n=223 22.1 vs 10.9 0.40 (0.27-0.62)	n=125[d] NR vs 10.8 0.40 (0.23-0.68)	n=391 56.0 vs 13.8 0.33 (0.25-0.43)	n=115 NR vs 14.7 0.40 (0.21-0.75)	n=90 37.2 vs 21.7 0.31 (0.20-0.47)[b]	n=29 NR
Median duration of follow-up, months	13.8	27.5	59	NA	22.9	28.7

[a] HR for disease progression or death. [b] Non-*gBRCA*m/HRp. [c] Non-*gBRCA*m/HRd. [d] g*BRCA*m population. 1LM, first-line maintenance; *BRCA*wt, *BRCA* wild type; g*BRCA*m, germline *BRCA* mutant; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention-to-treat; NA, not available; NR, not reached; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

1. Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-2402. 2. Li N, et al. Presented at SGO 2022. Abstract 244. 3. Banerjee S, et al. *Lancet Oncol*. 2021;22(12):1721-1731. 4. Clovis Oncology. News Release. March 31, 2022.
5. Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428. 6. Hardesty M, et al. Presented at SGO 2022. Abstract 170B.

A woman in her 50s with Stage IIIB ovarian cancer and a germline BRCA1 mutation is s/p hysterectomy/bilateral salpingo-oophorectomy/omentectomy and 6 cycles of carboplatin/paclitaxel. What would you most likely recommend as maintenance therapy?

1. None
2. Bevacizumab
3. Olaparib
4. Niraparib
5. Olaparib/bevacizumab
6. Other

RTP
RESEARCH
TO PRACTICE

A 73-year-old woman with ascites and a fixed pelvic mass that are confirmed to be BRCA wild-type, high-grade serous ovarian cancer receives neoadjuvant carboplatin/paclitaxel/bevacizumab and undergoes near-complete gross resection. Tumor testing for HRD is 19%. What would you most likely recommend as maintenance therapy?

1. **None**
2. Bevacizumab
3. Olaparib
4. Niraparib
5. Olaparib/bevacizumab
6. Other

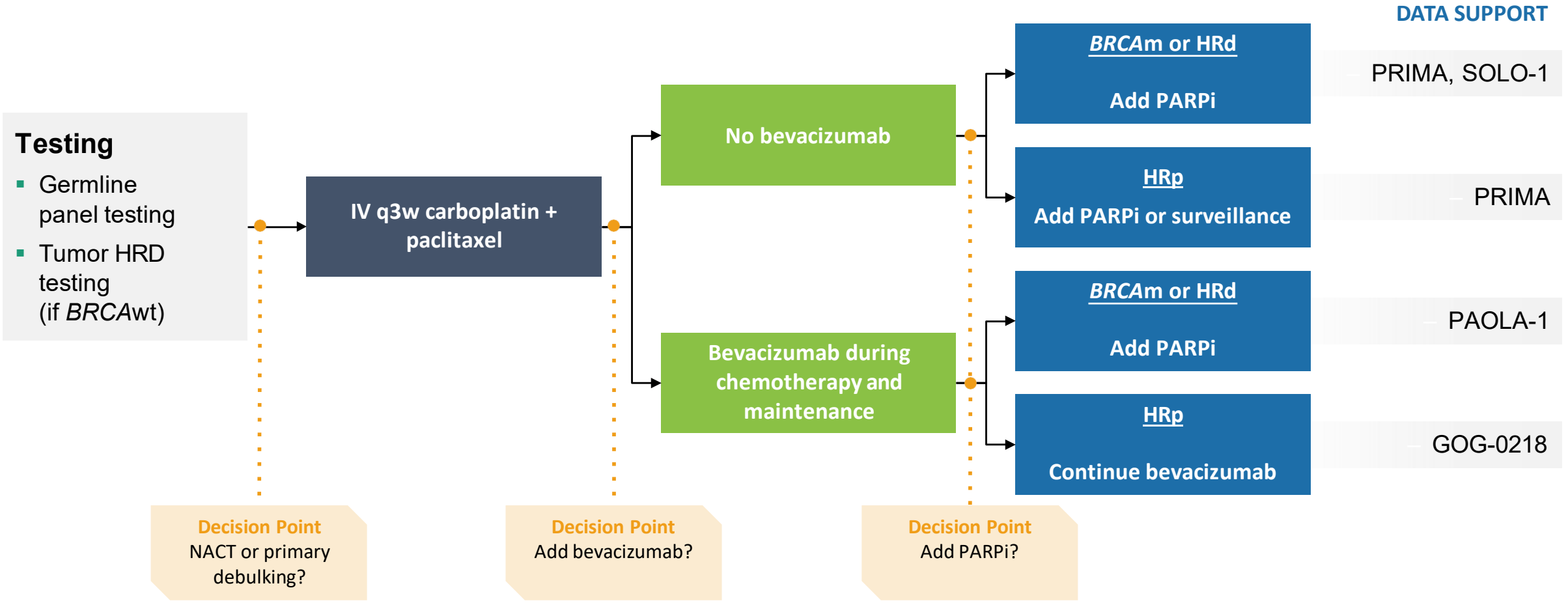
Future Directions in the Front Line: What is Potentially Exciting?

Trial	Size	Anti-angiogenic	PARPi	ICI	Start	Estimated Primary Completion
FIRST[a] ENGOT OV-44	1405	± Bevacizumab	Niraparib	Dostarlimab	Oct 2018	Jan 2023
DUO-O[b] ENGOT OV-46	~1254	Bevacizumab	Olaparib	Durvalumab	Jan 2019	June 2023
ATHENA[c] GOG-3020 ENGOT OV-45	~1000	-	Rucaparib	Nivolumab	May 2018	Dec 2024
ENGOT OV-43[d] KEYLYNK-001	~1086	± Bevacizumab	Olaparib	Pembrolizumab	Dec 2018	Aug 2025

- a. ClinicalTrials.gov. NCT03602859; b. ClinicalTrials.gov. NCT03737643; c. ClinicalTrials.gov. NCT03522246; d. NCT03740165.

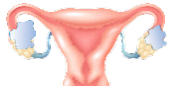
Patients may have more than one option for treatment of advanced ovarian cancer

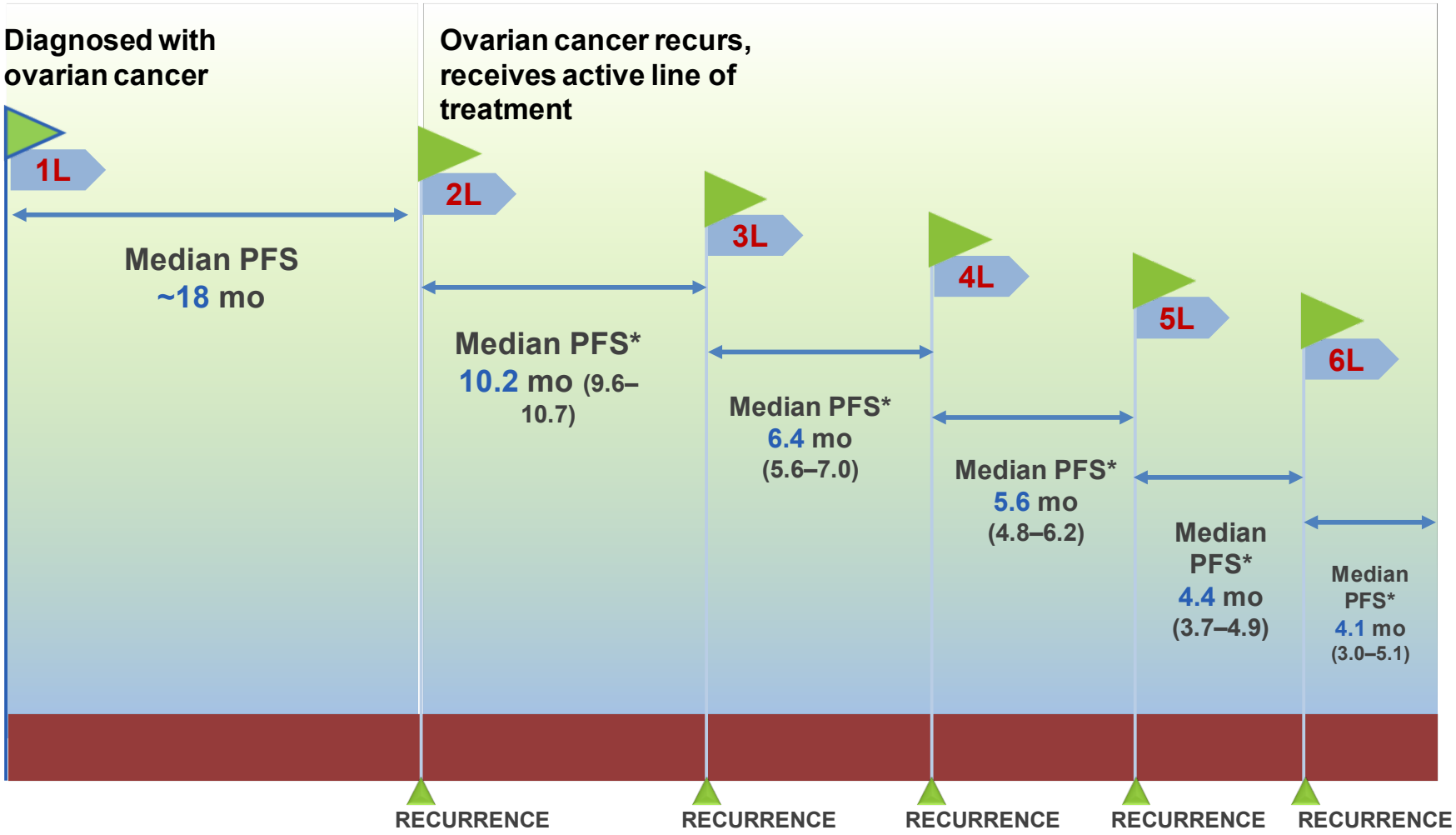
A recently published consensus of US physicians outlines one algorithmic approach



Adapted from: Chan JK et al. *Gynecol Oncol*. 2020;159(3):604-606 and Ledermann JA. *Ann Oncol*. 2013;24(suppl 6):vi24-vi32.

Now that we may be using all our best agents “up front” what do we do here?….





***PFS was calculated from the day of randomization (day of first cycle of chemotherapy) to the first disease progression.**

PFS = progression-free survival; L = line.

Hanker LC, et al. *Ann Onc.* 2012;23:2605-2612. Lorusso D, et al. *Int J Surg Oncol*. 2012;2012:613980.

Platinum sensitive paradigm shift : bevacizumab in combination with chemotherapy

Study	Randomization	N	Median PFS (mo)	HR, p-value	Median OS (mo)	HR, p-value
OCEANS[1,2]	C/gem + placebo C/gem + bev until progression	242 242	8.4 12.4	HR = 0.484 p<0.0001	32.9 33.6	HR = 0.952 p = 0.6479
GOG-0213[3]	C/P C/P + bev	337 377	10.4 13.8	HR = 0.628 p<0.0001	37.3 42.2	HR = 0.829 p = 0.056 HR = 0.823* p = 0.0447*
AGO OVAR 2.21[4]	C/Gem + bev C/PLD + bev	294 277	11.7 13.3	HR = 0.807 P=0.0128	NR	NR

- 1. Aghajanian C et al. *J Clin Oncol* 2012;30(17):2039-45; 2. Aghajanian C et al. *Gynecol Oncol* 2015;139(1):10-6; 3. Coleman RL et al. *Lancet Oncol* 2017;18(6):779-91. 4. Pfisterer J ESMO 2018

Pivotal studies of PARP-inhibitors in patients with recurrent ovarian cancer after response to platinum

Study	Study 19[1]	SOLO-2[2] g*BRCA*m	NOVA[3] g*BRCA*m	NOVA[3] Non-g*BRCA*m	ARIEL-3[4] *BRCA*m	ARIEL-3[4] ITT
Agent	**Olaparib**	**Olaparib**	**Niraparib**	**Niraparib**	**Rucaparib**	**Rucaparib**
Difference in PFS (months)	8.4 vs 4.8	19.1 vs 5.5	21.0 vs 5.5	9.3 vs 3.9	16.6 vs 5.4	10.8 vs 5.4
PFS HR (investigator assessed)	**0.35** (95% CI 0.25 - 0.49; p<0.001)	**0.30** (95% CI 0.22-0.41; p<0.0001)	**0.27** (95% CI 0.18-0.40)	**0.53** (95% CI 0.41, 0.68)	**0.23** (95% CI 0.16-0.34, p<0.0001)	**0.36** (95% CI 0.30-0.45; p<0.0001)
PFS HR (BICR)	**0.39** (95% CI 0.27-0.55; P<0.001)	**0.25** (95% CI 0.18-0.35; p<0·0001)	**0.27** (95% CI 0.17-0.41; p<0.0001)	**0.45** (95% CI 0.34-0.61; p<0.0001)	**0.20** (95% CI 0.13-0.32; p<0.0001)	**0.35** (95% CI 0.28-0.45; p<0.0001)

All of these studies were for women with PARPi naïve tumors. Is this even relevant now?

•1. Ledermann J, et al. NEJM. 2012;366:1382-1392. 2. Pujade-Lauraine E et al. Lancet Oncol. 2017 Sep;18(9):1274-1284. 3. FDA NDA review ref 4074987, application no 208447. 4. Coleman RL et al. Lancet. 2017 Oct 28;390(10106):1949-1961.

NOVA Follow-up: OS

Dear HCP Letter May 2022

BRCAmut: mOS 43.6 vs. 41.6 for niraparib vs placebo (HR=0.93 (95% 0.63-1.36)

BRCAwt: mOS 31.1 vs. 36.5 months for niraparib vs placebo (HR =1.10 (95% CI 0.83-1.46)

BRCAwt/HRD mOS 37.3 vs. 41.4 months for niraparib vs placebo (HR 1.32 (95% CI 0.84-2.06)

The current OS result indicate a possible OS detriment to patients in the overall BRCAwt cohort who received niraparib

Figure 1: OS Kaplan Meier curve for the non-g*BRCA*mut cohort

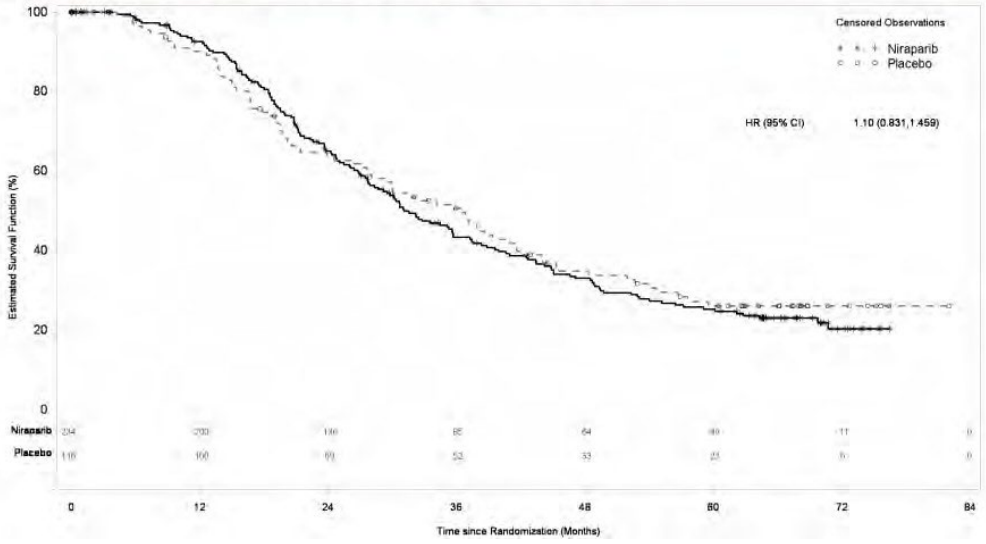
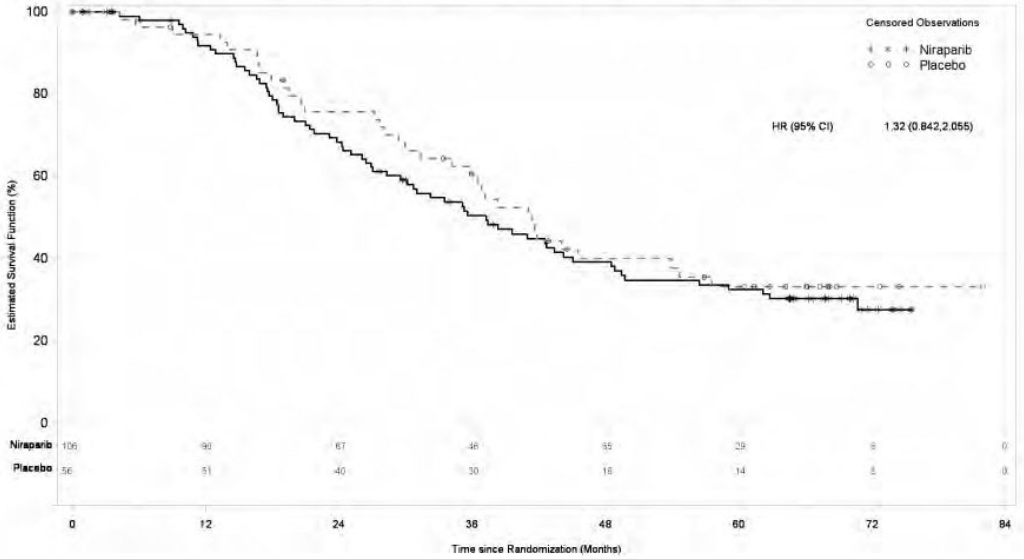


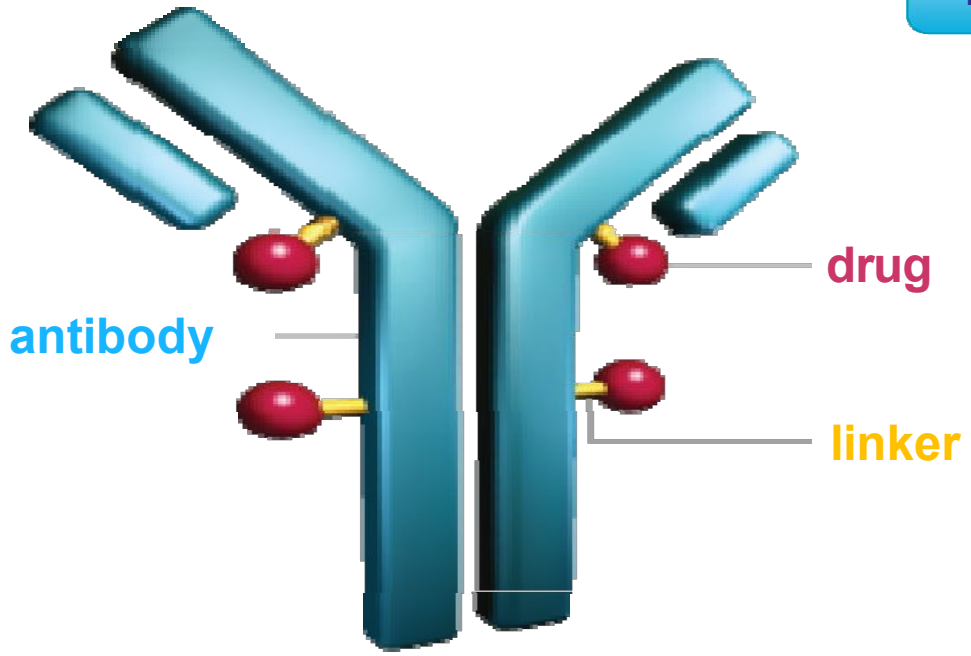
Figure 2: OS Kaplan Meier curve for the non-g*BRCA*mut HRD positive subgroup



Strategies in Platinum Resistant Ovarian Cancer

	Trial	Phase	Regimen	Tumor testing/ Prevalence
Taxanes	**GOG-3018 (OVAL)**	3	VB-111/placebo D1 (56 day cycle) + weekly paclitaxel vs. weekly Paclitaxel	no
	GOG-3029 (INNOVATE-3)	3	TTFields >18 hr/day + weekly paclitaxel vs. weekly Paclitaxel	no
	GOG-3044 (PROFECTA)	3	Afuresertib PO QD + Paclitaxel D1,8,15 Q3W vs. weekly Paclitaxel	yes
	GOG-3059 (AXLerate-OC)	3	AVB-S6-500 (D1&15) +Weekly paclitaxel (D 1, 8, 15 on a 28d cycle) vs. weekly Paclitaxel	no
	GOG-3073 (ROSELLA)	3	Relacorilant + nab-paclitaxel vs. nab-paclitaxel	no
Antibody Drug Conjugates	**GOG-3045 (MIRASOL)**	3	Mirvetuximab vs Investigator Choice chemotherapy	yes
	GOG-3048 (UPLIFT)	1b	XMT-1536 (Upifitimab) every 4 weeks	no
Immunotherapy	**NRG-GY009**	2/3	PLD/Atezolizumab (D1&15) vs. PLD/Bevacizumab(D1&15)/Atezo (D1&15) vs. PLD/Bevacizumab (D1&15)	no
	GOG-3063 (ARTISTRY 7)	3	Nemvaleukin + Pembrolizumab vs. Pembrolizumab vs. Nemvaleukin vs. Investigator Choice chemotherapy	no
Targeting DDR/ PARPi resistance	**NRG-GY005**	2/3	Olaparib vs. Olaparib/Cediranib vs. Cediranib vs. Investigator Choice chemotherapy	no
	NRG-GY023	2	Durvalumab/Olaparib/Cediranib vs. Olaparib/Cediranib vs. Durvalumab/Cediranib vs. Investigator Choice chemotherapy	no
	NRG-GY029 (approved)	2	Olaparib + copanlisib vs. Investigator Choice chemotherapy (PARPi resistant)	no
	GOG-3072	1b	ZN-c3 in combination with chemotherapy in patients with PROC	no

ADC Components

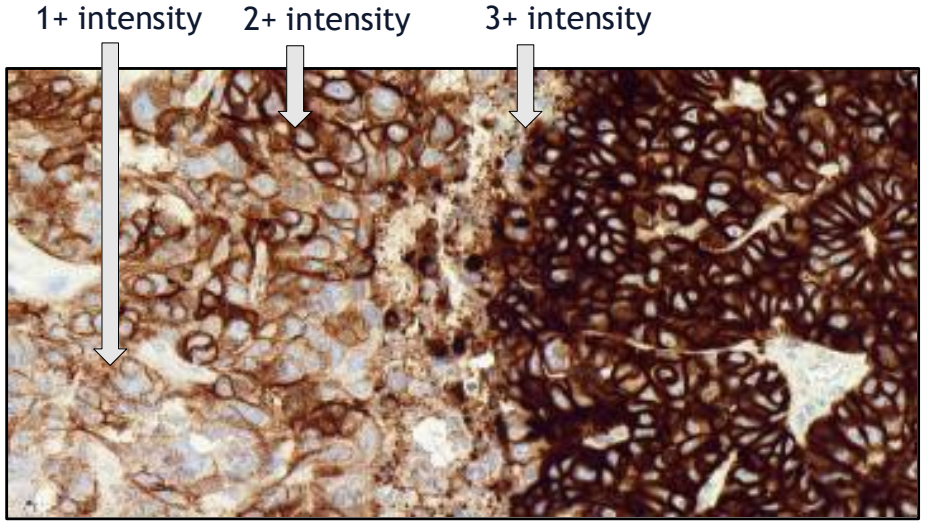


1. Antibody
2. Linker
3. Drug

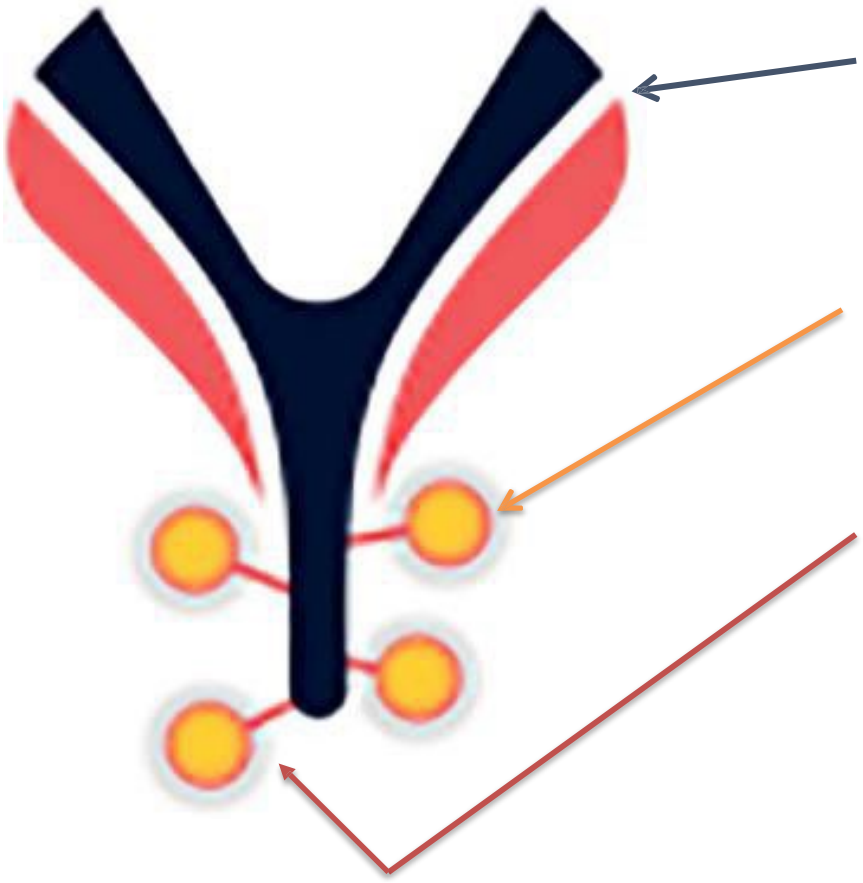
1. A highly selective monoclonal antibody for a tumor-associated antigen that has restricted expression on normal cells
2. A potent cytotoxic agent designed to induce target cell death when internalized in the cell and released
3. A linker that is stable in circulation, but releases the cytotoxic agent in target cells (controlled by altering stability and degree of hindrance around disulfide bond)

Targeting Folate Receptor Alpha (FRα) – an ideal target for ovarian cancer

- FRα is a cell surface folate receptor which mediates folate transport into epithelial cells
- FRα expression is limited on normal cells, but is upregulated on cancers, primarily ovarian, but also endometrial, and triple negative breast
- It is most highly expressed on the surface of serous epithelial ovarian cancers (EOC) – As assessed by immunohistochemistry (IHC)



FRα-targeting ADC: Mirvetuximab Soravtansine (IMGN853)



- Antibody – Humanized anti-FRα monoclonal
  - High affinity binding to FRα
  - Efficient internalization
- Maytansinoid Payload (DM4)
  - Potent tubulin-targeting agent
  - Drug-antibody ratio (DAR): ~3.4:1
- Linker
  - Cleavable sulfo-SPDB linker
  - Confers stability in circulation, controlled intracellular payload release, and bystander cell killing activity

FORWARD I

- Platinum-resistant ovarian cancer
- FRα-positive tumor expression
  - Medium (50-74% cells positive)
  - High (≥75% cells positive)
- ECOG performance status 0 or 1
- 1-3 prior therapies

Statistical Assumptions

- Hochberg procedure
- α=0.05 (two-sided), power = 90%
  HR=0.58; control arm mPFS 3.5 mos

Mirvetuximab Soravtansine (n=248)

6 mg/kg (adjusted ideal body weight) once every 3 weeks

2:1 Randomization

Stratification Factors:
FRα expression (medium or high)
Prior therapies (1 and 2, or 3)
Choice of chemotherapy

Investigator's Choice Chemotherapy
Paclitaxel, PLD†, or Topotecan (n=118)

***Paclitaxel**: 80 mg/m² weekly*
***PLD**: 40 mg/m² once every 4 weeks*
***Topotecan**: 4 mg/m² on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m² on Days 1-5 every 3 weeks*

Primary Endpoint

Progression-free survival (PFS; by BIRC*) for ITT and high FRα populations

*BIRC = Blinded Independent Review Committee; analyzed by Hochberg procedure

Secondary Endpoints

Overall response rate (ORR)
Overall survival (OS)
Patient reported outcomes (PRO)

†Pegylated liposomal doxorubicin
ClinicalTrials.gov Identifier: NCT02631876

BASELINE CHARACTERISTICS

Disease Characteristics

	Mirvetuximab soravtansine (n=248)	IC Chemo (n=118)
Primary Diagnosis		
Ovarian	83%	89%
Fallopian Tube	6%	4%
Primary Peritoneal	11%	7%
Histology		
High Grade Serous	99%	97%
Other	1%	3%
ECOG		
0	57%	51%
1	43%	48%
Prior Therapy		
Bevacizumab	49%	47%
PARPi	11%	10%
Any BRCA Mutation		
Yes	9%	7%
Platinum-Free Interval		
0-3 months	39%	38%
3-6 months	57%	58%
≥ 6 months	4%	4%

Stratification Factors

	Mirvetuximab soravtansine (n=248)	IC Chemo (n=118)
FRα Status		
Medium	42%	42%
High	58%	58%
No. Prior Lines		
1 or 2	65%	65%
3	35%	35%
IC Chemotherapy		
Paclitaxel	32%	31%
PLD	44%	46%
Topotecan	23%	23%

Consistent Efficacy Signal in the FRα-high

Endpoint	ITT POPULATION		FRα-HIGH POPULATION	
	Treatment effect size [Mirv (n=248) vs IC Chemo (n=118)]	P value*	Treatment effect size [Mirv (n=147) vs IC Chemo (n=71)]	P value*
PFS by BIRC (mo.)	HR: 0.981 (0.734, 1.310) mPFS: 4.1 vs 4.4	0.897^	HR: 0.693 (0.480, 1.000) mPFS: 4.8 vs 3.3	0.049^
ORR by BIRC 95% CIs	22% vs 12% (17%, 28%) vs (7%, 19%)	0.015	24% vs 10% (17%, 32%) vs (4%, 19%)	0.014
OS (mo.)	HR: 0.855 (0.644, 1.134) mOS: 15.6 vs 13.9	0.276	HR: 0.706 (0.489, 1.020) mOS: 17.3 vs 12.0	0.063

*Nominal p-value
^Not significant based on Hochberg Procedure
NR: not reached; ORR: confirmed overall response rate; PFS: progression-free survival; BIRC: Blinded Independent Review Committee; OS: overall survival; HR: hazard ratio; mPFS: median progression-free survival; CI: confidence interval
Final PFS and ORR data cut January 2019; Final OS data cut January 2020

- Efficacy benefit observed **across secondary endpoints** in FRa-high patients compared to chemotherapy
- Generated robust data to inform new pivotal trials and improve the likelihood of **technical success**

SORAYA

SINGLE-ARM PIVOTAL TRIAL FOR MIRVETUXIMAB USING PS2+ SCORING IN FRα-HIGH, PLATINUM-RESISTANT OVARIAN CANCER

Matulonis et al SGO 2022

PRIMARY ENDPOINT
ORR by Investigator

SECONDARY ENDPOINT
DOR by Investigator

ENROLLMENT AND KEY ELIGIBILITY
~100 patients
Platinum-resistant disease (primary PFI >3 mos)
Prior bevacizumab required
Prior PARPi allowed
Patients with BRCA mutations allowed

FPI: first patient in; DOR: duration of response; PFI: platinum-free interval

Baseline Demographics and Clinical Characteristics

Characteristic		All Patients (N=106)
Age, median (range)		62 (35–85 years)
Primary cancer diagnosis,* n (%)	Epithelial ovarian cancer	85 (80)
	Fallopian tube cancer	8 (8)
	Primary peritoneal cancer	12 (11)
Stage at initial diagnosis,† n (%)	I–II	2 (2)
	III	63 (59)
	IV	40 (38)
BRCA mutation, n (%)	Yes	21 (20)
	No/unknown	85 (80)
No. of prior systemic therapies, n (%)	1	10 (9)
	2	41 (39)
	3	54 (51)
Prior exposure, n (%)	Bevacizumab	106 (100)
	PARP inhibitor	51 (48)
Primary platinum-free interval, n (%)	3–12 months‡	64 (60)
	>12 months	42 (40)
Platinum-free interval, n (%)	0–3 months	39 (37)
	3–6 months	64 (60)

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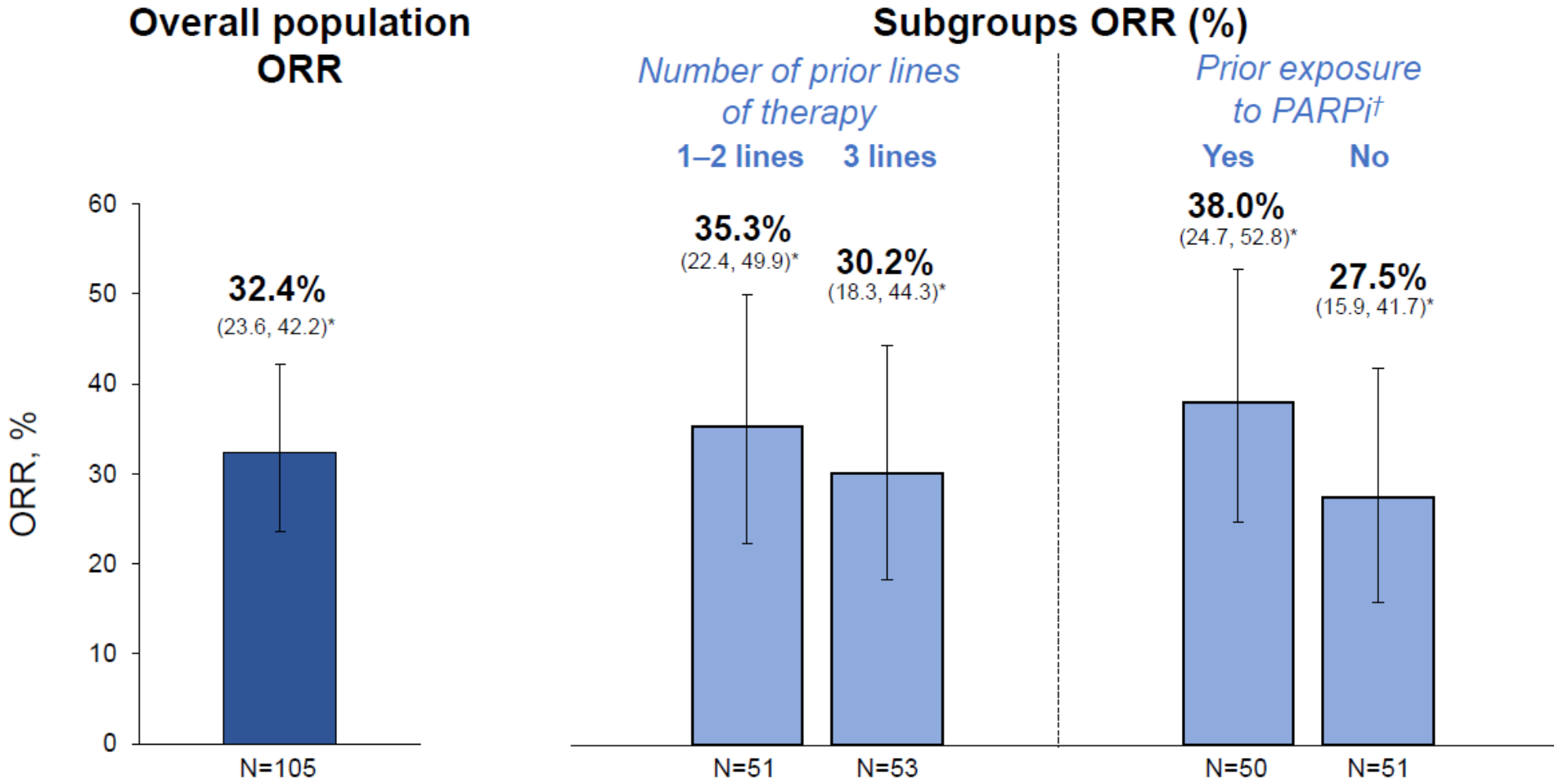
Investigator-Assessed Objective Response Rate by Prior Therapy



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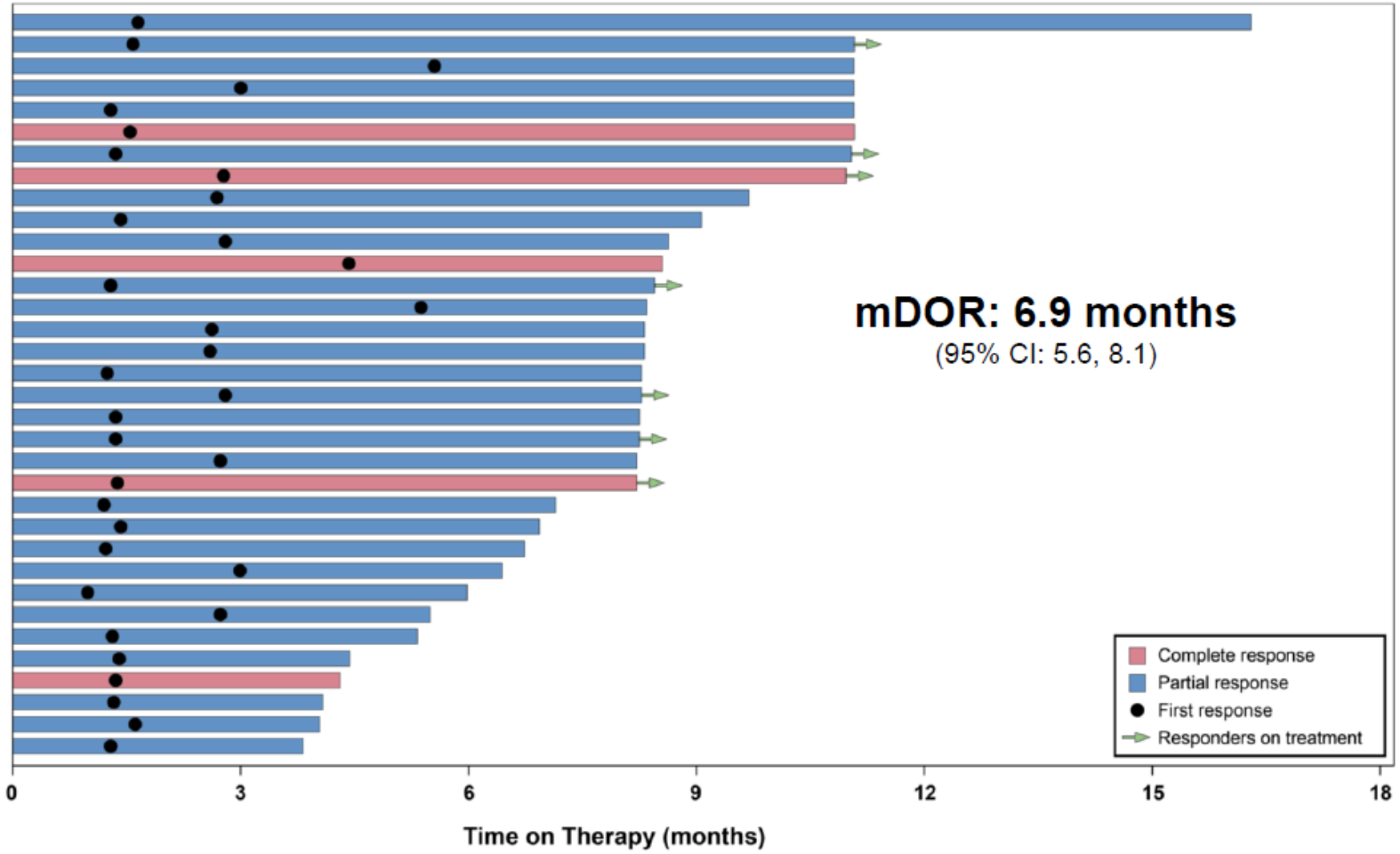
Investigator-Assessed Duration of Response for Patients With Complete and Partial Responses



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Treatment-Related Adverse Events (≥10%)

TRAEs, n (%)	All Grades	Grade 3	Grade 4
Patients with any event	91 (86)	29 (27)	1 (1)
Blurred vision	43 (41)	6 (6)	0 (0)
Keratopathy*†	38 (36)	8 (8)	1 (1)
Nausea	31 (29)	0 (0)	0 (0)
Dry eye	24 (23)	2 (2)	0 (0)
Fatigue	24 (23)	1 (1)	0 (0)
Diarrhea	23 (22)	2 (2)	0 (0)
Asthenia	16 (15)	1 (1)	0 (0)
Photophobia	15 (14)	0 (0)	0 (0)
Peripheral neuropathy	13 (12)	0 (0)	0 (0)
Decreased appetite	13 (12)	1 (1)	0 (0)
Vomiting	12 (11)	0 (0)	0 (0)
Neutropenia	11 (10)	1 (1)	0 (0)

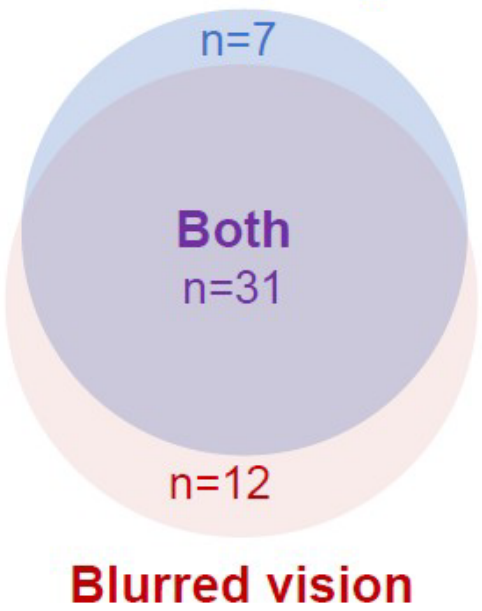
Data cutoff: November 16, 2021.

- Most AEs were low-grade, reversible ocular and GI events
- Serious grade ≥3 TRAEs were reported in 8% of patients
- TRAEs led to dose delay in 32% and dose reduction in 19%
- 7 patients (7%) discontinued treatment due to TRAEs
- 1 death was recorded as possibly related to study drug
  - Respiratory failure
  - Autopsy: No evidence of drug reaction; lung metastases

Matulonis et al SGO 2022

Unique Events Specific to MIRV: Keratopathy and Blurred Vision

Events developed in 50/106 (47%) patients: mostly low grade



- **Proactive supportive care**
  - Lubricating artificial tears
  - Corticosteroid eye drops
- **Predictable**
  - Median time to onset: cycle 2 (~1.5 months)
- **Manageable with dose modifications, if needed**
  - 22% of patients (23/106) had dose delay and/or reduction
- **Reversible**
  - At data cutoff: >80% of patients with grade 2–3 events had resolved to grade 0–1
    - 9 patients still receiving MIRV or being followed up for resolution
- **<1% discontinuation due to ocular events**
  - 1 of 106 patients discontinued due to grade 4 keratopathy,† which resolved within 15 days

Matulonis et al SGO 2022

FDA D.I.S.C.O. Burst Edition: FDA approval of (mirvetuximab soravtansine-gynx) for FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or peritoneal cancer

November 14, 2022
Accelerated approval
FDA approved companion diagnostic test: VENTANA FOLR1 RxDx Assay

MIRASOL

PHASE 3 RANDOMIZED TRIAL FOR MIRVETUXIMAB IN FRα-HIGH PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER

1:1 RANDOMIZATION

Mirvetuximab

STRATIFICATION FACTORS
IC Chemotherapy (Paclitaxel, PLD, Topotecan)
Prior Therapies (1 vs 2 vs 3)

Investigator's Choice Chemotherapy
Paclitaxel, PLD, or Topotecan

PRIMARY ENDPOINT
PFS by Investigator
BICR for Sensitivity Analysis

SECONDARY ENDPOINTS
ORR by Investigator, OS, and PRO

ENROLLMENT AND KEY ELIGIBILITY
430 patients/330 events for PFS by Investigator
Platinum-resistant disease (primary PFI >3 months)
1 to 3 prior lines of therapy
Prior bevacizumab* and prior PARPi allowed
Patients with BRCA mutations allowed

TARGET TIMELINES

- ENROLLING GLOBALLY
- TOP-LINE DATA Q3 2022
- EXPECTED APPROVAL 2023

*Eligibility criterion different than SORAYA
FRα: folate receptor alpha; IC: investigator's choice; PLD: pegylated liposomal doxorubicin; PFS: progression-free survival; BICR: blinded independent central review; OS: overall survival
PRO: patient-reported outcomes; PFI: platinum-free interval; PARPi: poly ADP-ribose polymerase inhibitor; BRCA: BReast CAncer gene

Mirvetuximab Development and Combinations

MIRVETUXIMAB PSOC MONOTHERAPY

PHASE 1 EFFICACY DATA[1]

64% ORR

FRα-HIGH RECURRENT OVARIAN CANCER
n= 11

- Potential for a clinically meaningful benefit in FRα-high recurrent platinum-sensitive ovarian cancer
  - 64% ORR (7/11); 2 CRs and 5 PRs

PICCOLO

- Single-arm Phase 2 trial for mirvetuximab in FRα-high patients with platinum-sensitive ovarian cancer
- Now enrolling
- Potential for label expansion in 2024

MIRVETUXIMAB IN COMBINATION

MIRVETUXIMAB + BEVACIZUMAB[2,3]

64% ORR

FRα-HIGH RECURRENT OVARIAN CANCER
n= 33

- Compelling activity in FRα-high recurrent ovarian cancer, regardless of plaWnum status
  - 59% ORR (10/17), 9.4 month mDOR, 9.7 month mPFS in the platinum-resistant subgroup
  - 69% ORR (11/16), 12.7 month mDOR, 13.3 month mPFS in the platinum-sensitive subgroup

GLORIOSA

- Randomized Phase 3 trial for mirvetuximab + bevacizumab maintenance in FRα-high platinum-sensitive ovarian cancer
- Aligned with FDA on trial design

MIRVETUXIMAB + CARBOPLATIN[4]

80% ORR

15 MOS mPFS
FRα-MED and -HIGH
n= 10

- Highly active in recurrent platinum-sensitive ovarian cancer with mDOR of 24 months
- Supporting ongoing ISTs in recurrent platinum-sensitive ovarian cancer: ~70 patient neo-adjuvant study initiated in H1 2021; and a randomized Phase 2 ~140 patient study

TRIAL 420

- Single-arm Phase 2 trial for mirvetuximab + carboplatin followed by MIRV continuation in FRα-low, medium, and high pabents with platinum-sensitive ovarian cancer

[1]Immunogen internal data on file. [2]ASCO 2020 Oral Presenta9on; Gilbert, L., et al. [3]ASCO 2021 Oral Presenta9on; O'Malley, D., et al. [4]Gynecologic Oncology 151 (2018) 46-52.

FORWARD2: Efficacy Comparison of Mirvetuximab + Bevacizumab **PROC**

	AURELIA	FORWARD II	Anetumab/Bev
Regimen	Chemo/Bev	**Mirv/Bev**	**Anetumab/Bev**
Median age	61	**60**	**63**
Patient population	Platinum resist 1-2 priors **60% - 1 prior** **40% - 2 prior**	**Median of 2 priors** **33%-1 prior** **37% -2 prior** **30% 3 or more**	**Median of 3 priors (1-8)**
Prior bevacizumab	7%	**64%**	**43%**
ORR	27%	**59%**	**22%**
mPFS	6.7 (95% 5.7, 7.9)	**immature**	**5.3 months (comparison PAC/Bev = 9.6 mos)**

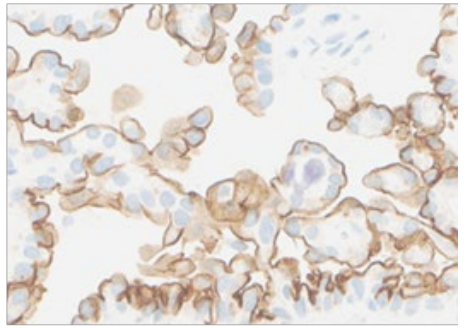
Aghajanian C et al. JCO. 2012;30: 2039-2045,

NaPi2b (Sodium Dependent Phosphate Transporter) is an Ideal Antibody-Drug Conjugate (ADC) Target

- ADC internalizing sodium phosphate transporter; not an oncogene
- Broadly expressed in ovarian cancer and NSCLC adenocarcinoma
- Limited expression in normal tissues
- IHC assay calibrated to distinguish wide range of expression

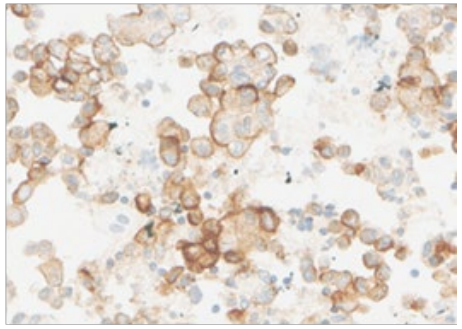
Epithelial ovarian cancer

H score = 293



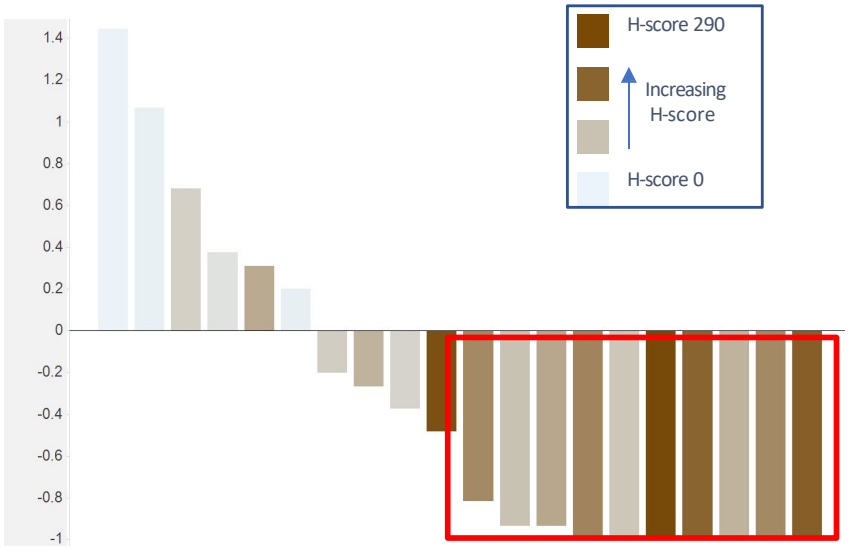
Lung adenocarcinoma

H score = 265



Ovarian Cancer Patient-Derived Xenograft Models

Response correlated with NaPi2b Expression



H-score measures the percentage of cells staining multiplied by their intensity (0, 1+, 2+, 3+) for a range of 0 - 300

UPLIFT (ENGOT-ov67 / GOG-3048)

Global
US, Europe, Australia, Canada

UpRi Single-Arm Registrational Trial in Platinum-Resistant Ovarian Cancer

Patient Population: HGSOC[a] progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1; enrolling regardless of NaPi2b expression

Key Inclusion Criteria

- Platinum-resistant ovarian cancer (PROC)
- 1–4 prior lines of therapy
- Grade ≤2 peripheral neuropathy
- Archival or fresh tissue required for biomarker evaluation

Key Exclusion Criteria

- 1–2 prior lines bevacizumab-naive
- Primary platinum-refractory disease

UpRi 36 mg/m^2 up to max 80 mg; IV Q4W

Primary Endpoint

- Confirmed ORR in NaPi2b-high (N = ~100)

Secondary Endpoint

- Confirmed ORR in overall population (N = up to ~180 including 100 NaPi2b-high)

Other Secondary Endpoints

- DoR
- Safety

Prospectively-defined retrospective analysis to validate NaPi2b biomarker cutoff

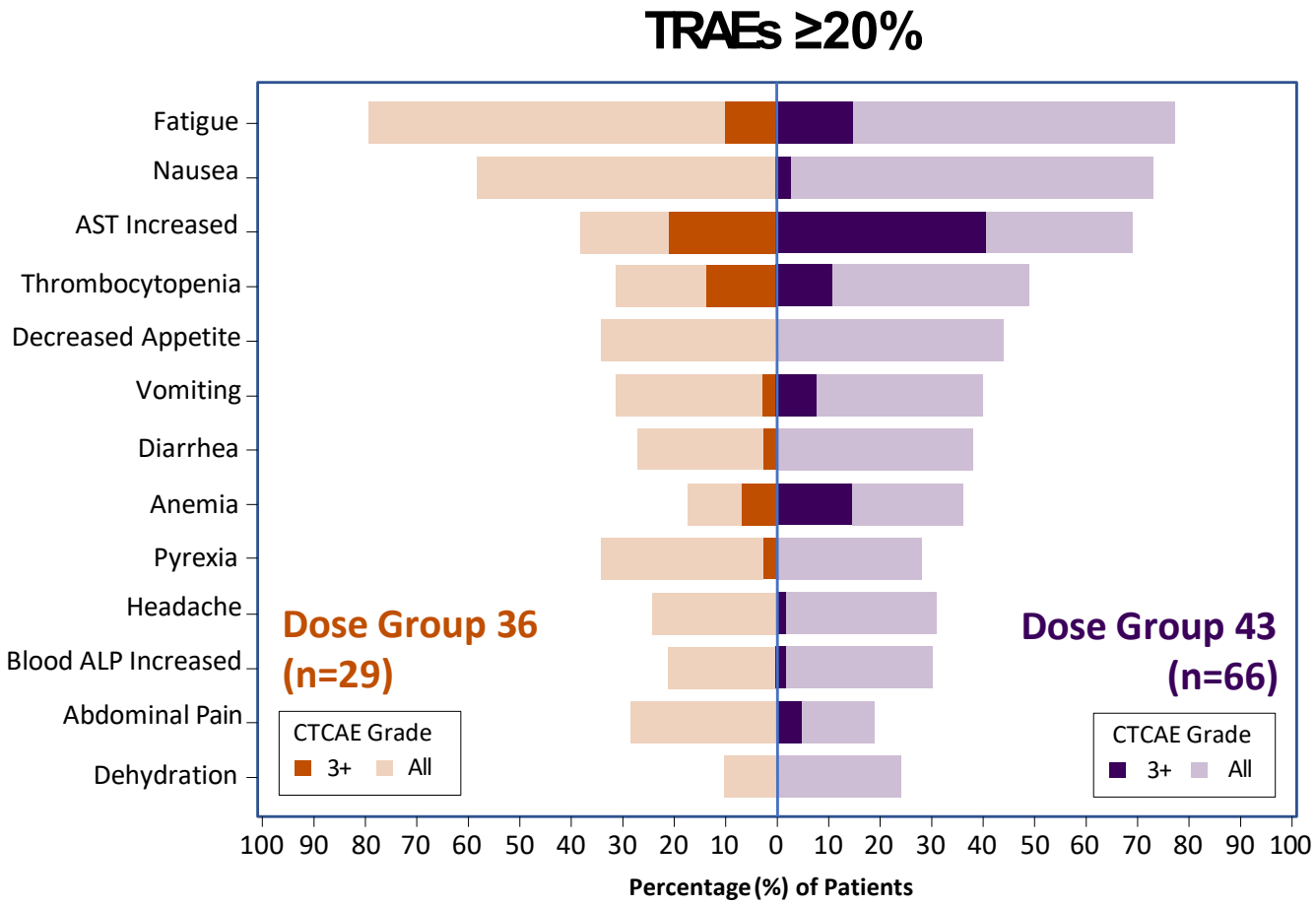
NCT03319628: Trial Closed to Enrollment

[a] HGSOC including fallopian tube and primary peritoneal cancer.

HGSOC, high-grade serous ovarian cancer; IV, intravenous; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; FPD, first patient dosed; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate, PROC, platinum-resistant ovarian cancer; PS, performance score; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin.

Treatment-Related AEs by UpRi Dose Group

Dose Group 36 Had a More Favorable Safety Profile Compared to Dose Group 43



- No severe ocular toxicity, neutropenia, or peripheral neuropathy in either dose group
- 4 (14%) patients had treatment-related SAEs in Dose Group 36 vs 18 (27%) in Dose Group 43
- Lower frequencies and lower grade pneumonitis occurred in Dose Group 36 (with no Grade 3+) vs Dose Group 43[a]

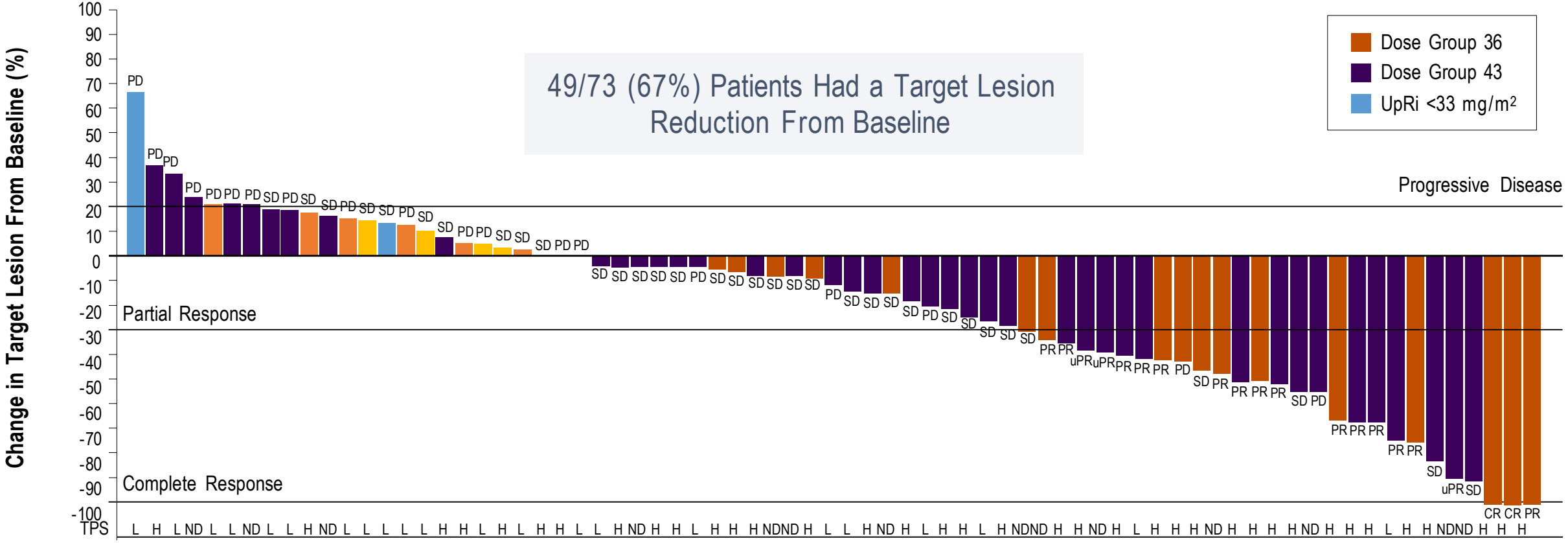
Data cut: June 10, 2021. Analysis with 95 patients. Two patients received <30 mg/m^2 and therefore were not included in either dose group.

[a] Dose Group 36 pneumonitis: Grade 1–2 (n=2), Grade 3+ (n=0); Dose Group 43 pneumonitis: Grade 1–2 (n=5), Grade 3+ (n=4).

AE, adverse event; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; TRAE, treatment-related adverse event; UpRi, upifitamab rilsodotin.

Best Response by UpRi Dose Group

Similar Tumor Reduction in Both Dose Groups: Two-thirds of Patients Had Reductions in Target Tumor Lesions by RECIST 1.1



Data cut: June 10, 2021. Analysis with 73 evaluable patients. Two patients excluded as post-baseline tumor measurement shows "Not Measurable", yet "PD" was assigned by investigator in response dataset. There were 22 unevaluable patients: 4 in Dose Group 36, 2 patient withdrawals (1 enrolled in hospice), 2 patient deaths; 18 in Dose Group 43, 5 patient withdrawals, 1 clinical progression, 3 due to adverse events, 8 deaths, 1 had not reached first scan.

CR, complete response; H, high; L, low; ND, not yet determined; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TPS, tumor proportion score; uPR, unconfirmed partial response; UpRi, upifitamab rilsodotin.

Conclusion

- Mirvetuximab is the 1st FDA-approved ADC for the treatment of PROC, FOLR1 positive
  - Confirmatory trial Mirasol completed enrollment
- UpRi targets Napi2b
  - UPLIFT completed enrollment
  - UP-NEXT currently enrolling PSOC
- ADCs targeting Her2neu new data pending in ovarian cancer; look promising for uterine serous and carcinosarcoma,
- Many other ADCs are under development

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