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Maintenance olaparib plus bevacizumab after platinum-based chemotherapy with bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: Efficacy by timing of surgery and residual tumor status in the Phase III PAOLA-1 trial

Christoph Grimm,[1] Laurence Gladieff,[2] Philipp Harter,[3] Claire Cropet,[4] Claudio Zamagni,[5] Maria Jesús Rubio,[6] Toyomi Satoh,[7] Peter Vuylsteke,[8] Annalisa Garbi,[9] Sakari Hietanen,[10] Sophie Abadie-Lacourtoisie,[11] Antje Belau,[12] Anna Maria Mosconi,[13] Yolanda García,[14] Jerome Alexandre,[15] Martina Gropp-Meier,[16] Annick Chevalier-Place,[17] Hans-Joachim Lück,[18] Marie-Christine Kaminsky,[19] Isabelle Ray-Coquard[20]

[1]Medical University of Vienna, Vienna and AGO-Austria, Austria; [2]Institut Claudius Regaud, IUCT Oncopole, Toulouse, and GINECO, France; [3]Kliniken Essen Mitte, Essen and AGO, Germany; [4]Centre Léon Bérard, Lyon, France; [5]Policlinico S.Orsola-Malpighi, Bologna and MITO, Italy; [6]Reina Sofia Hospital, Córdoba and GEICO, Spain; [7]University of Tsukuba, Tsukuba and GOTIC, Japan; [8]CHU UCL Namur, Sainte Elisabeth, Namur and BGOG, Belgium; [9]European Institute of Oncology, IRCCS , Milan and MANGO, Italy; [10]Turku University Hospital, Turku and NSGO, Finland; [11]Institut de Cancérologie de l'Ouest, Paul Papin, Angers, and GINECO, France; [12]University Hospital Greifswald, Greifswald and AGO, Germany; [13]Ospedale Santa Maria Della Misericordia, Perugia, and MITO, Italy; [14]Parc Tauli Hospital Universitari, Sabadell and GEICO, Spain; [15]Hôpital Cochin, Paris and GINECO, France; [16]Oberschwabenklinik Hospital St. Elisabeth Ravensburg, Ravensburg, and AGO, Germany; [17]Centre Oscar Lambret, Lille and GINECO, France; [18]Gynäkologisch-Onkologische Praxis Hannover, Hannover, and AGO, Germany; [19]Institut de Cancérologie de Lorraine, Vandoeuvre-Lès-Nancy and GINECO, France; [20]Centre Léon Bérard and University Claude Bernard Lyon 1, Lyon and GINECO, France

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Introduction

- The randomized, double-blind Phase III PAOLA-1/ENGOT-ov25 trial evaluated maintenance olaparib when added to bevacizumab in women with advanced, high-grade ovarian cancer who were in response to first-line platinum-based chemotherapy plus bevacizumab[1]
- The PAOLA-1 population was unselected by biomarker status or surgical outcome, meaning it is representative of the majority of patients in clinical practice
- In PAOLA-1, the addition of maintenance olaparib to bevacizumab led to a statistically significant PFS benefit, compared with placebo plus bevacizumab:[1]
  - HR for PFS by investigator assessment 0.59 (95% CI 0.49–0.72) [median 22.1 vs 16.6 months]

BICR, blinded independent central review; CI, confidence interval; HR hazard ratio; PFS, progression-free survival

1. Ray-Coquard I *et al*. *N Engl J Med* 2019;381:2416–28

Introduction

We evaluated the efficacy of olaparib plus bevacizumab in PAOLA-1 by timing of surgery and presence of residual tumor after surgery:

- Prespecified analyses evaluated PFS by timing of surgery (upfront or interval surgery)
- Post hoc analyses evaluated PFS by timing of surgery (upfront or interval surgery) combined with residual disease status (macroscopic residual disease or no macroscopic residual disease)

Patient characteristics

	Olaparib plus bevacizumab (N=537)	Placebo plus bevacizumab (N=269)
Upfront surgery, n (%)	271 (50)	138 (51)
No macroscopic residual disease	160 (59)	85 (62)
Macroscopic residual disease	111 (41)	53 (38)
Interval surgery, n (%)	228 (42)	110 (41)
No macroscopic residual disease	163 (71)	75 (68)
Macroscopic residual disease	65 (29)	35 (32)
No surgery*, n (%)	38 (7)	21 (8)

Percentages may not total 100% because of rounding. *PFS data in patients who did not undergo surgery are not presented, although this subgroup was integrated into the Cox proportional hazards model used to calculate HRs in the other subgroups

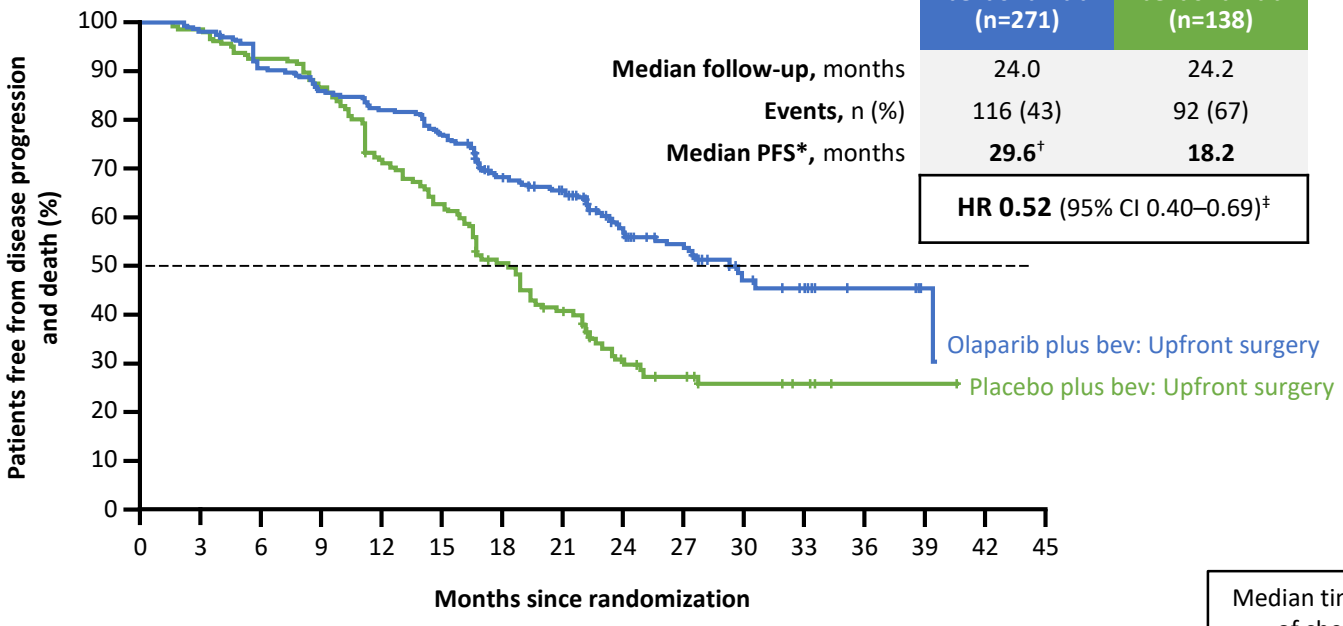
Patient characteristics

	Olaparib plus bevacizumab (N=537)	Placebo plus bevacizumab (N=269)
tBRCAm*, n (%)	158 (29)	77 (29)
Upfront surgery	84 (53)	46 (60)
Interval surgery	69 (44)	25 (32)
No surgery	5 (3)	6 (8)
HRD positive, excluding tBRCAm†, n (%)	97 (34)	55 (39)
Upfront surgery	61 (63)	33 (60)
Interval surgery	31 (32)	20 (36)
No surgery	5 (5)	2 (4)
HRD status negative, n (%)	192 (36)	85 (32)
Upfront surgery	104 (54)	46 (54)
Interval surgery	70 (36)	32 (38)
No surgery	18 (9)	7 (8)
HRD unknown, n (%)	90 (17)	52 (19)
Upfront surgery	22 (24)	13 (25)
Interval surgery	58 (64)	33 (63)
No surgery	10 (11)	6 (12)

Percentages may not total 100% because of rounding. *Results of central Myriad testing; †HRD positive (excluding tBRCAm) is an HRD score of ≥42 by Myriad MyChoice® HRD Plus.
HRD, homologous recombination repair deficiency; tBRCAm, tumor BRCA mutation

PFS by timing of surgery: Upfront surgery

	Upfront surgery	
	Olaparib + bevacizumab (n=271)	Placebo + bevacizumab (n=138)
Median follow-up, months	24.0	24.2
Events, n (%)	116 (43)	92 (67)
Median PFS*, months	**29.6**†	**18.2**
HR 0.52 (95% CI 0.40–0.69)‡		



No. patients at risk

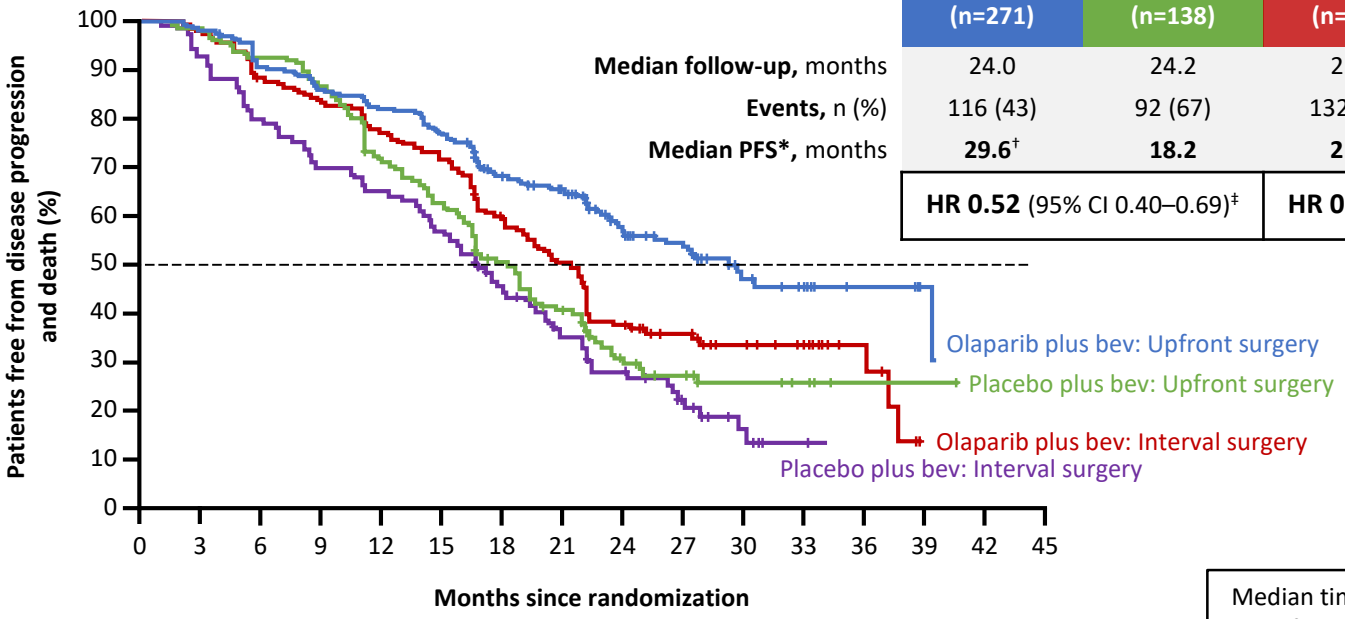
Olaparib plus bev: Upfront surgery	271	260	237	225	214	199	156	144	89	73	33	22	6	3	0
Placebo plus bev: Upfront surgery	138	133	125	117	95	84	62	49	27	22	9	7	1	1	0

Median time from first cycle of chemotherapy to randomization = 7 months

*Investigator-assessed PFS; †The median is unstable due to a lack of events; ‡HR calculated using a Cox proportional hazards model performed on the overall population containing: a term for treatment, the subgroup covariate in 3 modalities (upfront surgery/interval surgery/no surgery) and the treatment by subgroup interaction term

PFS by timing of surgery: Upfront and interval surgery

	Upfront surgery		Interval surgery	
	Olaparib + bevacizumab (n=271)	Placebo + bevacizumab (n=138)	Olaparib + bevacizumab (n=228)	Placebo + bevacizumab (n=110)
Median follow-up, months	24.0	24.2	22.2	24.1
Events, n (%)	116 (43)	92 (67)	132 (58)	83 (75)
Median PFS*, months	**29.6**†	**18.2**	**21.4**	**16.7**
	HR 0.52 (95% CI 0.40–0.69)‡		**HR 0.66** (95% CI 0.50–0.87)‡	



No. patients at risk

Olaparib plus bev: Upfront surgery	271	260	237	225	214	199	156	144	89	73	33	22	6	3	0
Placebo plus bev: Upfront surgery	138	133	125	117	95	84	62	49	27	22	9	7	1	1	0
Olaparib plus bev: Interval surgery	228	218	196	184	170	157	111	89	47	36	22	15	6	0	
Placebo plus bev: Interval surgery	110	101	87	76	71	62	44	33	23	13	6	2	0		

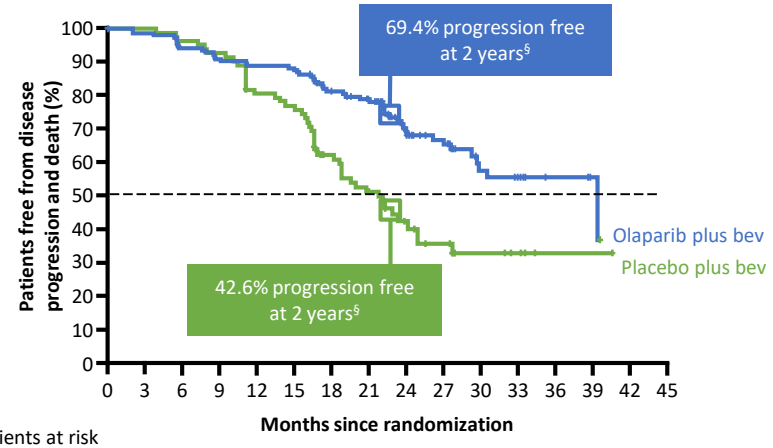
Median time from first cycle of chemotherapy to randomization = 7 months

*Investigator-assessed PFS; †The median is unstable due to a lack of events; ‡HR calculated using a Cox proportional hazards model performed on the overall population containing: a term for treatment, the subgroup covariate in 3 modalities (upfront surgery/interval surgery/no surgery) and the treatment by subgroup interaction term

PFS by timing of surgery and no residual disease

Upfront surgery, no residual disease

	Olaparib + bevacizumab (n=160)	Placebo + bevacizumab (n=85)
Events, n (%)	50 (31)	48 (56)
Median PFS*, months	**39.3**†	**22.1**
	HR 0.47 (95% CI 0.29–0.75)‡	



No. patients at risk

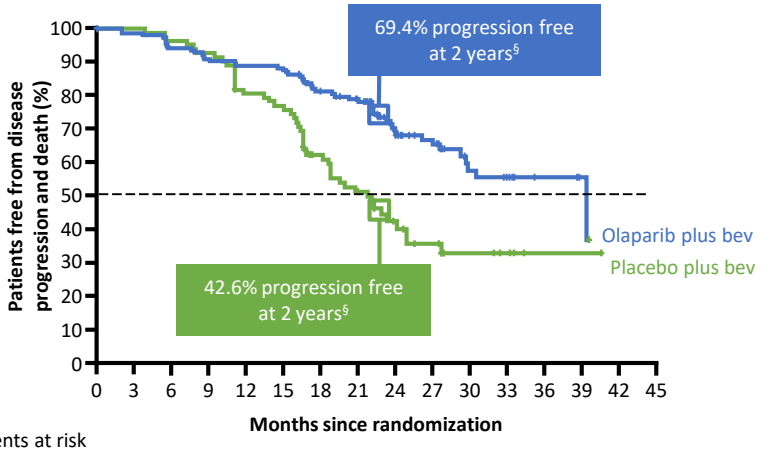
Olaparib plus bev	160	154	145	140	136	134	107	100	61	50	27	20	6	3	0
Placebo plus bev	85	83	80	77	66	63	46	37	20	15	7	5	1	1	0

*Investigator-assessed PFS; †The median is unstable due to a lack of events; ‡HR calculated using a Cox proportional hazards model performed on the overall population containing: a term for treatment, the subgroup covariate in 5 modalities (upfront surgery with no residual disease/interval surgery with no residual disease/interval surgery with residual disease/ upfront surgery with residual disease/no surgery) and the treatment by subgroup interaction term; §Kaplan-Meier estimates

PFS by timing of surgery and no residual disease

Upfront surgery, no residual disease

	Olaparib + bevacizumab (n=160)	Placebo + bevacizumab (n=85)
Events, n (%)	50 (31)	48 (56)
Median PFS*, months	**39.3**†	**22.1**
	HR 0.47 (95% CI 0.29–0.75)‡	

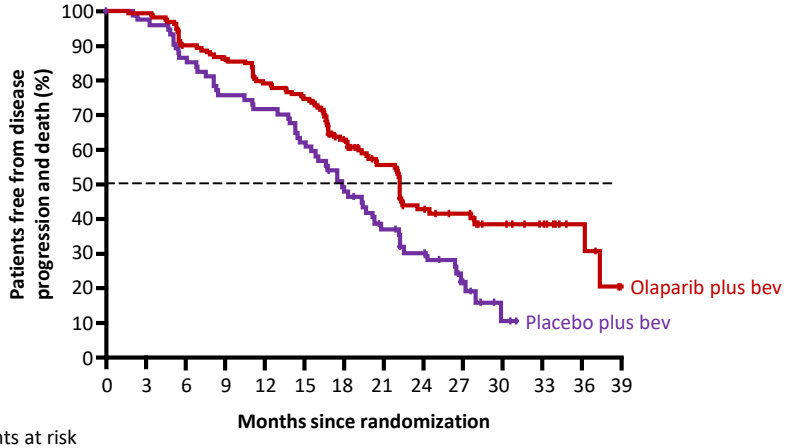


No. patients at risk

Olaparib plus bev	160	154	145	140	136	134	107	100	61	50	27	20	6	3	0
Placebo plus bev	85	83	80	77	66	63	46	37	20	15	7	5	1	1	0

Interval surgery, no residual disease

	Olaparib + bevacizumab (n=163)	Placebo + bevacizumab (n=75)
Events, n (%)	85 (52)	56 (75)
Median PFS*, months	**22.1**	**17.7**
	HR 0.61 (95% CI 0.41–0.91)‡	



No. patients at risk

Olaparib plus bev	163	158	142	135	124	117	81	66	37	32	19	12	5	0
Placebo plus bev	75	72	64	56	53	46	32	23	17	8	2	0		

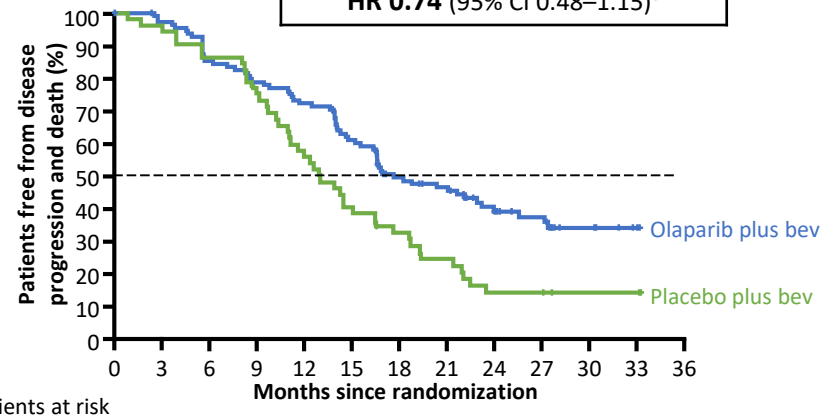
*Investigator-assessed PFS; †The median is unstable due to a lack of events; ‡HR calculated using a Cox proportional hazards model performed on the overall population containing: a term for treatment, the subgroup covariate in 5 modalities (upfront surgery with no residual disease/interval surgery with no residual disease/interval surgery with residual disease/upfront surgery with residual disease/no surgery) and the treatment by subgroup interaction term; §Kaplan-Meier estimates

PFS by timing of surgery and no residual disease

Upfront surgery, residual disease

	Olaparib + bevacizumab (n=111)	Placebo + bevacizumab (n=53)
Events, n (%)	66 (59)	44 (83)
Median PFS*, months	**17.6**	**13.0**

HR 0.74 (95% CI 0.48–1.15)†



No. patients at risk

Olaparib plus bev	111	106	92	85	78	65	49	44	28	23	6	2	0
Placebo plus bev	53	50	45	40	29	21	16	12	7	7	2	2	0

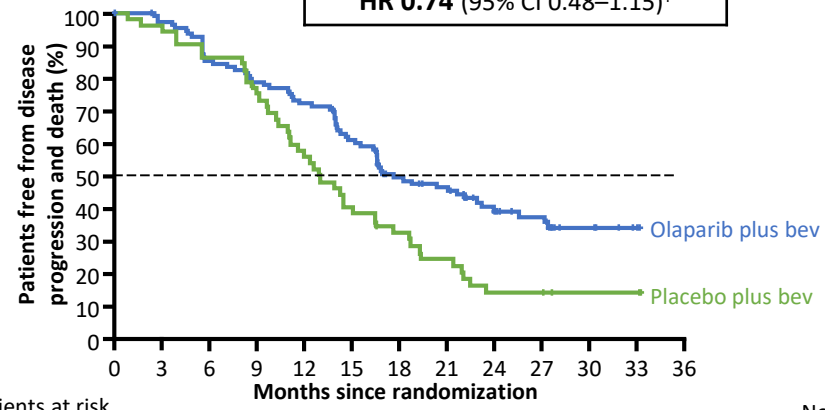
*Investigator-assessed PFS; †HR calculated using a Cox proportional hazards model performed on the overall population containing: a term for treatment, the subgroup covariate in 5 modalities (upfront surgery with no residual disease/interval surgery with no residual disease/interval surgery with residual disease/upfront surgery with residual disease/no surgery) and the treatment by subgroup interaction term

PFS by timing of surgery and no residual disease

Upfront surgery, residual disease

	Olaparib + bevacizumab (n=111)	Placebo + bevacizumab (n=53)
Events, n (%)	66 (59)	44 (83)
Median PFS†, months	**17.6**	**13.0**

HR 0.74 (95% CI 0.48–1.15)‡



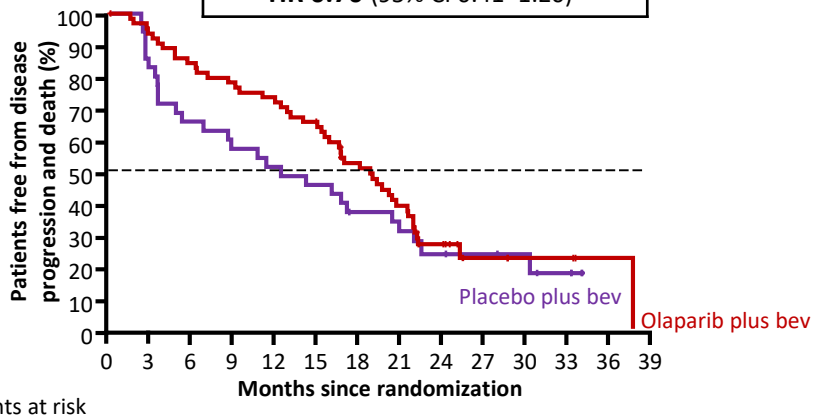
No. patients at risk

Olaparib plus bev	111	106	92	85	78	65	49	44	28	23	6	2	0
Placebo plus bev	53	50	45	40	29	21	16	12	7	7	2	2	0

Interval surgery, residual disease*

	Olaparib + bevacizumab (n=65)	Placebo + bevacizumab (n=35)
Events, n (%)	47 (72)	27 (77)
Median PFS†, months	**18.7**	**12.3**

HR 0.70 (95% CI 0.41–1.20)‡

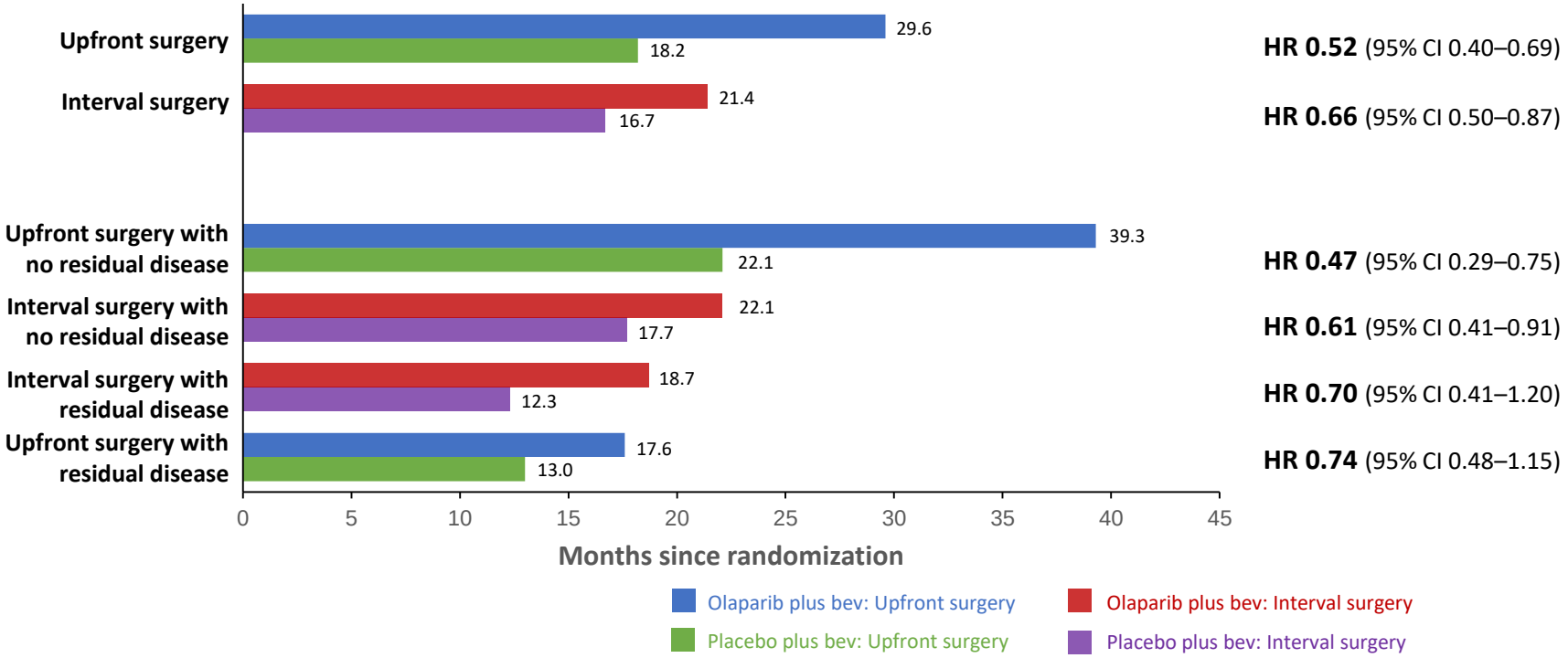


No. patients at risk

Olaparib plus bev	65	60	54	49	46	40	30	23	10	4	3	3	1	0
Placebo plus bev	35	29	23	20	18	16	12	10	6	5	4	2	0	

*Results should be interpreted with caution given the small number of patients in this subgroup; †Investigator-assessed PFS; ‡HR calculated using a Cox proportional hazards model performed on the overall population containing: a term for treatment, the subgroup covariate in 5 modalities (upfront surgery with no residual disease/interval surgery with no residual disease/interval surgery with residual disease/upfront surgery with residual disease/no surgery) and the treatment by subgroup interaction term

Summary of PFS: Timing of surgery and residual disease status



Conclusions

- Compared with bevacizumab alone, maintenance olaparib plus bevacizumab improved PFS regardless of the timing of surgery or residual disease status after surgery
- Importantly, the magnitude of the PFS benefit was greatest when surgery achieved complete surgical debulking, particularly in the upfront setting:
  - —HR 0.47 (the percentage of patients who were progression-free at 2 years was 69% in the olaparib plus bevacizumab arm vs 43% in the control arm)
- Expert gynecologic oncologists are critical for high-grade ovarian cancer management in order to achieve complete surgical resection and optimize maintenance therapy with olaparib plus bevacizumab

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S Armanet, B Votan

Study group coordinators
AGO De: G Elser, N Cron
AGO Au: R Berger, A Riha
MITO and **MANGO:** J Bryce
GEICO: C Larios
GOTIC: H Naito
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