First-line maintenance therapy changing the landscape

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DECLARATION OF INTERESTS

Allarity Therapeutics, Advisory Board, Personal
Astra Zeneca, Advisory Board & Invited Speaker, Personal
Biocad, Advisory Board, Personal
Boehringer Ingelheim, Advisory Board, Personal
Clovis, Advisory Board, Personal
Daiichi-Sankyo, Advisory Board, Personal
Genmab, Advisory Board & Invited Speaker, Personal
GSK, Advisory Board & Invited Speaker, Personal
Immunogen, Advisory Board, Personal
Karyopharm, Advisory Board, Personal
Merck, Advisory Board, Personal
Mersana, Advisory Board & Invited Speaker, Personal
Novartis, Advisory Board, Personal
Roche, Advisory Board, Personal
SeaGen, Advisory Board & Invited Speaker, Personal
Takeda, Advisory Board & Invited Speaker, Personal
Zailab, Advisory Board, Personal
Karyopharm, Member of Board of Directors, Stocks/Shares, Personal
Sera Prognostics, Member of Board of Directors, Stocks/Shares, Personal

No financial interest

Allarity, Research Grant, Institutional,
Apexigen, Research Grant, Institutional,

Astra Zeneca, Research Grant, Institutional,
Boehringer Ingelheim, Research Grant, Institutional
Clovis, Research Grant, Institutional
Deciphera, Trial Chair, Institutional,
GSK, Research Grant, Institutional,
Mersana, Trial Chair, Institutional,
Novartis, Research Grant, Institutional,
NuvationBio, Trial Chair, Institutional,
Ultimovacs, Research Grant, Institutional,

First-Line Treatment for Advanced Ovarian Cancer- standard of care – the need for improvement

The ultimate goal of first-line treatment is to achieve cure
To date, relapsed ovarian cancer remains incurable
There is a significant need for better frontline treatment to improve outcomes for women with ovarian cancer

Surgery
(primary or Interval debulking)
Carboplatin and Paclitaxel +/- Bevacizumab

10-20 months

time before progression after standard of care[1-3]

~70%

of women relapse within 3 years of first line treatment[4]

20%

5-year survival rate for Stage III patients[3]

5%

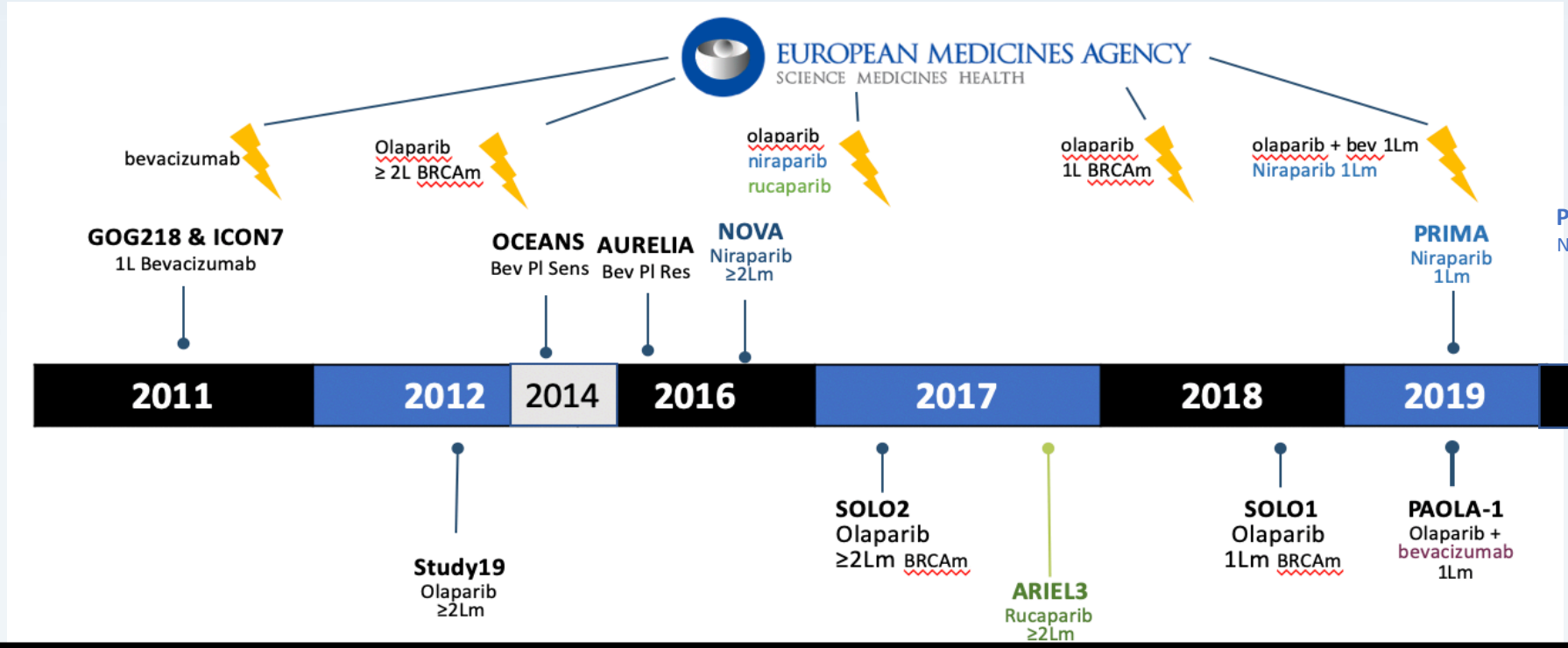
5-year survival rate for Stage IV patients[5]

Around 15-20% women with high grade serous sub-type has a *BRCA1 or BRCA2* mutation

1. Burger RA et al. N Engl J Med. 2011;365(26):2473-2483. 2. Perren TJ ... Mirza MR et al. N Engl J Med. 2011;365(26):2484-2496 3. Clamp AR et al. Presented at: ESMO Annual Meeting; 2017. 4. Ledermann JA, et al. Ann Oncol 2013;24(Suppl 6):vi24–32 5. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/survival

MAINTENANCE THERAPY IN ADVANCED OVARIAN CANCER

NSGO-CTU Nordic Society of Gynaecological Oncology - Clinical Trial Unit



Bevacizumab	PARPi in relapse	PARPi in first-line
Perren T…Mirza MR, et al. NEJM 2011	Lederman J, et al. NEJM 2012	Moore K, et al. NEJM 2018
Burger R, et al. NEJM 2011	Mirza MR, et al. NEJM 2016	Gonzales-Martin A…Mirza MR, et al. NEJM 2019
Aghajanian C, et al. JCO 2012	Pujade-Lauraine, et al. Lancet Oncol 2017	Ray-Coquard I, et al NEJM 2019
Pujade-Lauraine E…Mirza MR et al. JCO 2014	Coleman RL, et al. Lancet 2017	Li N, et al. SGO 2022
		Monk B, et al. ASCO 2022

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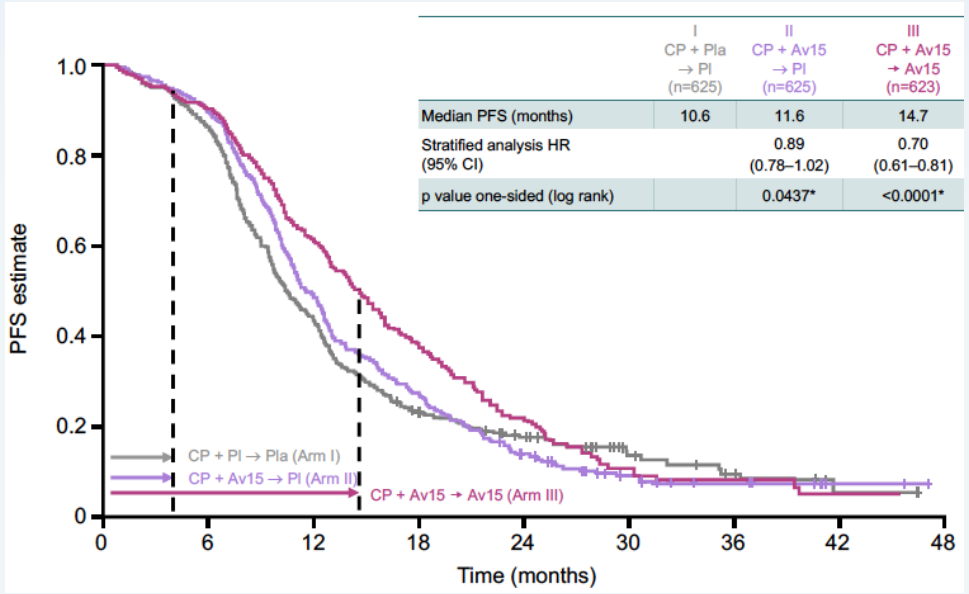
ENGOT European Network of Gynaecological Oncological Trial groups

Antiangiogenic therapy Bevacizumab in First-Line:

PFS

GOG-218

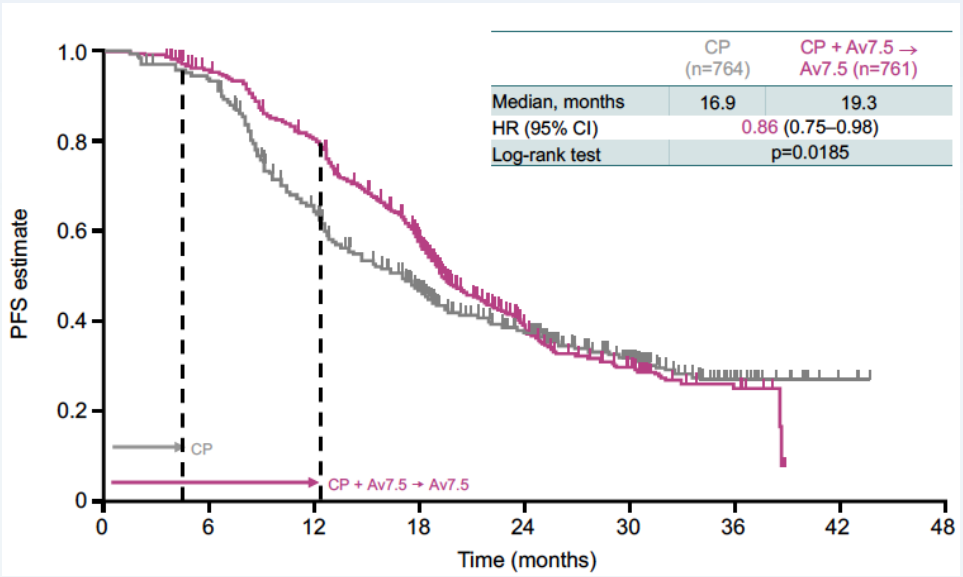


	I CP + Pla → Pl (n=625)	II CP + Av15 → Pl (n=625)	III CP + Av15 → Av15 (n=623)
Median PFS (months)	10.6	11.6	14.7
Stratified analysis HR (95% CI)		0.89 (0.78–1.02)	0.70 (0.61–0.81)
p value one-sided (log rank)		0.0437*	<0.0001*

HR: 0.73
10.4 vs 13.9 mos
Median D: 3.5 mos

Burger et al. *N Engl J Med 2011*

ICON7



	CP (n=764)	CP + Av7.5 → Av7.5 (n=761)
Median, months	16.9	19.3
HR (95% CI)	0.86 (0.75–0.98)	
Log-rank test	p=0.0185	

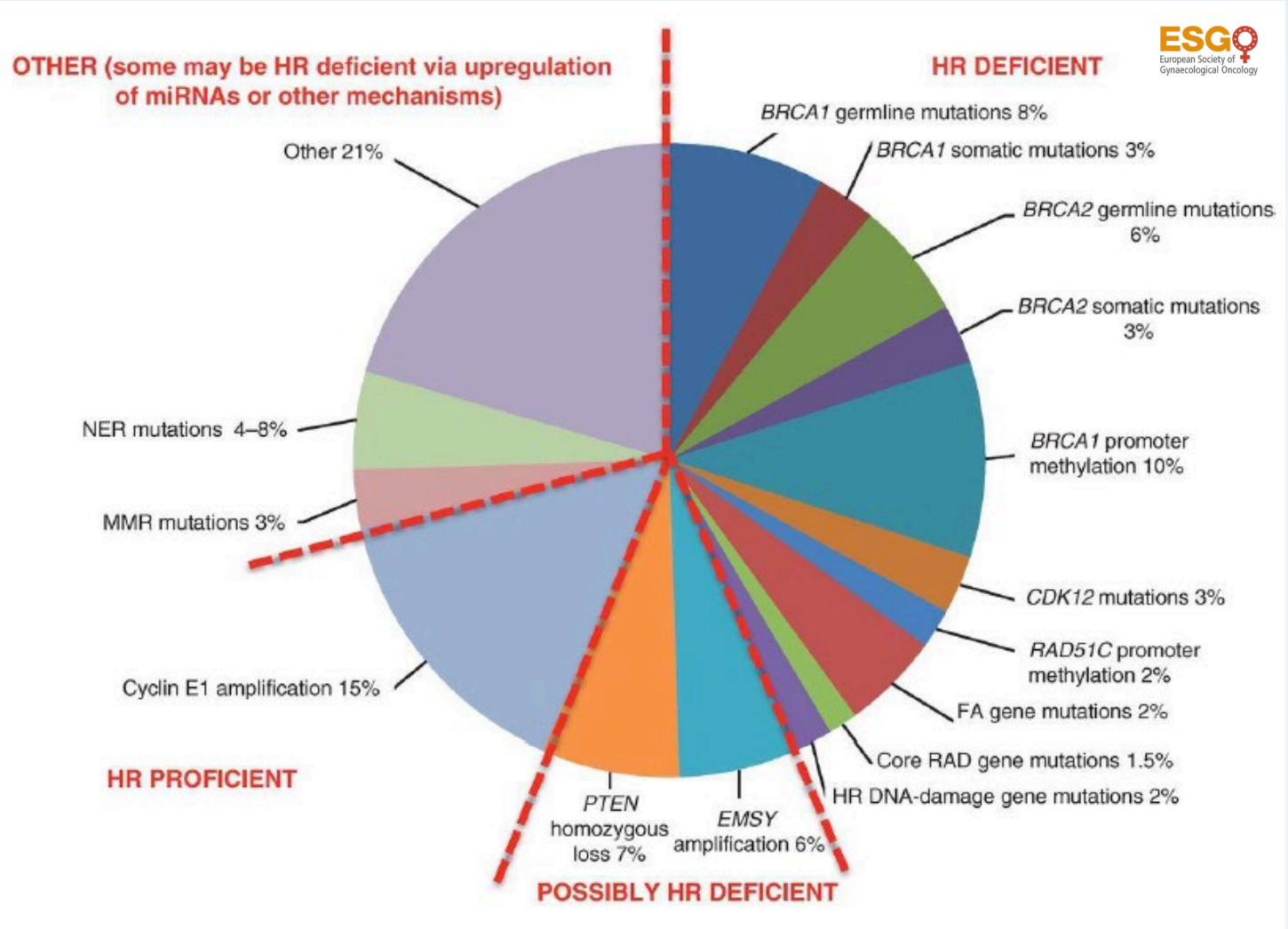
HR: 0.87
17.4vs 19.8 mos
Median D: 2.4 mos

Perren T… Mirza MR et al. *N Engl J Med 2011*

Homologous Recombination Defects in High-Grade Serous Ovarian Cancer

- Ovarian Cancer is a genetically heterogeneous disease

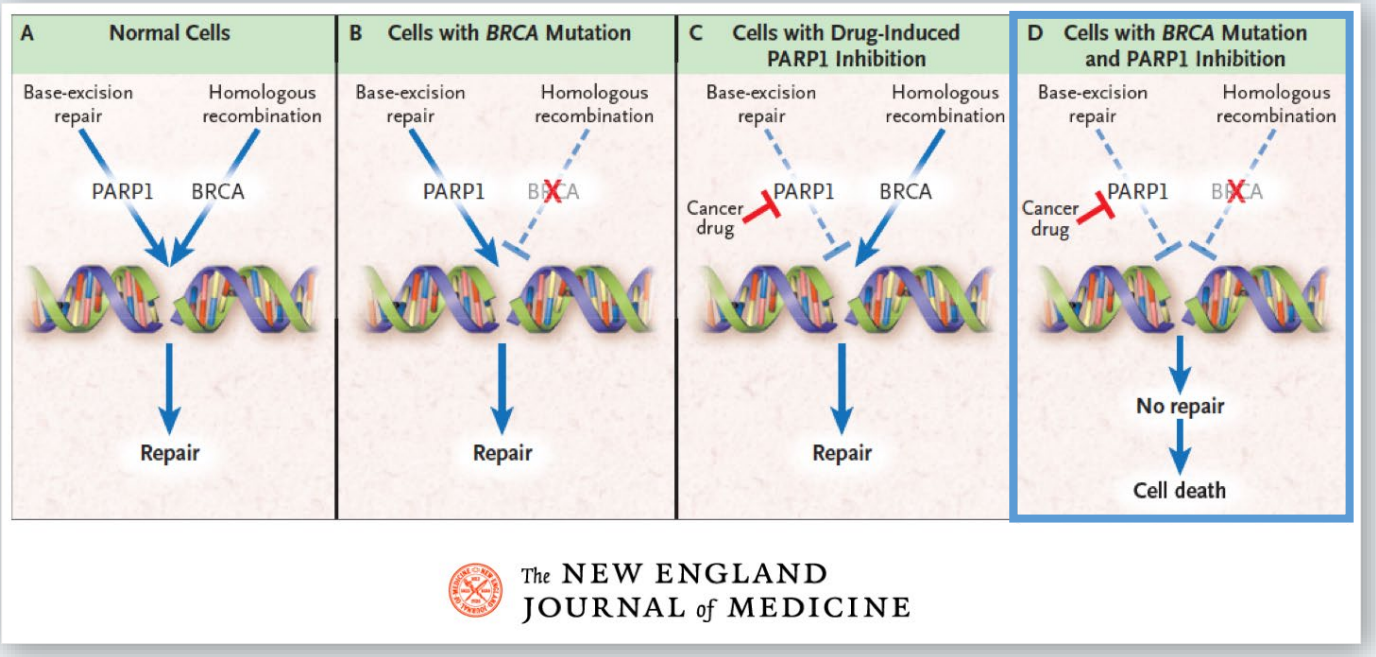
- *BRCA*1/2 deleterious mutations or chromosomal damage result in similar biology



Levine D. *The Cancer Genome Atlas, 2011*
Konstantinopoulos et al. *Cancer Discov 2015*

How PARP inhibition works

- DNA damage:
  - Single-strand breaks (SSB)
  - Double-strand breaks (DSB)
- Various DNA repair mechanisms
  - **PARP enzymes** are involved in **SSB** repair via base excision repair
  - ***BRCA1/2*** are involved in repair of **DSB** via **homologous recombination** (**HR**)



- Unrepaired SSB can lead to DSB in dividing cells
- Accurate repair of DSB is largely reliant upon HR (including, but not limited to *BRCA*)
- ▶ HR-deficient cells are highly reliant on PARP enzymes to maintain genomic stability

BRCA, breast cancer gene; DSBs, double-strand breaks; HR, homologous recombination; PARP, poly(ADP-ribose)polymerase; SSBs, single-strand breaks.

Iglehart JD, et al. N Engl J Med 2009;361:189-91.

Maintenance

PARP inhibitors in first-line

PARP INHIBITORS IN PATIENTS WITH PRIMARY ADVANCED OVARIAN CANCER

SOLO1[1] *BRCA*mut	ENGOT-OV25 PAOLA1[2]	ENGOT-OV26 PRIMA[3]	PRIME[4]	ENGOT-OV45 ATHENA$_{mono}$[5]
Olaparib	Olaparib + bevacizumab	Niraparib	Niraparib	Rucaparib*

1. Moore K, et al. NEJM 2018 2. Ray-Coquard I, et al. NEJM 2019 3. Gonzales-Martin A…Mirza MR, et al. NEJM 2019 **4**. Li N, et al. SGO2022. 5. Monk et al. ASCO2022

SOLO1: Study design and updated PFS analysis

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- BRCAm
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete† or partial response after platinum-based chemotherapy

Olaparib 300 mg bid (N=260)

2:1 randomization

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

For up to 2 years or until disease progression‡

Primary endpoint

- PFS (investigator-assessed)

Secondary endpoints included:

- OS
- TFST
- TSST
- Safety

Primary PFS analysis[1] (DCO 17 May 2018)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
3-year PFS rate, %	60.4	26.9
	HR 0.30 (95% CI 0.23–0.41)	
	P<0.001	

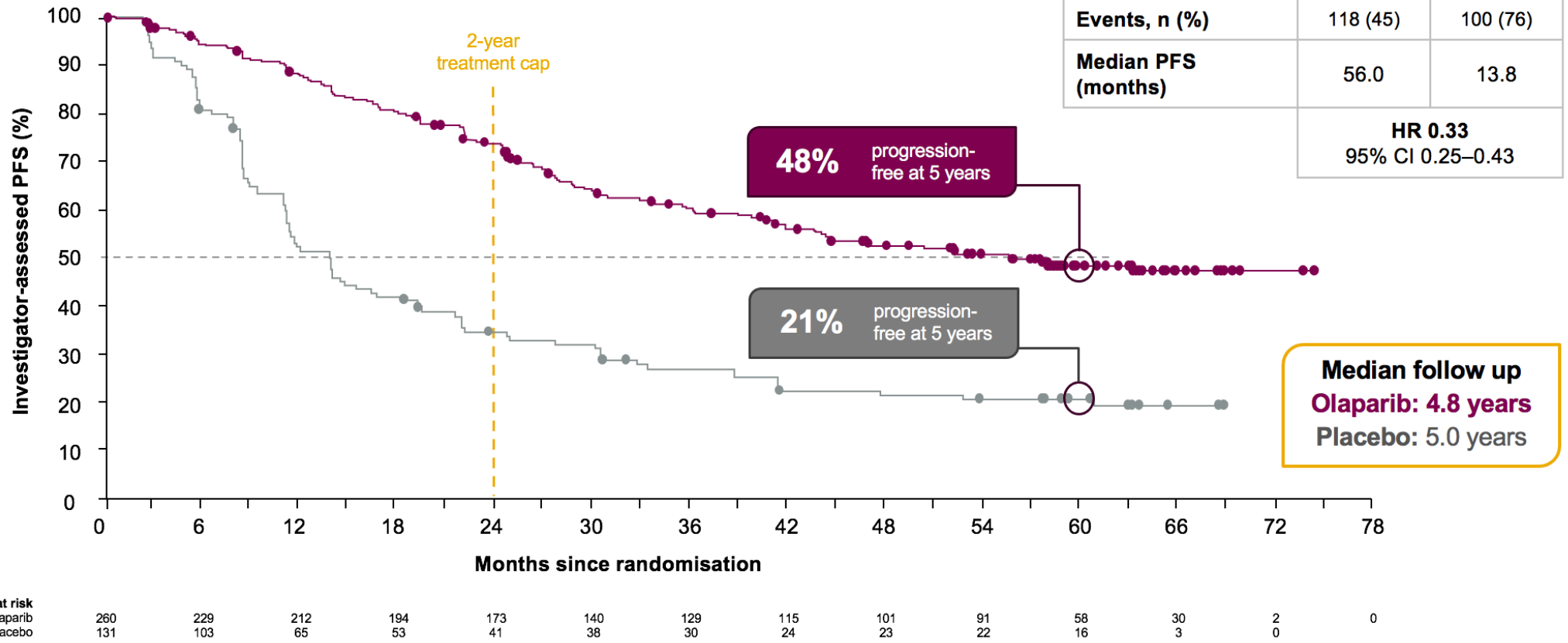
Updated PFS analysis[2] (DCO 5 March 2020)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45.4)	100 (76.3)
Median PFS, months	56.0	13.8
5-year PFS rate, %	48.3	20.5
	HR 0.33 (95% CI 0.25–0.43)	

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease; †Including patients with no evidence of disease; ‡Patients with evidence of disease at 2 years could continue to receive study treatment if, in the investigator's opinion, this was in the patient's best interest
bid, twice daily; CI, confidence interval; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NR, not reached; PFS, progression-free survival; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

1. Moore K *et al. N Engl J Med* 2018;379:2495–505; 2. Banerjee S *et al. Lancet Oncol* 2021;22:1721–31

SOLO1: Updated PFS analysis



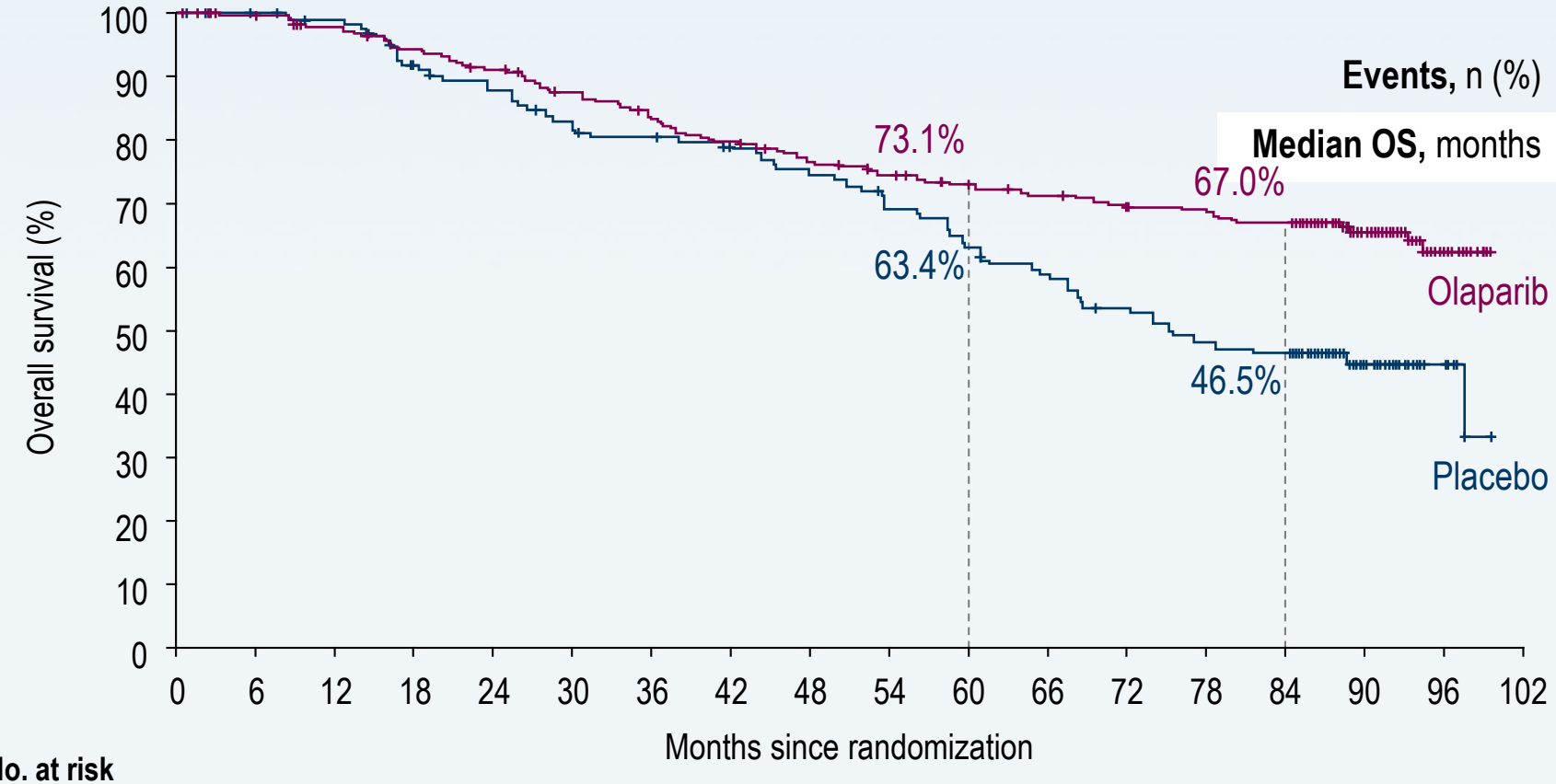
	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	118 (45)	100 (76)
Median PFS (months)	56.0	13.8
	HR 0.33 95% CI 0.25–0.43	

Median follow up
Olaparib: 4.8 years
Placebo: 5.0 years

Investigator-assessed PFS
DCO: March 2020; Median follow-up: olaparib, 4.8 years, placebo, 5.0 years
CI=confidence interval; HR=hazard ratio; PFS=progression-free survival

Banerjee S et al. Lancet Oncol 2021

SOLO1: Maintenance olaparib provided a clinically meaningful OS benefit



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**

HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*

No. at risk																		
Olaparib	260	252	246	236	227	214	203	194	185	177	170	165	159	157	153	79	21	0
Placebo	131	128	125	114	108	100	97	92	87	80	73	67	60	54	52	21	6	0

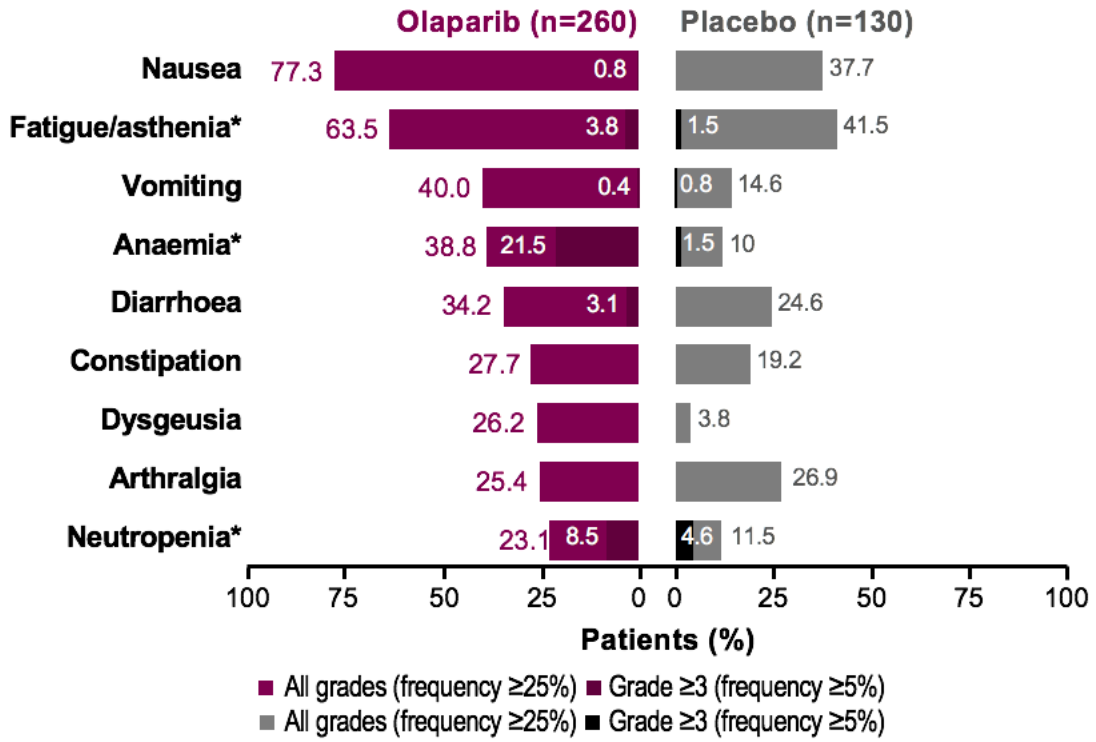
*$P<0.0001$ required to declare statistical significance

PARIS 2022 ESMO congress

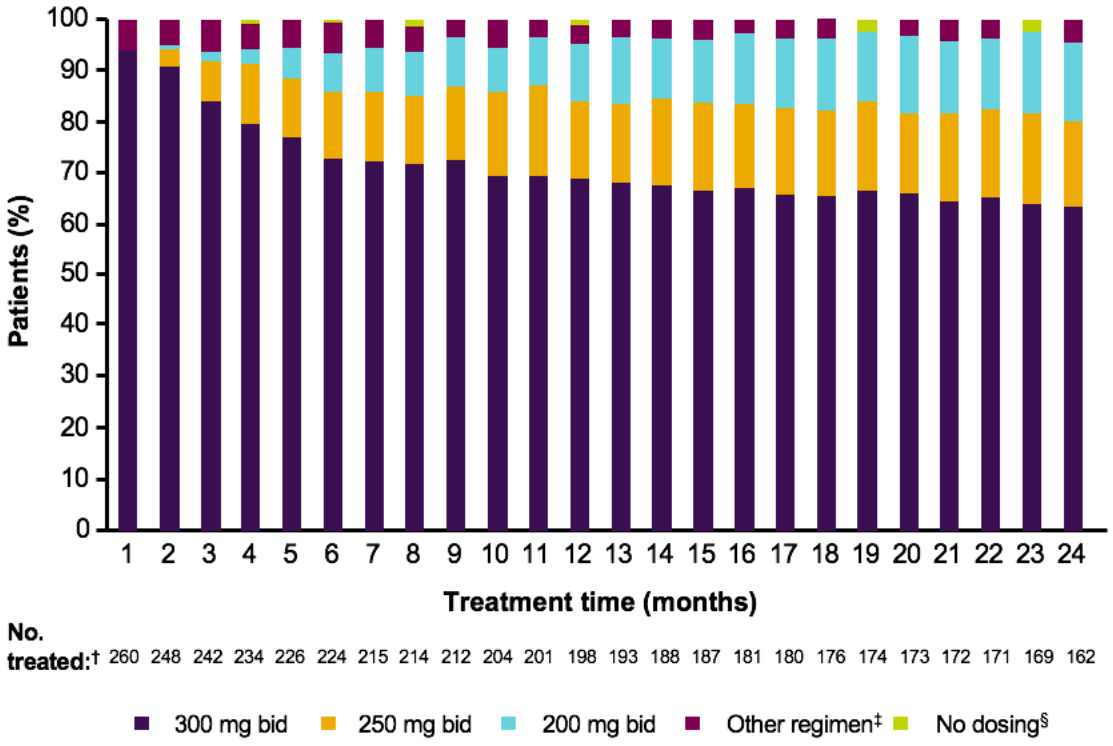
DiSilvestro P et al. ESMO 2022

SOLO-1: Adverse events and dose modification

Most common adverse events[1]



Most patients receiving olaparib could remain on the starting dose[2]



*Grouped terms. All-grade thrombocytopenia (grouped term) occurred in 11.2% of patients in the olaparib group and 3.8% of patients in the placebo group and grade ≥3 thrombocytopenia (grouped term) occurred in 0.8% and 1.5%, respectively; †Number of patients treated at the start of each month; ‡Other regimen' includes 150 mg qd, 150 mg bid, 200 mg qd, 250 mg qd, 300 mg od, and 450 mg bid; §The category of 'no dosing' was assigned if the patient had dosing interrupted for the entire month window; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; bid, twice daily; qd, once daily

1. Moore K, et al. Presented at ESMO Annual Congress 2018; 19–23 October 2018; Munich, Germany. Presentation #LBA7_PR; 2. Colombo N, et al. Presented at ASCO 2019; Chicago, IL, USA. Poster 5539

Niraparib in combination with bevacizumab *versus* niraparib alone in recurrent platinum-sensitive ovarian cancer

NSGO-CTU
Nordic Society of Gynaecological Oncology - Clinical Trial Unit

Trial design

NCT02354131

- High-grade serous/endometrioid PSROC
- Any number of previous lines of therapies
- Measurable/evaluable disease
- Prior bevacizumab permitted

Randomize 1:1

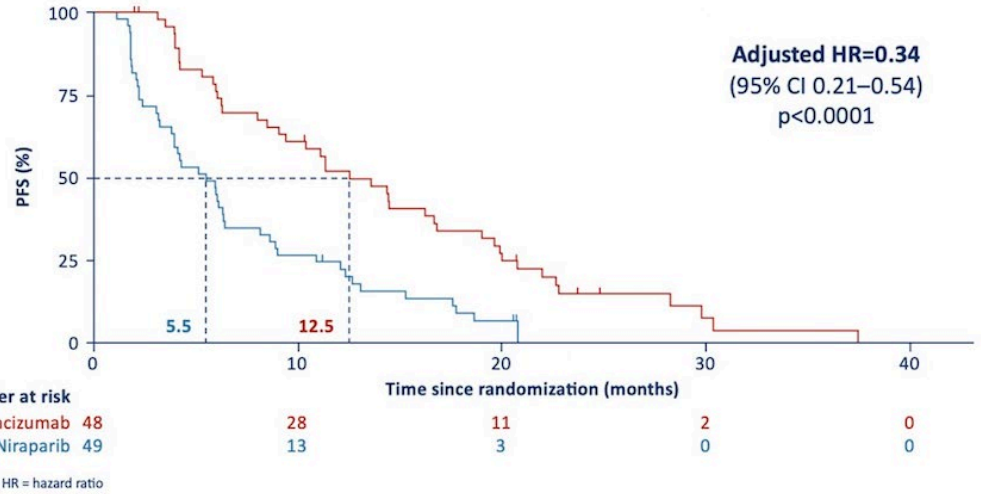
- Niraparib 300 mg QD d1–21
- Niraparib 300 mg QD d1–21 + bevacizumab 15 mg/kg q3w

Until disease progression or toxicity

Stratification factors
- HRD status (positive vs negative)
- Chemotherapy-free interval (6–12 vs >12 months)

Primary endpoint: Investigator-assessed PFS in the Intention-to-Treat population

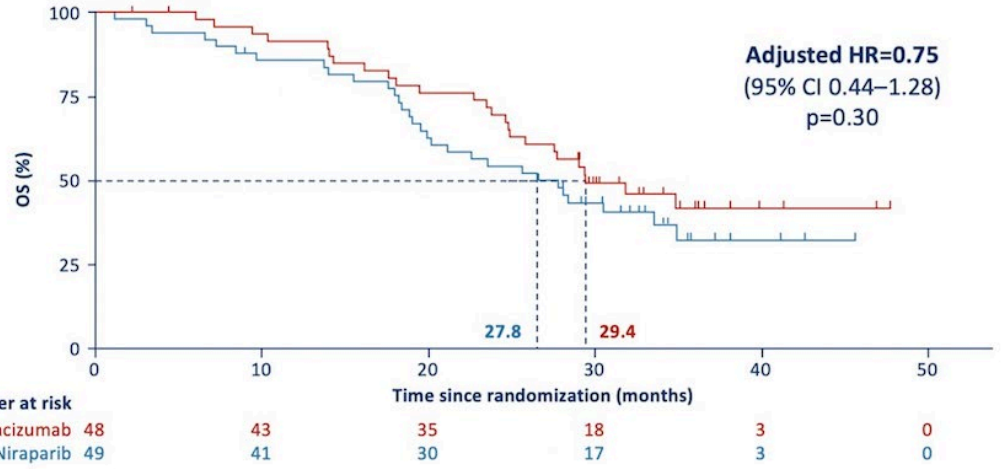
Updated PFS (Primary Endpoint) in the ITT Population



CI = confidence interval; HR = hazard ratio

Overall Survival

Event maturity: 52%



NSGO-AVANOVA2/ENGOT–OV24

Mirza et al. *Lancet Oncol 2019*

Mirza et al ASCO 2020

ENGOT-OV25 / PAOLA1

Patients
- Newly diagnosed, FIGO stage III–IV high-grade serous or endometrioid ovarian, fallopian tube and/or primary peritoneal cancer*

First-line treatment
- Upfront or interval surgery
- Platinum-taxane based chemotherapy plus ≥2 cycles of bevacizumab†,‡

≤9 weeks

NED/CR/PR

Maintenance therapy

Olaparib tablets 300 mg bid x 2 years

+ bevacizumab§

2:1 randomization stratified by:
- Tumour BRCAm status
- First-line treatment outcome¶

Placebo x 2 years

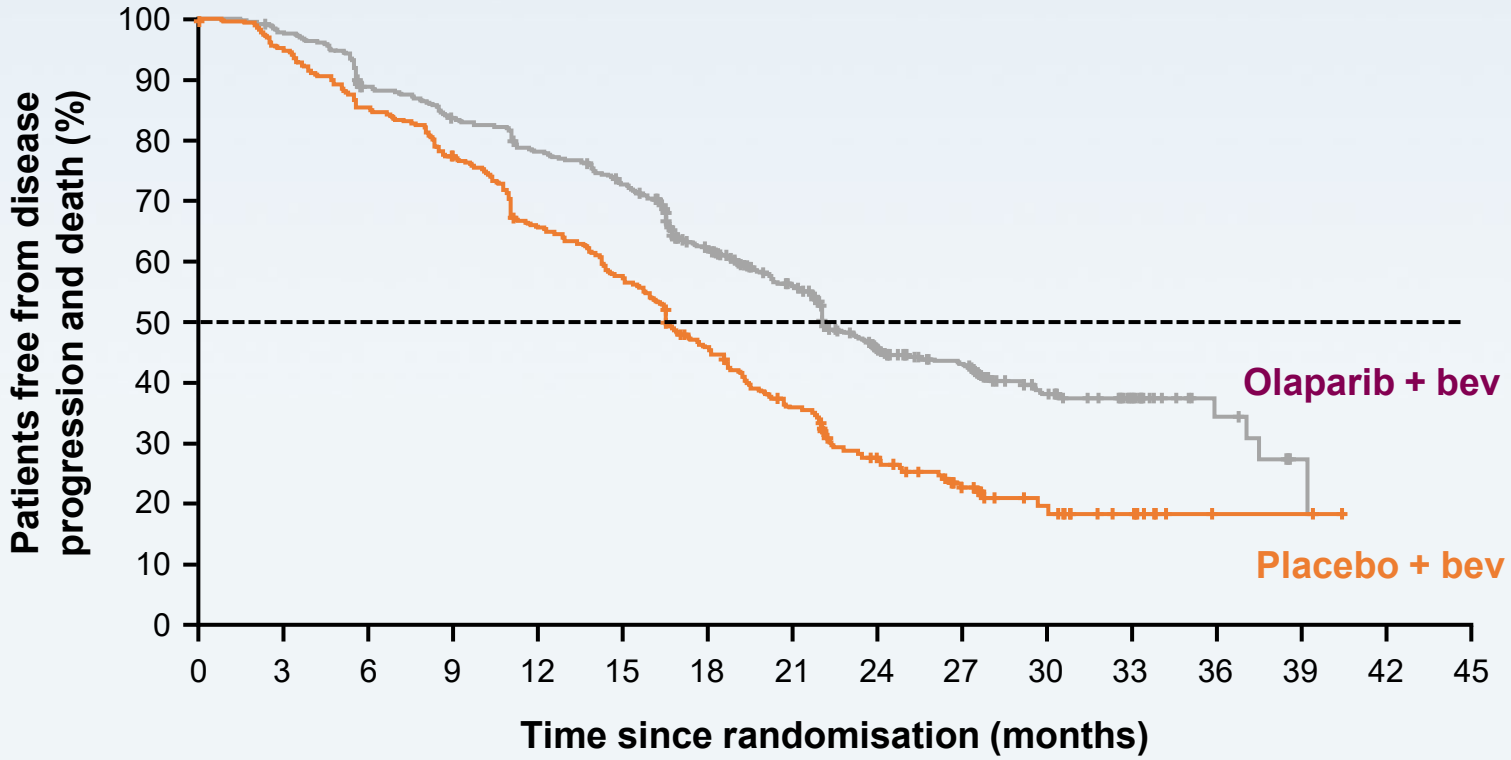
+ bevacizumab§

Primary endpoint
- Investigator-assessed PFS (RECIST v1.1)

Key secondary endpoints
- PFS2
- OS (planned for 3 years after the primary PFS analysis or 60% data maturity)

*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a gBRCAm; †Patients must have received ≥4 and ≤9 cycles of platinum-based chemotherapy; ‡Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy; §Bevacizumab 15 mg/kg every 3 weeks for a total of 15 months, including when administered with chemotherapy; ¶According to timing of surgery and NED/CR/PR.
bid, twice daily; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; gBRCAm, germline BRCA mutation; NED, no evidence of disease; PBC, platinum-based chemotherapy; PFS2, time from randomization to second progression or death; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.

PAOLA-1: investigator-assessed PFS (ITT population)[1]



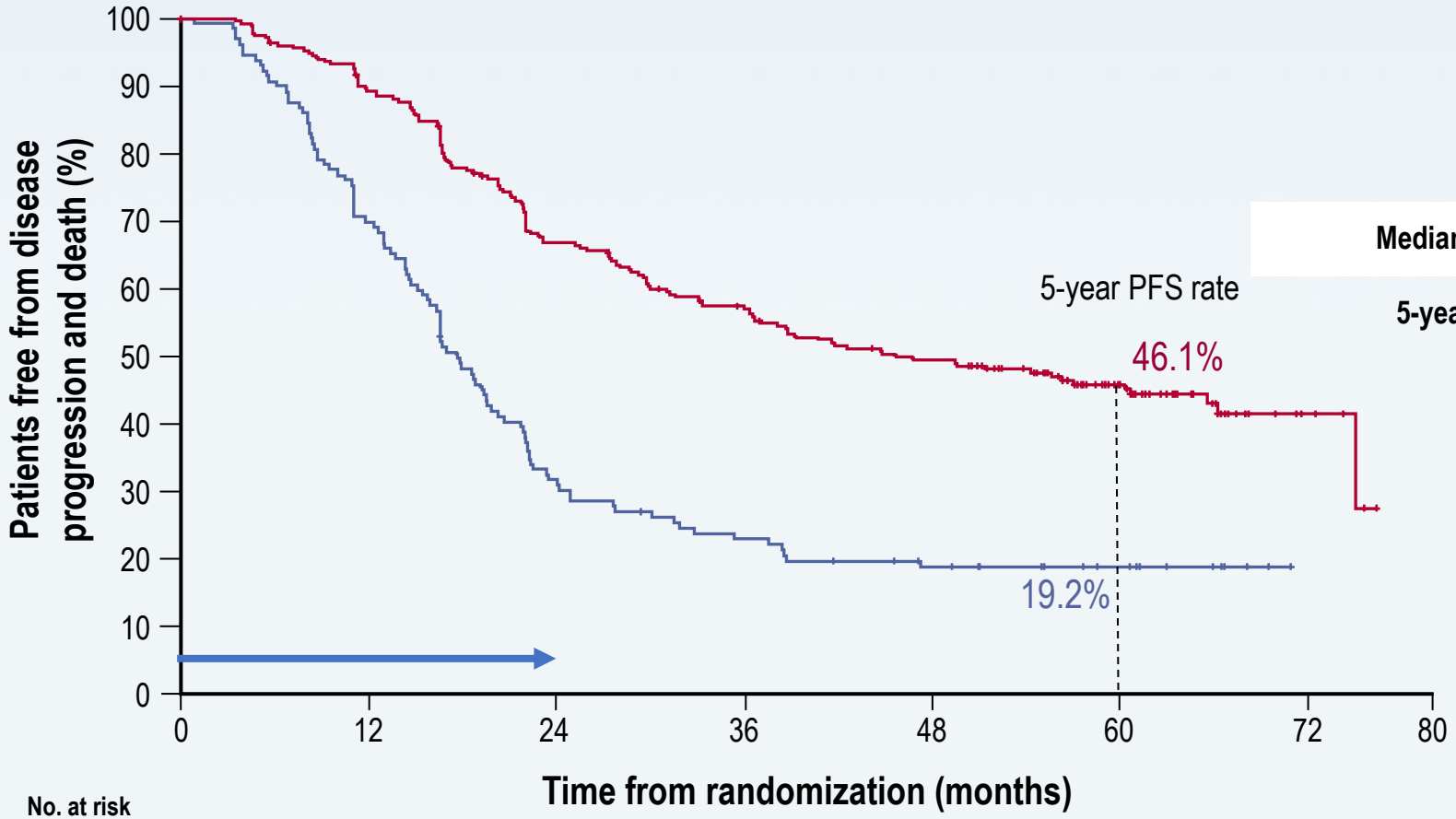
	Olaparib + bevacizumab (n=537)	Placebo + bevacizumab (n=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months (IA)	**22.1**	**16.6**
Δ Median PFS, months	**5.5**	
HR (95% CI)	0.59 (0.49–0.72); P<0.0001	
Median PFS, months (BICR)	**26.1**	**18.3**
Δ Median PFS, months	**7.8**	
HR (95% CI)	0.63 (0.51–0.77); P<0.0001	

Median time from first cycle of chemotherapy to randomisation: 7 months[2]

BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; IA= investigator assessed; ITT=intent-to-treat; PFS=progression-free survival

1. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–2428; 2. Ray-Coquard I, et al Presented at the ESMO Annual Conference 2019; 27 September -1 October; Barcelona, Spain. Abstract #LBA2

ENGOT-OV25 / PAOLA1: Updated PFS in HRD-positive population*



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	136 (53.3)	104 (78.8)
Median PFS, months	**46.8**	**17.6**
5-year PFS rate, %	**46.1**	**19.2**
HR 0.41 (95% CI 0.32–0.54)		

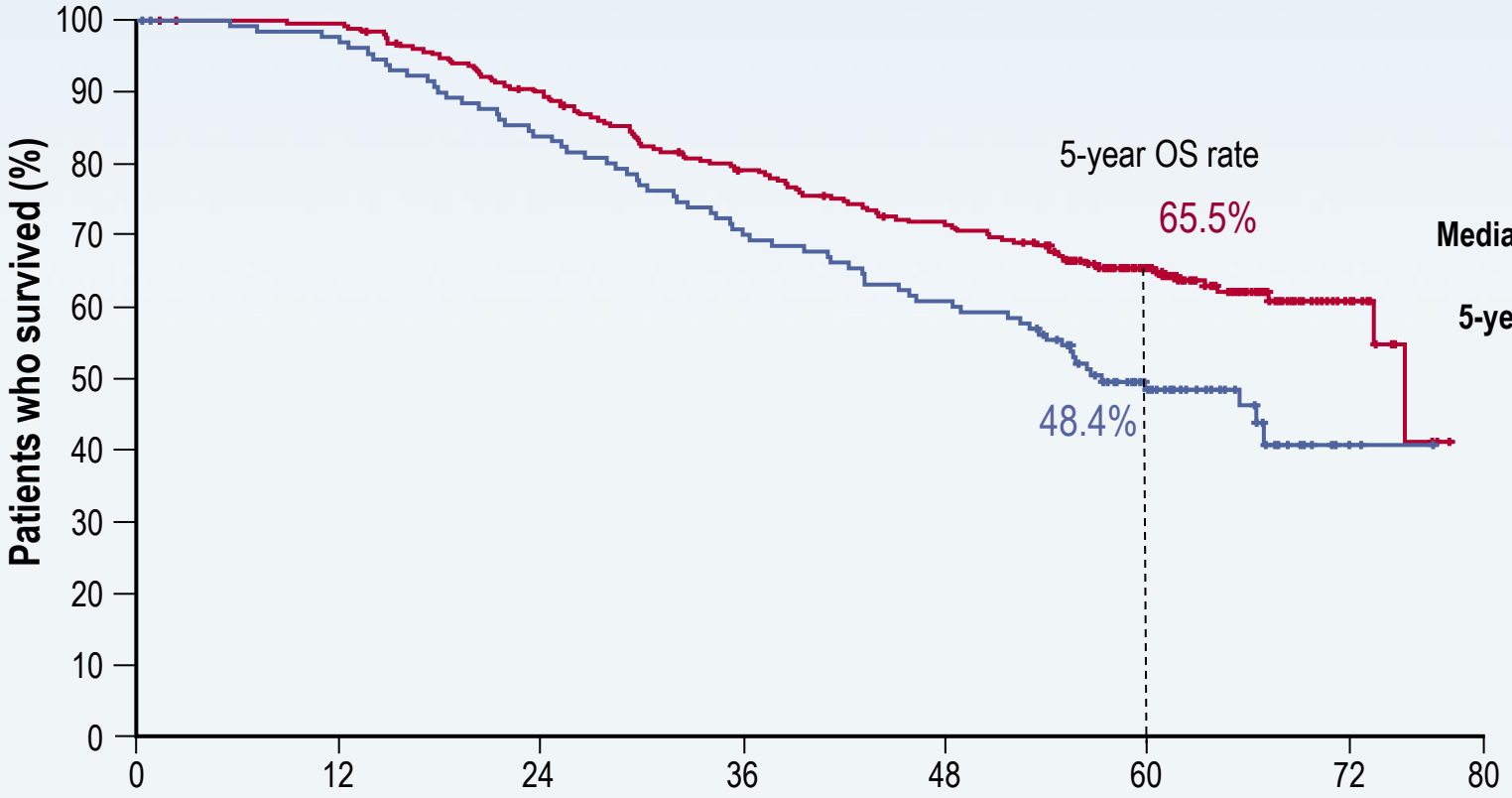
No. at risk

Olaparib + bevacizumab	255	252	242	236	223	214	194	183	165	162	147	143	138	127	123	119	117	112	103	79	63	40	31	8	5	3	0
Placebo + bevacizumab	132	129	118	103	91	79	62	52	41	37	34	30	29	25	24	24	21	20	19	15	13	8	6	2	0		

*Descriptive analysis; PFS by investigator-assessment (modified RECIST v1.1).

Isabelle Ray-Coquard

PAOLA-1 Overall survival in HRD-positive subgroup



No. at risk																										
Olaparib + bevacizumab	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Placebo + bevacizumab	132	130	129	128	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	9	2	1	0

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**

HR 0.62 (95% CI 0.45–0.85)

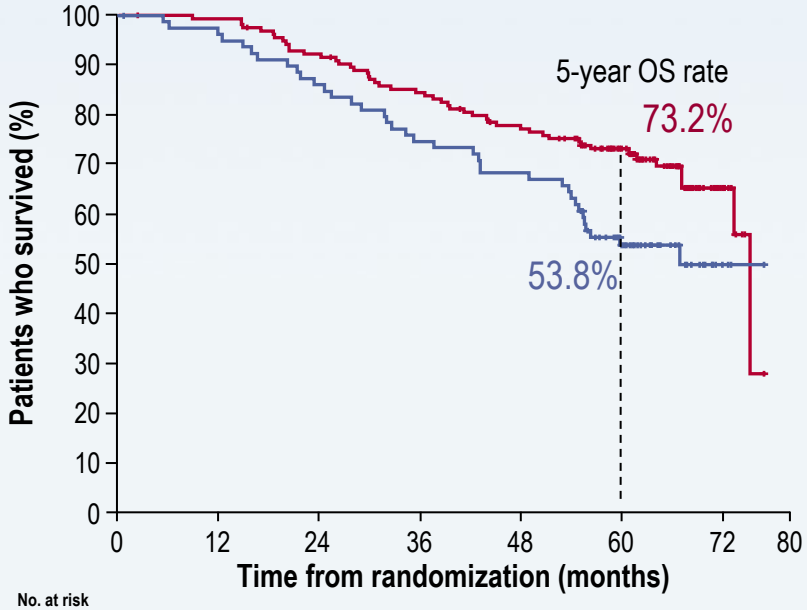
38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

*Median unstable; <50% data maturity.
HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.

ENGOT-OV25 / PAOLA1: OS subgroup analysis by BRCAm & HRD status

BRCAm*

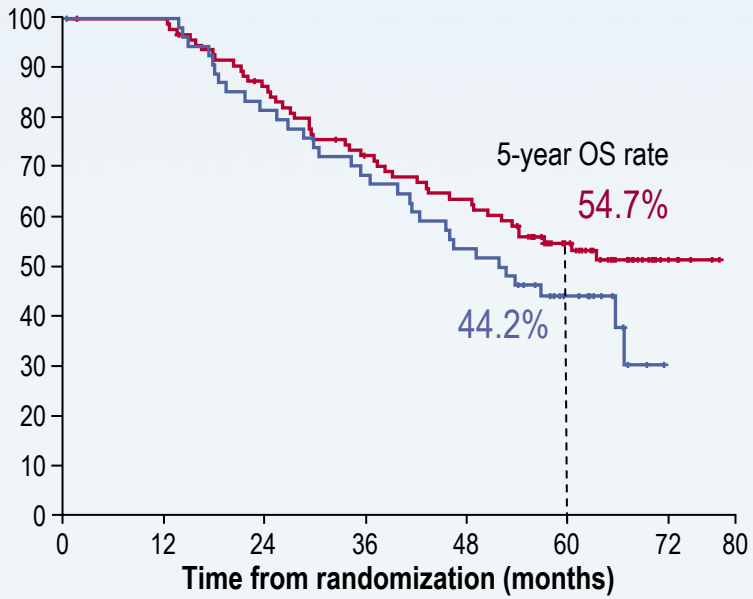


No. at risk

Olaparib + bevacizumab	157	156	156	155	155	152	150	144	143	139	134	131	130	127	123	118	117	115	112	99	80	55	42	21	11	2	0
Placebo + bevacizumab	80	79	78	77	76	74	72	71	68	66	64	61	59	58	58	54	54	53	50	40	33	22	17	10	3	1	0

	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
	HR 0.60 (95% CI 0.39–0.93)	

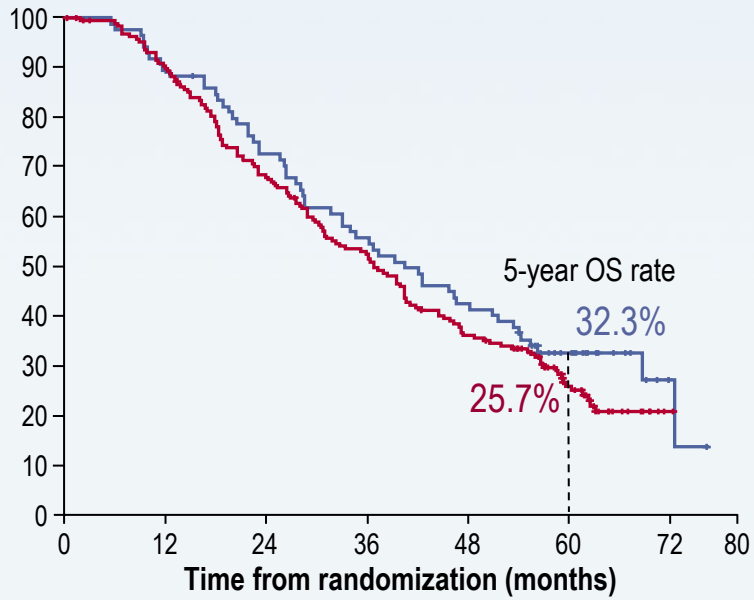
HRD positive‡ excluding BRCAm



Olaparib + bevacizumab	97	96	96	96	96	91	87	86	81	76	71	70	66	63	61	59	58	55	52	45	37	29	22	12	5	2	0
Placebo + bevacizumab	55	54	54	54	54	51	48	46	44	42	40	39	37	36	33	32	29	28	24	21	15	9	6	2	0		

	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
Events, n (%)	44 (45.4)	32 (58.2)
Median OS, months	NR	52.0
5-year OS rate, %	**54.7**	**44.2**
PARPi as subsequent treatment, n (%)	9 (9.3)	23 (41.8)
	HR 0.71 (95% CI 0.45–1.13)	

HRD negative†



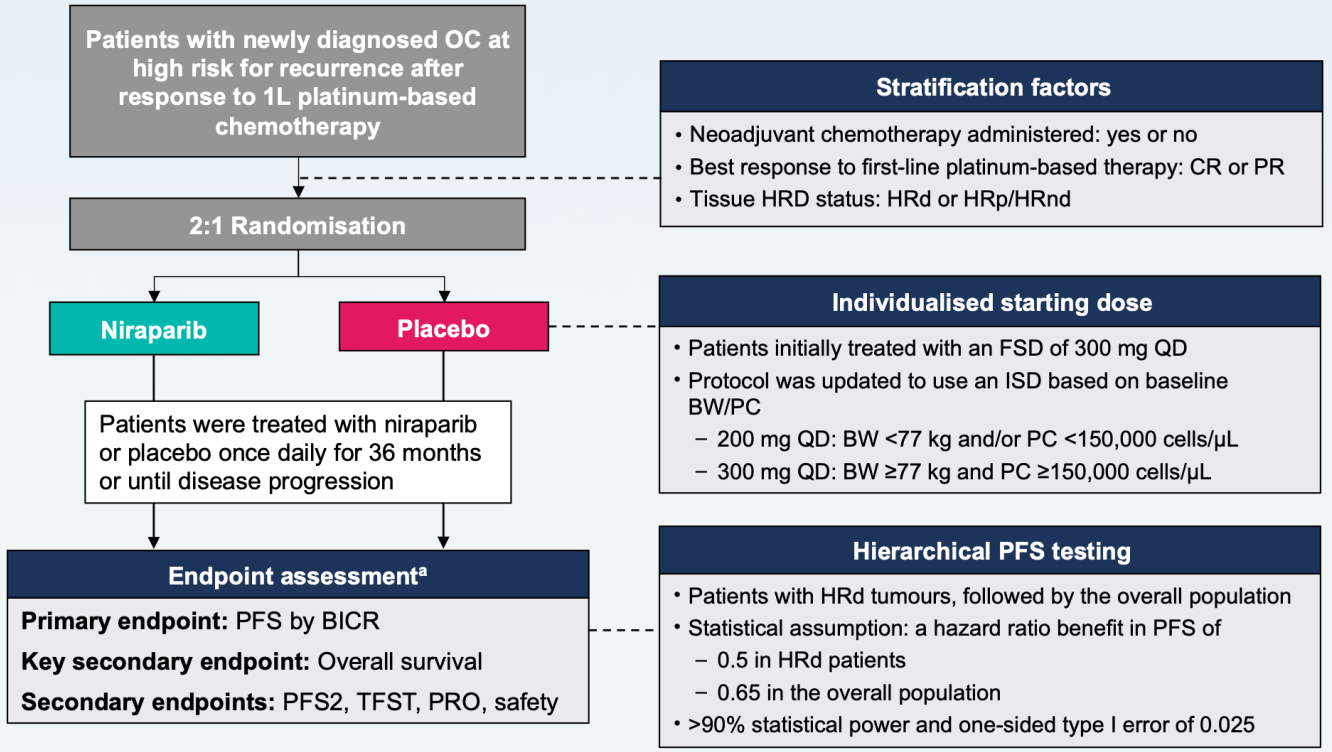
Olaparib + bevacizumab	192	187	186	179	169	157	146	135	126	119	109	100	97	89	77	72	66	62	57	43	30	16	11	5	1	0	
Placebo + bevacizumab	85	85	84	83	76	74	71	65	60	56	51	48	46	43	41	38	35	33	31	21	17	11	8	5	2	1	0

	Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
Events, n (%)	140 (72.9)	58 (68.2)
Median OS, months	36.8	40.4
5-year OS rate, %	**25.7**	**32.3**
PARPi as subsequent treatment, n (%)	46 (24.0)	34 (40.0)
	HR 1.19 (95% CI 0.88–1.63)	

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported

ENGOT-OV26 / PRIMA

Figure 1. PRIMA Study Design



[a]At study start, patients were monitored every 12 weeks (3 cycles). Subsequently, the protocol was amended in August 2019 so that patients who stayed on study treatment for over 2 years (≈26 cycles) were monitored for disease progression (CT/MRI) every 24 weeks (6 cycles). In response to the COVID-19 pandemic, additional guidance was released in March 2020 allowing flexibility regarding monitoring including use of phone visits and alternative locations for lab work and imaging.
1L, first-line; BICR, blinded independent central review; BW, body weight; COVID-19, coronavirus disease 2019; CR, complete response; CT, computed tomography; FSD, fixed starting dose; HRD, homologous recombination deficiency; HRd, homologous recombination–deficient; HRnd, homologous recombination not determined; HRp, homologous recombination–proficient; ISD, individualised starting dose; MRI, magnetic resonance imaging; OC, ovarian cancer; PC, platelet count; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; QD, once daily; TFST, time to first subsequent therapy.

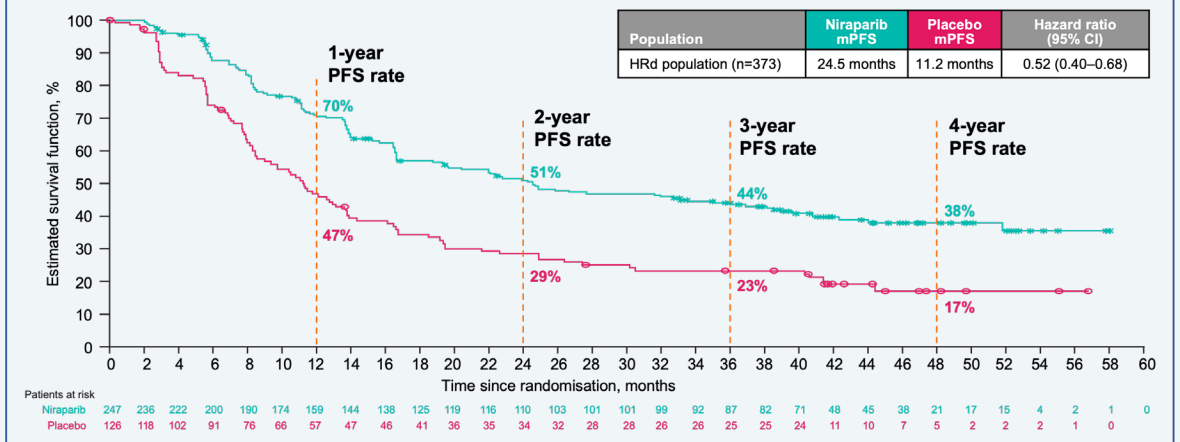
González-Martín A,…Mirza MR, et al. *N Engl J Med*. 2019;381:2391–2402.

ENGOT-OV26 / PRIMA: Investigator-Assessed PFS in the HRd and Overall Populations

17 November 2021 Clinical Cutoff Date

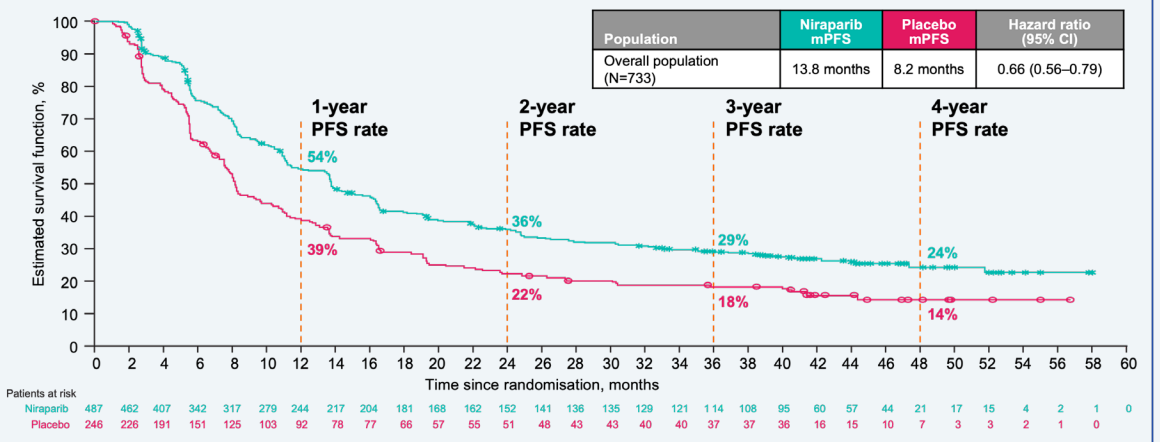
- As of the 17 November 2021 clinical cutoff date, the median PFS in the HRd population was 24.5 months in the niraparib arm compared with 11.2 months in the placebo arm (hazard ratio, 0.52; 95% CI, 0.40–0.68; *P*<0.001; **Figure 2**)
- As of the 17 November 2021 clinical cutoff date, the median PFS in the overall population was 13.8 months in the niraparib arm compared with 8.2 months in the placebo arm (hazard ratio, 0.66; 95% CI, 0.56–0.79; *P*<0.001; **Figure 3**)

Figure 2. Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment in the HRd Population, 17 November 2021 Clinical Cutoff Date



HRd, homologous recombination–deficient; mPFS, median progression-free survival; PFS, progression-free survival.

Figure 3. Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment in the Overall Population, 17 November 2021 Clinical Cutoff Date



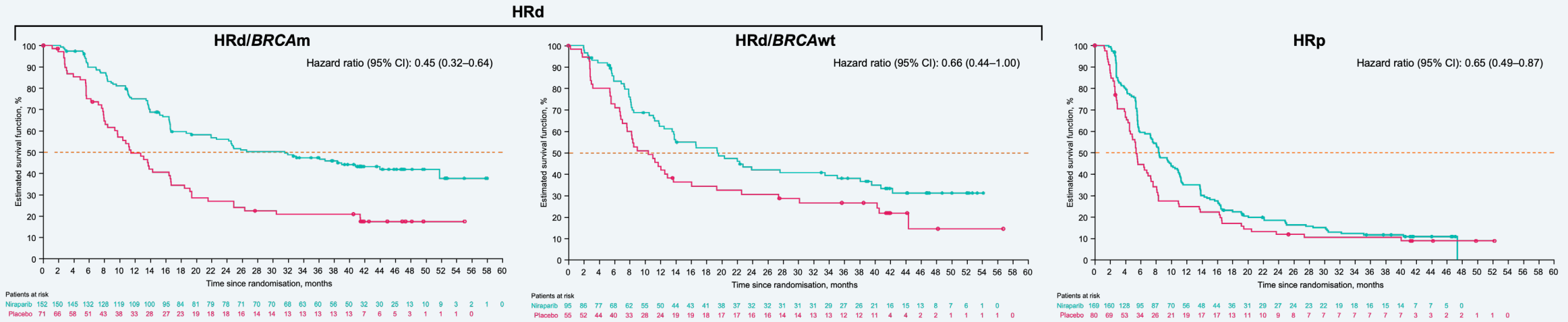
mPFS, median progression-free survival; PFS, progression-free survival.

ENGOT-OV26 / PRIMA: Investigator-Assessed PFS across Biomarker Subgroups

17 November 2021 Clinical Cutoff Date

- Niraparib treatment increased PFS duration compared with placebo treatment across biomarker subgroups
- The greatest treatment benefit was seen in patients with HRd tumours that were *BRCA* mutated (hazard ratio, 0.45; 95% CI, 0.32–0.64)

Figure 4. Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment Across Biomarker Subgroups, 17 November 2021 Clinical Cutoff Date



*BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild-type; HRd, homologous recombination–deficient; HRp, homologous recombination–proficient.

Gonzales-Martin A…Mirza MR et al. ESMO 2022

PRIME study

Efficacy and Safety of Niraparib as Maintenance Treatment in Patients with Newly Diagnosed Advanced Ovarian Cancer Using an Individualized Starting Dose (PRIME Study): A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial

Ning Li*, Jianqing Zhu, Rutie Yin, Jing Wang, Lingya Pan, Beihua Kong, Hong Zheng, Jihong Liu, Xiaohua Wu, Li Wang, Yi Huang, Ke Wang, Dongling Zou, Hongqin Zhao, Chunyan Wang, Weiguo Lu, An Lin, Ge Lou, Guiling Li, Pengpeng Qu, Hongying Yang, Xiaoa Zhen, Wenzhao Hang, Jianmei Hou, Lingying Wu*

* National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

- PRIME is a randomized, double-blind, placebo-controlled phase III trial (NCT03709316).

Schema

Eligible Patients
- Age ≥18 years
- FIGO stage III/IV ovarian cancer
- High-grade serous or endometroid tumor[a]
- Receipt of primary or interval cytoreductive surgery, irrespective of postoperative residual disease status
- CR/PR to 1L Pt-based chemotherapy

Stratified randomization
- Status of g*BRCA* mutations (g*BRCA*mut/non-g*BRCA*mut)
- Tumor HRD status[b] (positive/negative)
- Receipt of neoadjuvant chemotherapy (Y/N)
- Response to 1L Pt-based chemotherapy (CR/PR)

2:1 Randomization

→ **Niraparib*** / **Placebo***

→ 36 months or until disease progression or unacceptable toxicity

*Individualised starting dose (ISD) was adopted in **ALL** patients: *starting dose of 200 mg administered orally, once daily, but 300 mg for patients with body weight ≥77 kg AND platelet count ≥150,000/μL*

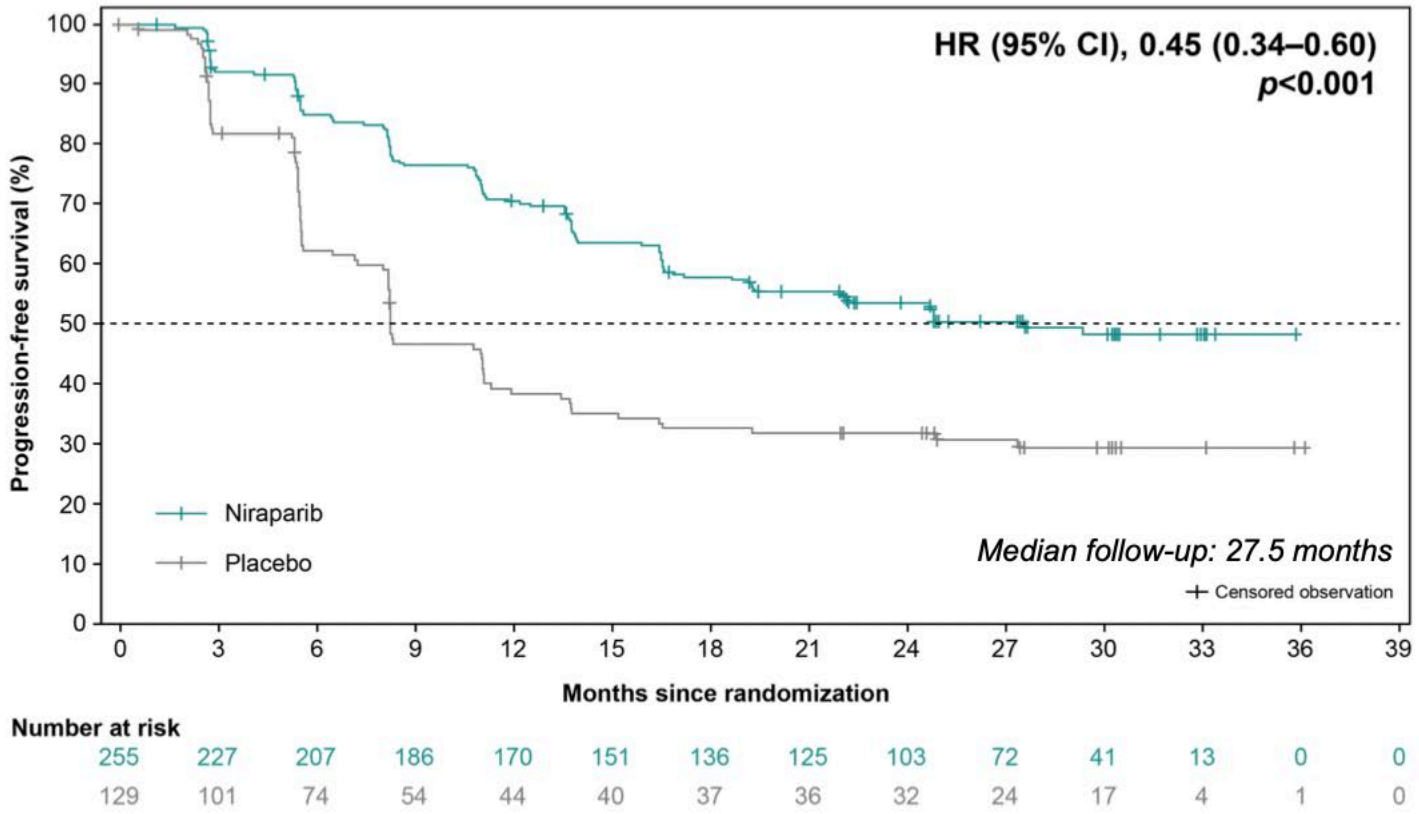
Primary Endpoint
- **PFS by BICR in the ITT population**

Secondary Endpoints
- OS and TFST in the ITT population
- PFS and OS in the HRD subgroup[c]
- Safety

Li N et al. SGO 2022

PRIME Primary Endpoint: PFS (by BICR) in the ITT population

PFS (by BICR) in the ITT Population
PRIME Study Primary Endpoint



16.5 months longer median PFS with niraparib versus placebo

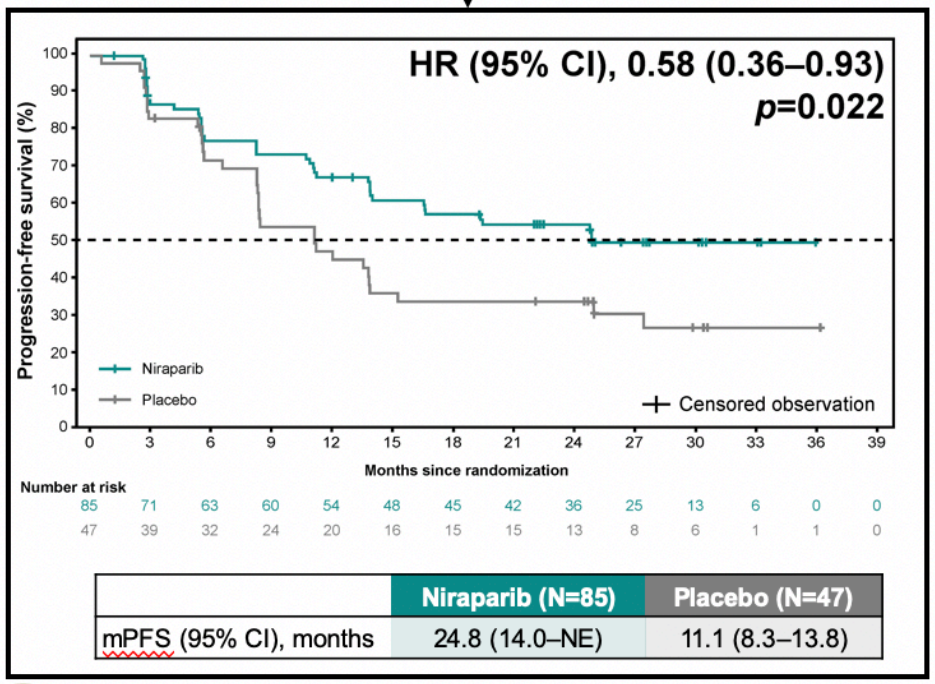
	Niraparib (N=255)	Placebo (N=129)
PFS (54.4% data maturity)		
Events, n (%)	123 (48.2)	86 (66.7)
mPFS (95% CI), months	24.8 (19.2–NE)	8.3 (7.3–11.1)
Patients without PD or death (%)		
24 months	52.6	30.4

Li N et al. SGO 2022

PRIME: Non-gBRCAmut subgroup - PFS (by BICR)

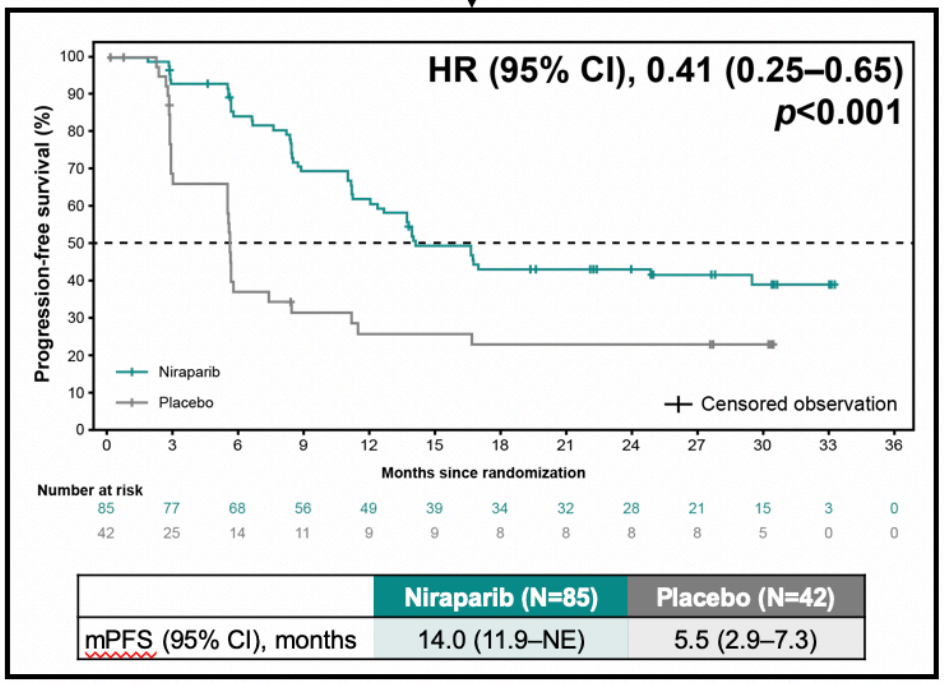
PFS Benefit in Non-g*BRCA*mut Subgroups

Non-g*BRCA*mut/HRd



	Niraparib (N=85)	Placebo (N=47)
mPFS (95% CI), months	24.8 (14.0–NE)	11.1 (8.3–13.8)

Non-g*BRCA*mut/HRp



	Niraparib (N=85)	Placebo (N=42)
mPFS (95% CI), months	14.0 (11.9–NE)	5.5 (2.9–7.3)

Li N et al. SGO 2022

ENGOT-OV45 / ATHENA$_{mono}$ study

Key Patient Eligibility

- Newly diagnosed, stage III–IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR
  - Received cytoreductive surgery (primary or interval; R0/complete resection permitted)
- ECOG PS 0 or 1
- No prior treatment for ovarian cancer, including any maintenance treatment, other than frontline platinum regimen

Randomization 4:4:1:1

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab 480 mg IV

Arm D (n≈100)
placebo PO + placebo IV

Randomization Stratification Factors

- Tumor HRD test status[†]
- Disease status post-chemotherapy
- Timing of surgery

Treatment for 24 months*, or until radiographic progression, unacceptable toxicity, or other reason for discontinuation

Study Analyses

ATHENA–MONO

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm D (n≈100)
placebo PO + placebo IV

ATHENA–COMBO

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

*After initiation of oral/IV combination study treatment (IV drug was initiated cycle 2 day 1; 28-day cycles). [†]Centrally assessed, determined by FoundationOne CDx (BRCA^{mut}, BRCA^{wt}/LOH^{high} [LOH ≥16%], BRCA^{wt}/LOH^{low} [LOH <16%], BRCA^{wt}/LOH^{indeterminate}). BID, twice daily; BRCA, *BRCA1* or *BRCA2*; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; IV, intravenous; LOH, loss of heterozygosity; mut, mutant; PO, by mouth; PR, partial response; wt, wild type.

Monk B et al. JCO 2022

ENGOT-OV45 / ATHENA$_{mono}$

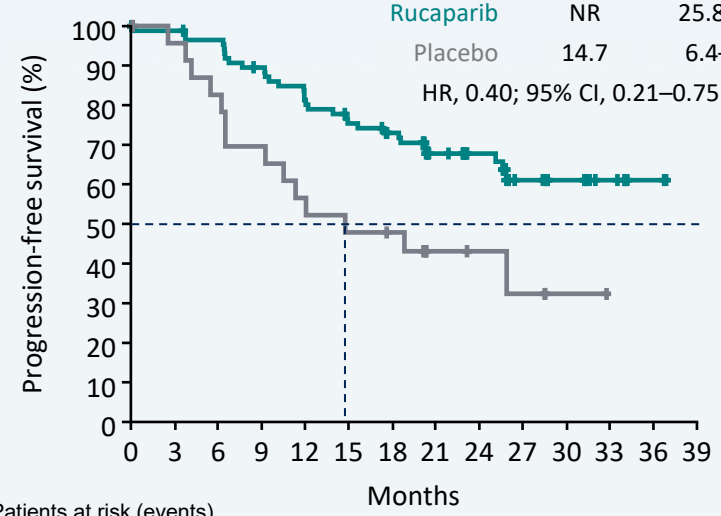
Investigator Assessed in Exploratory Subgroups

HRD positive

BRCA^{mut}

	Median	95% CI
Rucaparib	NR	25.8–NR
Placebo	14.7	6.4–NR

HR, 0.40; 95% CI, 0.21–0.75



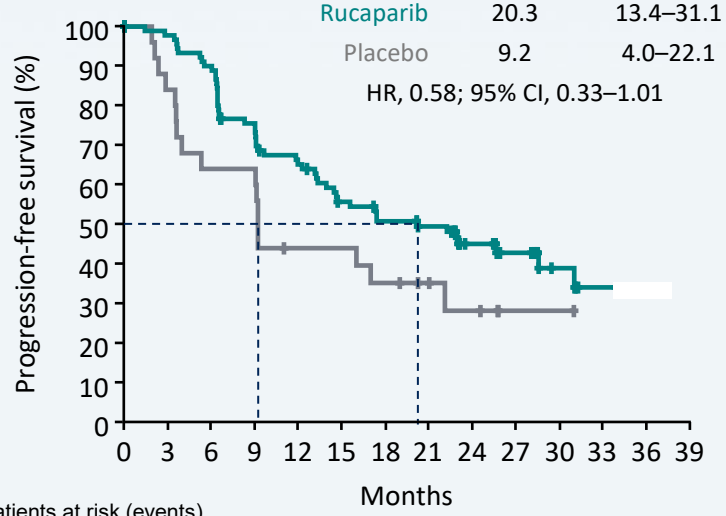
Patients at risk (events)

Rucaparib	91 (0)	84 (3)	70 (16)	59 (23)	34 (27)	14 (30)	2 (30)
Placebo	24 (0)	19 (4)	12 (11)	10 (12)	4 (13)	1 (14)	0 (14)

BRCA^{wt}/LOH^{high}

	Median	95% CI
Rucaparib	20.3	13.4–31.1
Placebo	9.2	4.0–22.1

HR, 0.58; 95% CI, 0.33–1.01



Patients at risk (events)

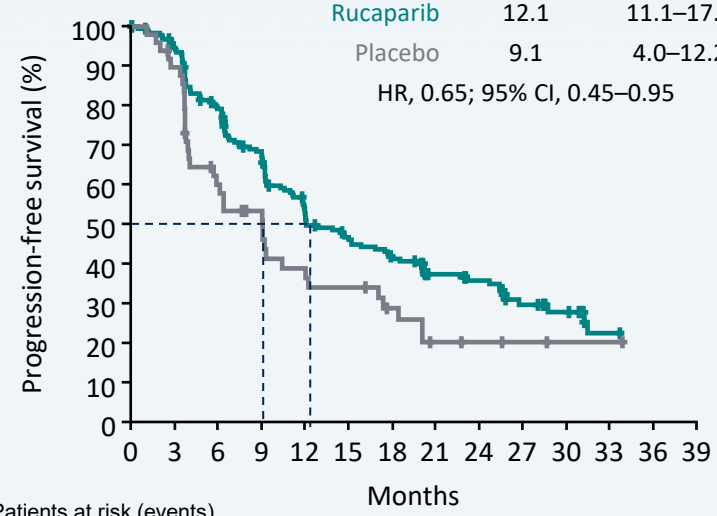
Rucaparib	94 (0)	81 (9)	57 (30)	41 (43)	25 (47)	8 (49)	4 (50)
Placebo	25 (0)	16 (9)	10 (14)	8 (16)	4 (17)	1 (17)	0 (17)

HRD negative

BRCA^{wt}/LOH^{low}

	Median	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)

- 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 et al. JCO 2022

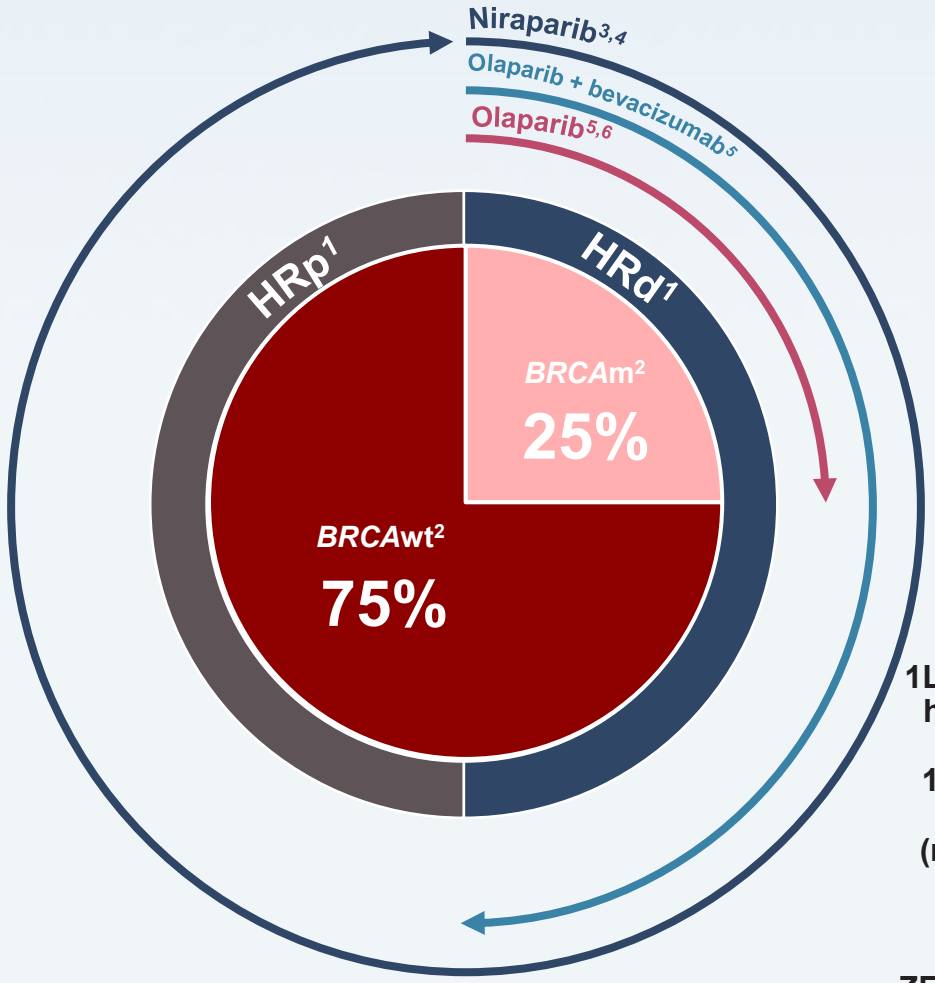
Why PARPi should be used in First-Line?

Safety (firstline maintenance PARPi)

	SOLO-1	PRIMA	PRIME	ATHENA-MONO	PAOLA-1
Discontinuation (%)	11.5	12	6.7	11.8	**20**
Dose interruption (%)	51.9	79.5	62	60.7	54
Dose reduction (%)	28.5	70.9	40.4	49.4	41
MDS/AML (%)	**1**	**0.2**	**0.7**	**0.4**	**1.1**

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

PARP inhibitor 1L maintenance treatments showed clinical benefit across biomarker subgroups

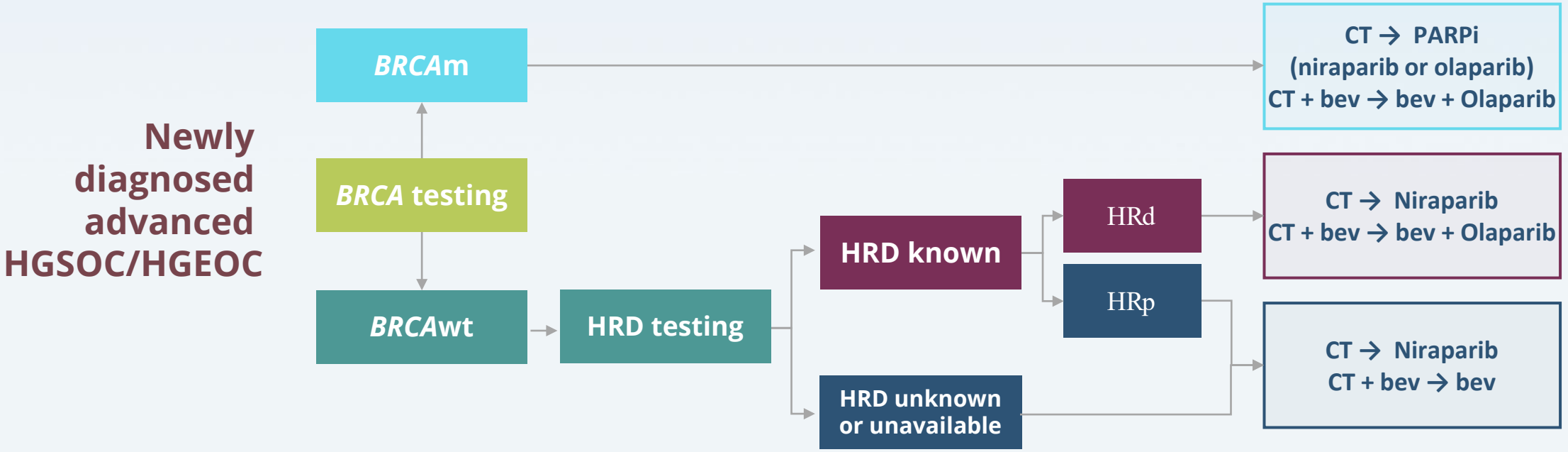


Niraparib[3,4]	Olaparib[5,6]	Olaparib + bevacizumab[5]
All comers	*BRCA*m	*BRCA*m or HRd

1L, first-line; *BRCA*m, breast cancer gene mutation; *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. European commission approves Zejula (niraparib) as first-line monotherapy maintenance treatment in advanced ovarian cancer. Press release. GlaxoSmithKline. October 29, 2020. Accessed November 4, 2020. https://www.gsk.com/en-gb/media/press-releases/european-commission-approves-zejula-niraparib-as-first-line-monotherapy-maintenance-treatment-in-advanced-ovarian-cancer/. 4. ZEJULA. Prescribing information. GlaxoSmithKline; 2020. 5. LYNPARZA. Prescribing information. AstraZeneca Pharmaceuticals LP; 2020. 6. LYNPARZA. Summary of product characteristics. AstraZeneca AB; 2020.

A biomarker-based algorithm for advanced ovarian cancer



Bev, bevacizumab; *BRCA*m, breast cancer gene mutant; *BRCA*wt; breast cancer gene wild type; CT, chemotherapy; HGEOC, high grade epithelial ovarian cancer; HGSOC, high grade serous ovarian cancer; HRd, homologous recombinant deficient; HRp, homologous recombinant proficient; PARPi, poly ADP ribose polymerase inhibitor.

Modified from: Mirza MR et al. *Ann Oncol*. 2020;31(9):1148-1159.

Key Takeaways

- 1st line maintenance therapy with PARP inhibitors improves PFS and OS in women with newly-diagnosed advanced, high grade HRD-positive ovarian, fallopian tube, primary peritoneal cancer

- Landscape of ovarian cancer management has changed dramatically

- Testing for BRCA mutations and HRD should be part of standard management of ovarian cancer

Key Takeaways – Challenges!

- Around 50% of patients treated with a PARP inhibitor will relapse
- How should they be treated?
- Should PARP inhibitors be given to all in front-line therapy?
- Can bevacizumab be given in combination with PARP inhibitors or be saved for relapsed disease?
- What are the mechanisms underlying resistance to PARP inhibitors, and their re-use

We can achieve these goals by working together