2023 ASCO® ANNUAL MEETING

Durvalumab with paclitaxel/carboplatin and bevacizumab followed by maintenance durvalumab, bevacizumab and olaparib in patients with newly diagnosed advanced ovarian cancer without a tumor *BRCA1/BRCA2* mutation: results from the randomized, placebo-controlled Phase III DUO-O/ENGOT-ov46/AGO-OVAR 23/GOG-3025 trial

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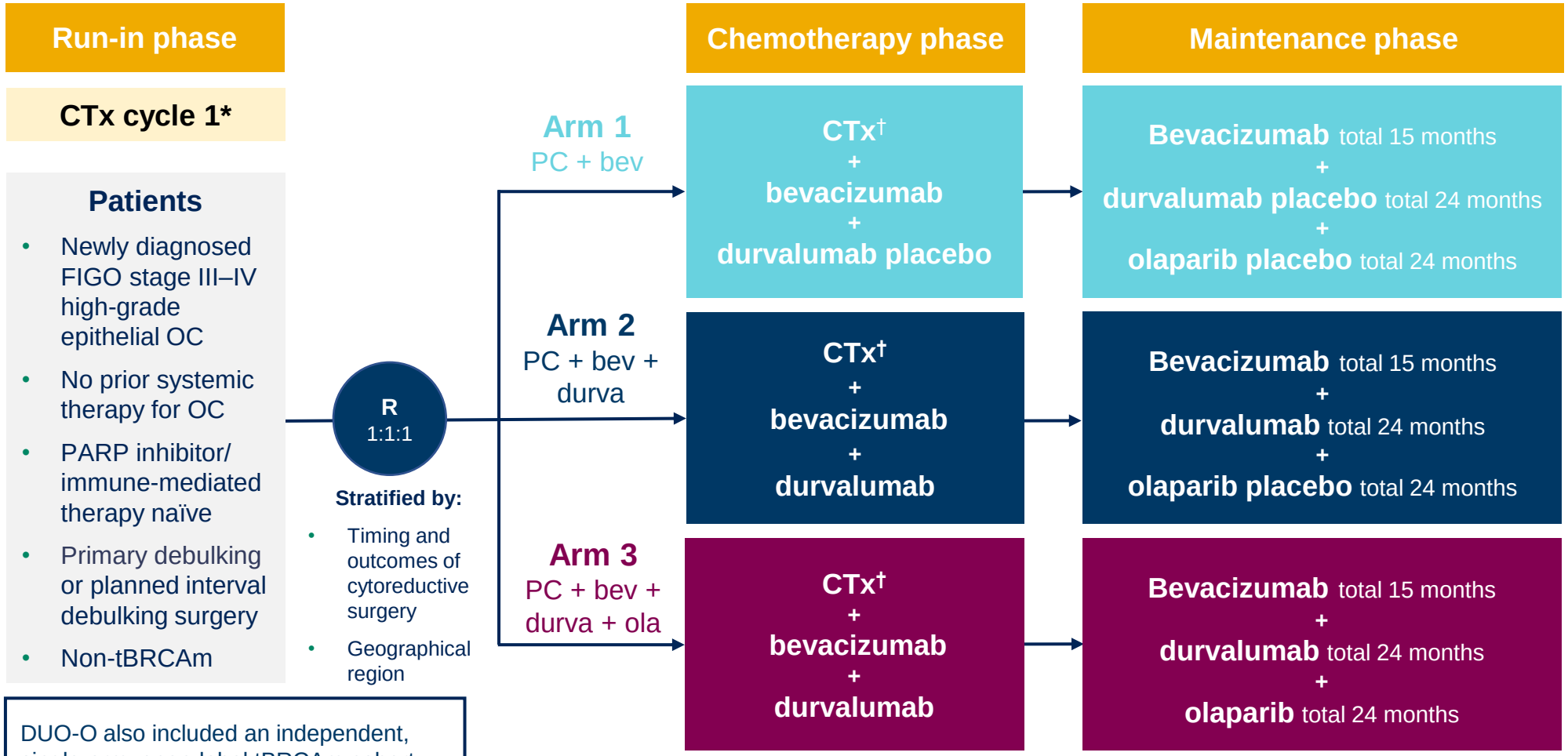
Background

- Maintenance therapy with olaparib ± bevacizumab has improved outcomes in first-line advanced OC.[1,2] However, unmet need remains, especially in some non-BRCAm patient subgroups
- To date, Phase III trials investigating the addition of immuno-oncology agents to standard of care in the newly diagnosed advanced OC setting have yet to demonstrate clinical benefit[3,4]
- However, in the Phase II MEDIOLA study, the combination of durvalumab + bevacizumab + olaparib has shown promising clinical activity in patients with non-gBRCAm PSR OC[5]
- The Phase III DUO-O study evaluates paclitaxel/carboplatin + bevacizumab + durvalumab followed by maintenance therapy with bevacizumab + durvalumab + olaparib in patients with newly diagnosed non-tBRCAm advanced OC
- We report results of the preplanned interim PFS analysis from the DUO-O study

1. DiSilvestro P *et al. J Clin Oncol* 2023;41:609–17; 2. Ray-Coquard IL *et al. Ann Oncol* 2022;33(Suppl. 7):abstr LBA29; 3. Moore KN *et al. J Clin Oncol* 2021;39:1842–55; 4. Monk BJ *et al. Lancet Oncol* 2021;22:1275–89; 5. Banerjee S *et al. Ann Oncol* 2022;33(Suppl. 7):abstr 529MO.
BRCAm, *BRCA1* and/or *BRCA2* mutation; gBRCAm, germline BRCAm; OC, ovarian cancer; PFS, progression-free survival; PSR, platinum-sensitive relapsed; tBRCAm, tumor BRCAm.

DUO-O study design

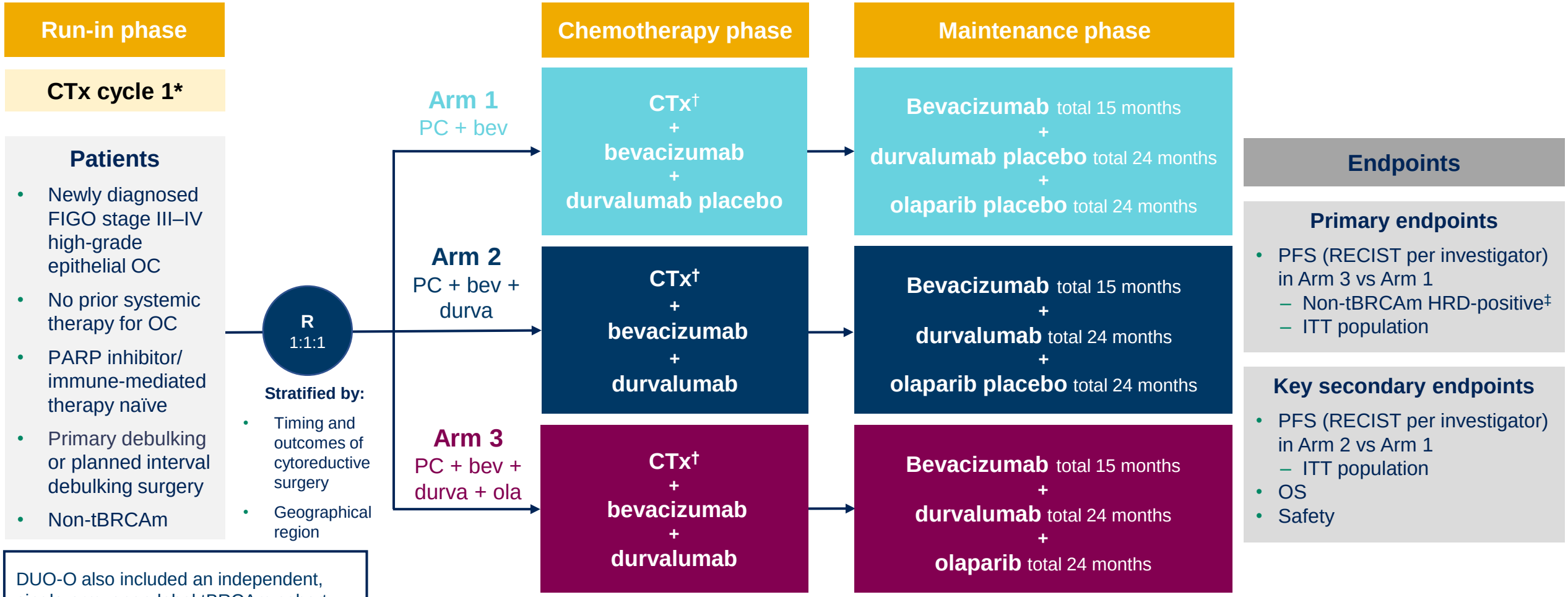


DUO-O also included an independent, single-arm, open-label tBRCAm cohort – results are not presented

Treatment continued until disease progression, study treatment was complete or other discontinuation criteria were met

Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m^2 IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO: December 5, 2022.
*With or without bevacizumab according to local practice; †Cycles 2–6; ‡Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay.
AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, data cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; ola, olaparib; OS, overall survival; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors.

DUO-O study design



DUO-O also included an independent, single-arm, open-label tBRCAm cohort – results are not presented

Endpoints

Primary endpoints

- PFS (RECIST per investigator) in Arm 3 vs Arm 1
  - Non-tBRCAm HRD-positive‡
  - ITT population

Key secondary endpoints

- PFS (RECIST per investigator) in Arm 2 vs Arm 1
  - ITT population
- OS
- Safety

Treatment continued until disease progression, study treatment was complete or other discontinuation criteria were met

Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m^2 IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO: December 5, 2022.
*With or without bevacizumab according to local practice; †Cycles 2–6; ‡Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay.
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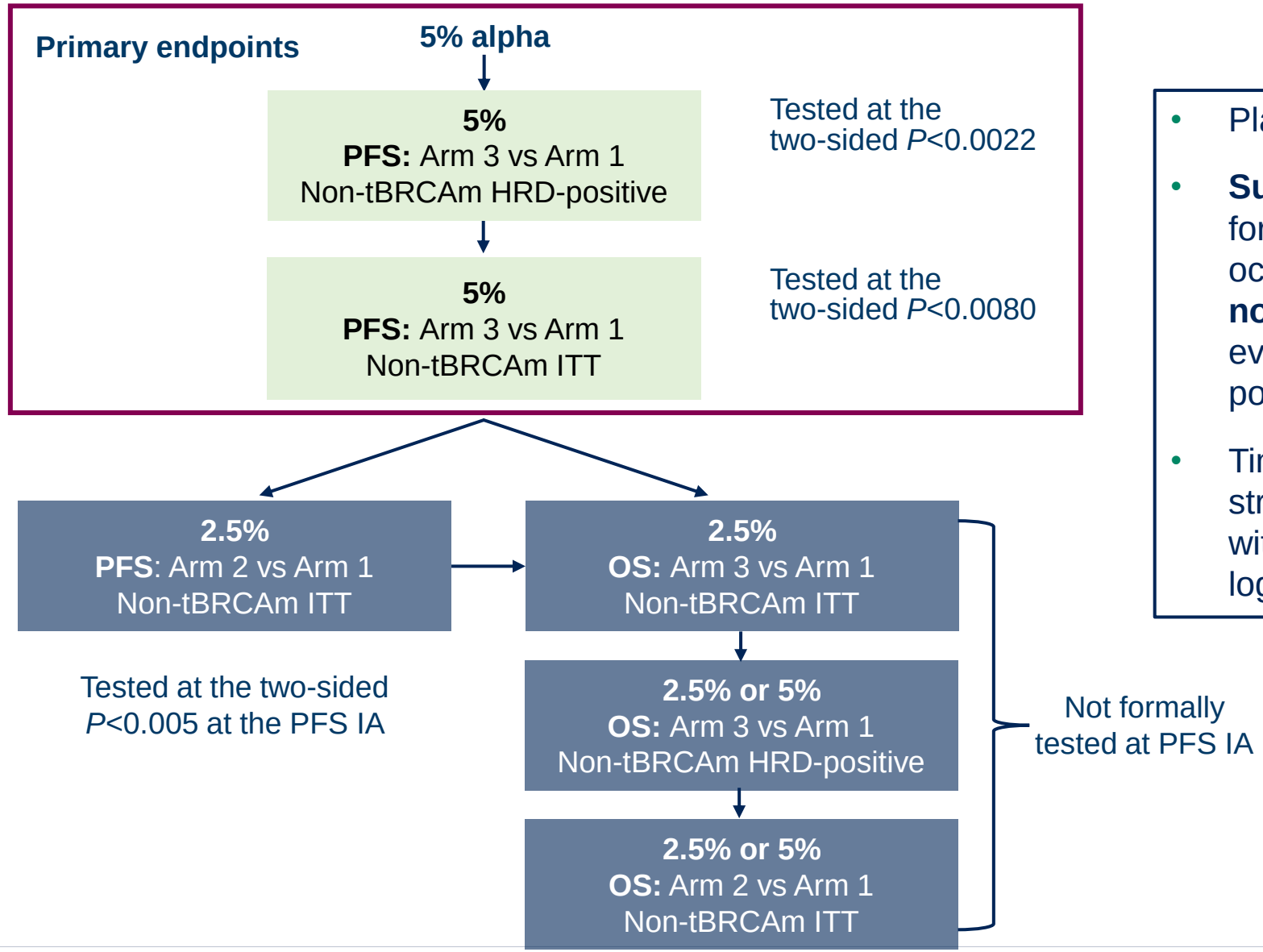
Multiple testing procedure and PFS interim analysis



- Planned sample size N~1104
- **Superiority interim PFS analysis** planned for when ~86% of target PFS events had occurred for **Arm 3 vs Arm 1 in both the non-tBRCAm HRD-positive** (~128 PFS events) **and ITT** (~390 PFS events) populations
- Time-to-event endpoints assessed using a stratified Cox proportional hazards model with *P* values calculated using a stratified log-rank test

For each PFS comparison, the alpha is controlled at the IA and FA timepoints by using a bespoke spending function separately.[1]
FA, final analysis; IA, interim analysis.
1. Stone A. *Pharmaceut Statist* 2010;9:151–61.

Patient characteristics

Characteristics		Arm 1 PC + bev N=378	Arm 2 PC + bev + durva N=374	Arm 3 PC + bev + durva + ola N=378
Age, years	Median age (range)	59.0 (32–83)	58.0 (29–85)	61.0 (21–84)
Geographical region,* %	Europe	66	66	66
	North America	12	12	12
	Rest of world	22	22	22
FIGO stage,† %	III	63	69	67
	IV	37	31	33
ECOG status, %	0	64	69	69
	1	36	31	31
Histology, %	High-grade serous	88	87	90
	Clear cell	5	6	3
	High-grade endometrioid	3	2	2
	Other‡	4	5	5

Characteristics		Arm 1 PC + bev N=378	Arm 2 PC + bev + durva N=374	Arm 3 PC + bev + durva + ola N=378
Surgery status at study entry, %	Upfront primary surgery	58	59	63
	Planned IDS	42	41	37
Timing and outcome of cytoreductive surgery (as per stratification),* %	No macroscopic residual disease after upfront surgery	38	38	38
	Macroscopic residual disease after upfront surgery **OR** Planned interval debulking surgery	62	62	62
HRD status,§ %	HRD-positive	38	40	37
	HRD-negative	57	53	56
	Unknown	5	7	7

Percentages may not total 100 because of rounding.
*Per IRT; †One patient in Arm 2 had unknown FIGO stage; ‡Includes mixed epithelial, carcinosarcoma and other histology types; §Genomic instability assessed using the Myriad MyChoice CDx assay and a cutoff of 42.
ECOG, Eastern Cooperative Oncology Group; IDS, interval debulking surgery; IRT, interactive response technology.

Patient disposition

		Arm 1 PC + bev N=378	Arm 2 PC + bev + durva N=374	Arm 3 PC + bev + durva + ola N=378
Randomized, n (%)		378 (100)	374 (100)	378 (100)
Received any treatment/started maintenance phase, n (%)		378 (100)/331 (88)	374 (100)/323 (86)	378 (100)/336 (89)
	Durvalumab/placebo	376 (99)	373 (100)	378 (100)
	Olaparib/placebo	331 (88)	323 (86)	336 (89)
	PC + bevacizumab	378 (100)	374 (100)	378 (100)
Still receiving treatment at DCO, n (%)	Durvalumab/placebo	39 (10)	34 (9)	58 (15)
	Olaparib/placebo	53 (16)	63 (20)	65 (19)
	Bevacizumab	7 (2)	8 (2)	15 (4)
	Carboplatin	0 (0)	0 (0)	0 (0)
	Paclitaxel	0 (0)	0 (0)	0 (0)
Median (range) duration of treatment, months	Durvalumab/placebo*	16.4 (0.0–46.0)	13.8 (0.5–35.9)	17.3 (0.7–40.5)
	Olaparib/placebo†	14.3 (0.7–42.5)	14.2 (0.2–34.3)	14.8 (0.2–36.8)
	Bevacizumab*	14.7 (0.0–26.7)	14.4 (0.7–22.3)	15.2 (0.7–26.0)
Median no. of cycles (range)	Carboplatin‡	6 (2–6)	6 (2–6)	6 (2–6)
	Paclitaxel§	6 (1–6)	6 (1–8)	6 (1–7)
Median (range) duration of follow up,‖ months		25.5 (0.0–44.8)	23.1 (0.0–42.6)	23.3 (0.0–41.7)

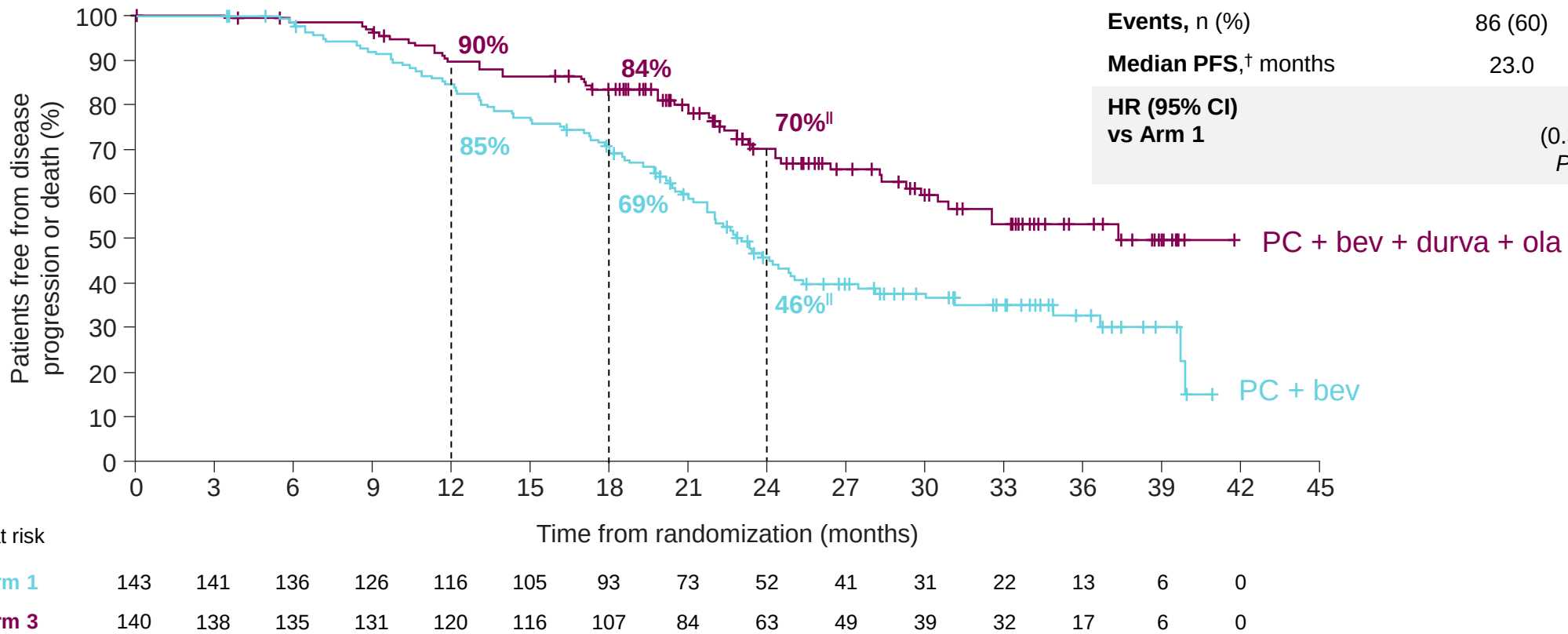
Across all arms, ~90% of patients completed all planned cycles of chemotherapy

Patients who discontinued one or more study treatment could continue to receive the remaining study treatments.
Percentages may not total 100 because of rounding.
*Total period from first dose to earliest date of last non-zero dose +20 days, death or DCO; †Total period from first dose of olaparib/placebo to earliest date of last non-zero dose, death or DCO; ‡Carboplatin or cisplatin substitute; §Paclitaxel or nab-paclitaxel, docetaxel or pegylated liposomal doxorubicin substitute; ‖In patients censored for PFS.

PFS: Non-tBRCAm HRD-positive population

Arm 3 vs Arm 1

	Arm 1 PC + bev N=143	Arm 3 PC + bev + durva + ola N=140
Median follow-up,* months	28.8	25.6
Events, n (%)	86 (60)	49 (35)
Median PFS,† months	23.0	37.3‡
HR (95% CI) vs Arm 1	**0.49** (0.34–0.69)§ *P*<0.0001	



Patients at risk

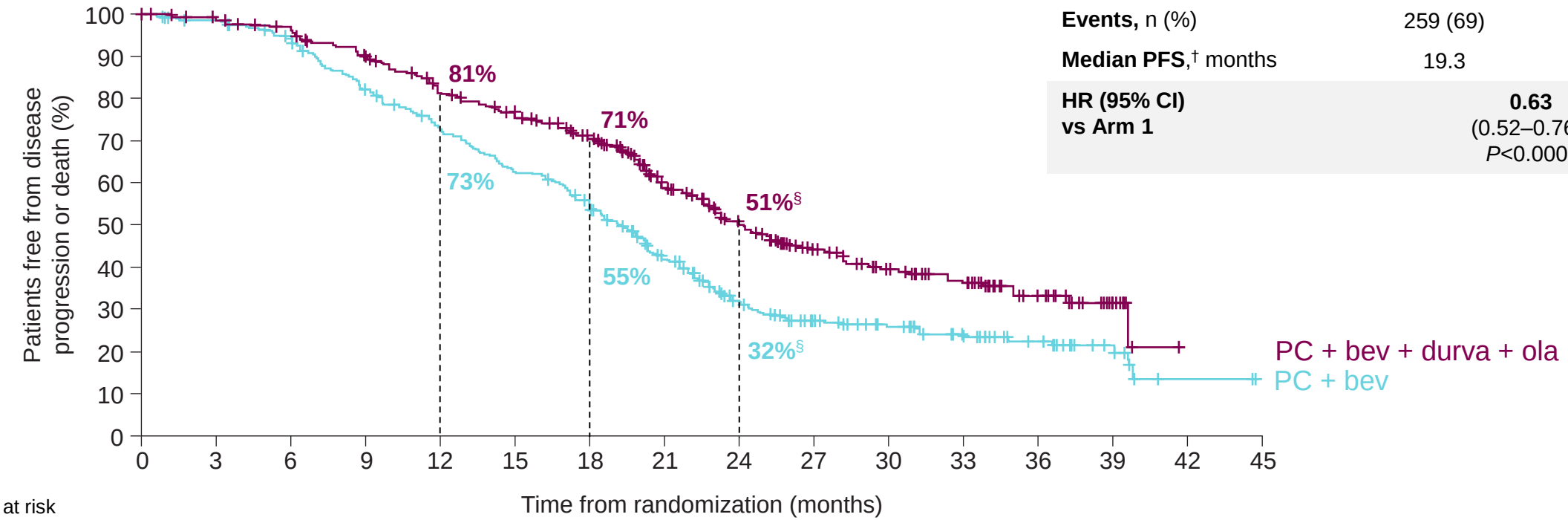
Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

*In censored patients; †Medians and rates were estimated by KM method; ‡Median PFS in Arm 3 unstable; §HR and CI were estimated from a stratified Cox proportional hazards model. *P* value from a stratified log rank text. Model stratified by timing and outcome of cytoreductive surgery; ‖24-month PFS rates unstable.
CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier.

PFS: ITT population

Arm 3 vs Arm 1

	Arm 1 PC + bev N=378	Arm 3 PC + bev + durva + ola N=378
Median follow-up,* months	25.5	23.3
Events, n (%)	259 (69)	193 (51)
Median PFS,† months	19.3	24.2
HR (95% CI) vs Arm 1	**0.63** (0.52–0.76)‡ *P*<0.0001	



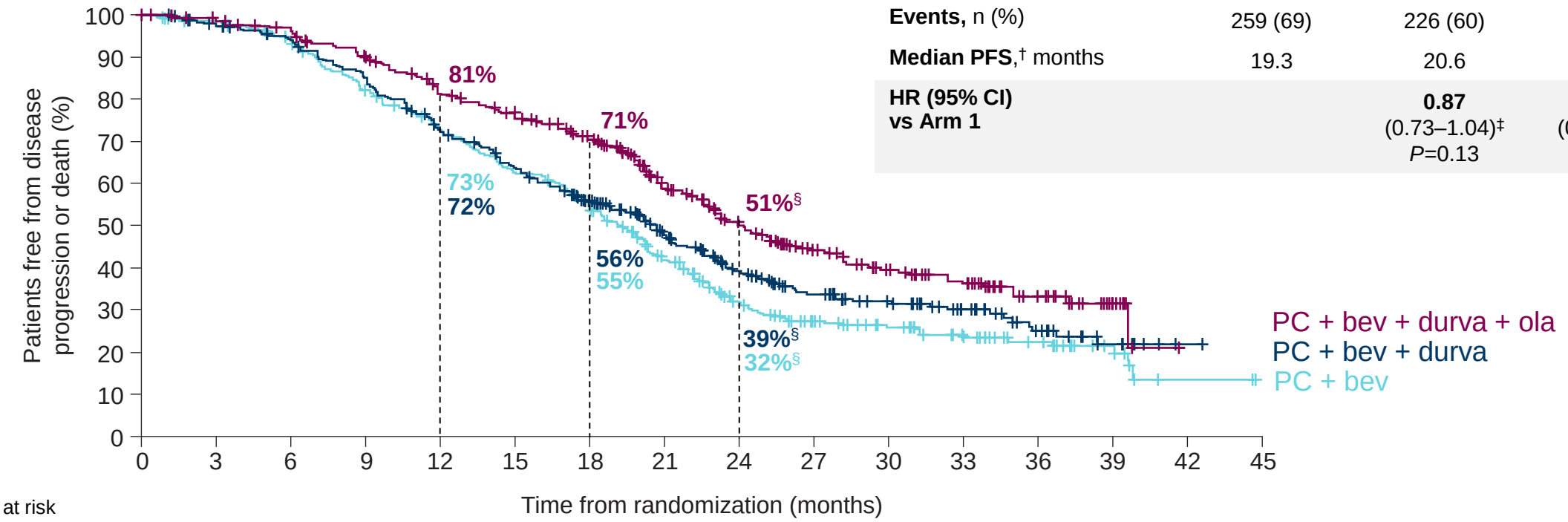
Patients at risk

Arm 1	378	363	341	297	260	223	189	130	87	63	51	35	23	11	2	0
Arm 3	378	366	351	323	286	266	228	163	123	84	65	52	27	9	0	

*In censored patients; †Medians and rates were estimated by KM method; ‡HR and CI were estimated from a stratified Cox proportional hazards model. Model stratified by timing and outcome of cytoreductive surgery and geographical region. *P* value from a stratified log rank text; §24-month PFS rates unstable.

PFS: ITT population

	Arm 1 PC + bev N=378	Arm 2 PC + bev + durva N=374	Arm 3 PC + bev + durva + ola N=378
Median follow-up,* months	25.5	23.1	23.3
Events, n (%)	259 (69)	226 (60)	193 (51)
Median PFS,† months	19.3	20.6	24.2
HR (95% CI) vs Arm 1		**0.87** (0.73–1.04)‡ *P*=0.13	**0.63** (0.52–0.76)‡ *P*<0.0001



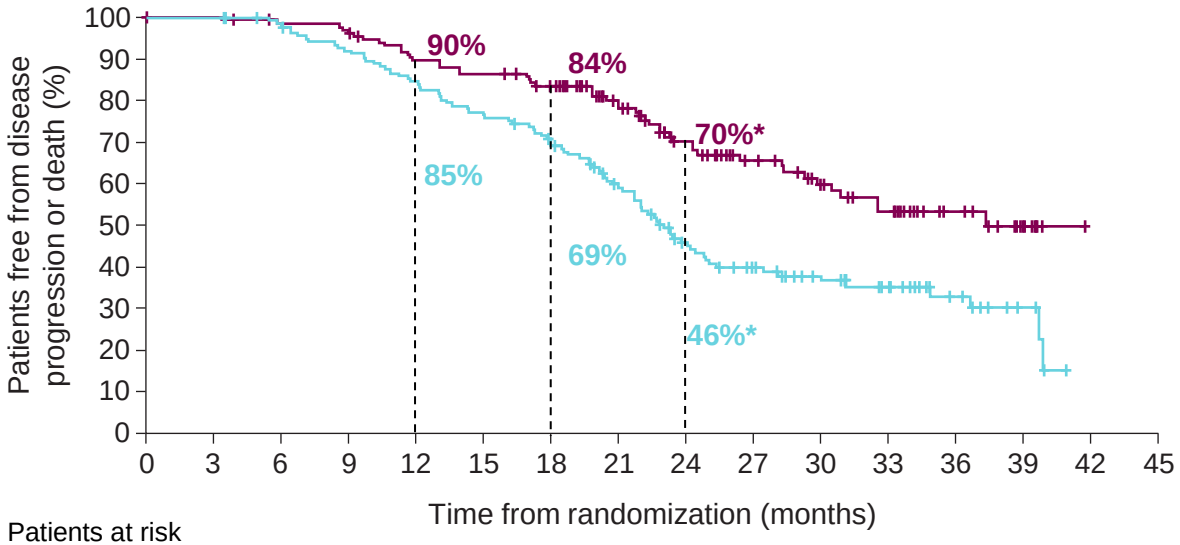
Patients at risk

Arm 1	378	363	341	297	260	223	189	130	87	63	51	35	23	11	2	0
Arm 2	374	354	336	301	254	221	180	130	93	70	54	39	23	11	1	0
Arm 3	378	366	351	323	286	266	228	163	123	84	65	52	27	9	0	

*In censored patients; †Medians and rates were estimated by KM method; ‡HR and CI were estimated from a stratified Cox proportional hazards model. Model stratified by timing and outcome of cytoreductive surgery and geographical region. *P* value from a stratified log rank text; §24-month PFS rates unstable.

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

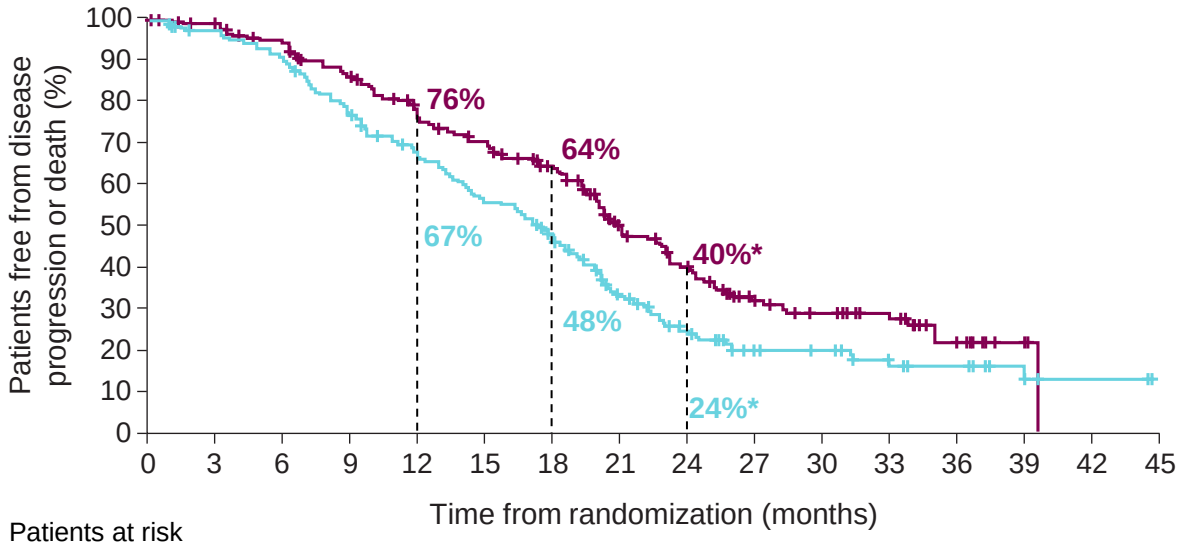


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	49 (35)
Median PFS, months†	23.0	37.3‡
HR (95% CI) vs Arm 1		**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

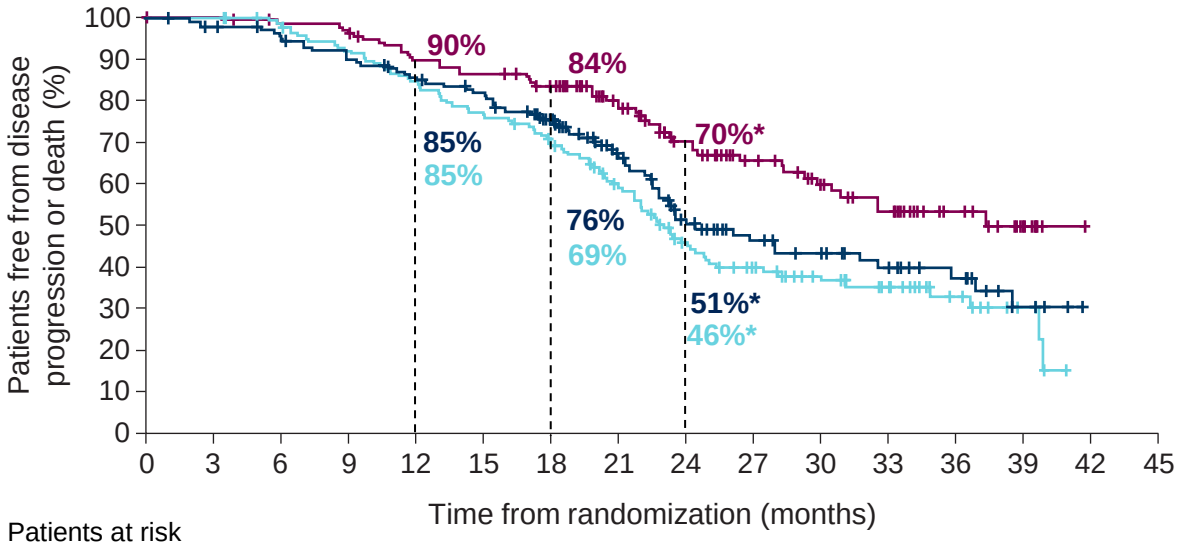
Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	127 (60)
Median PFS, months†	17.4	20.9
HR (95% CI) vs Arm 1		**0.68** (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

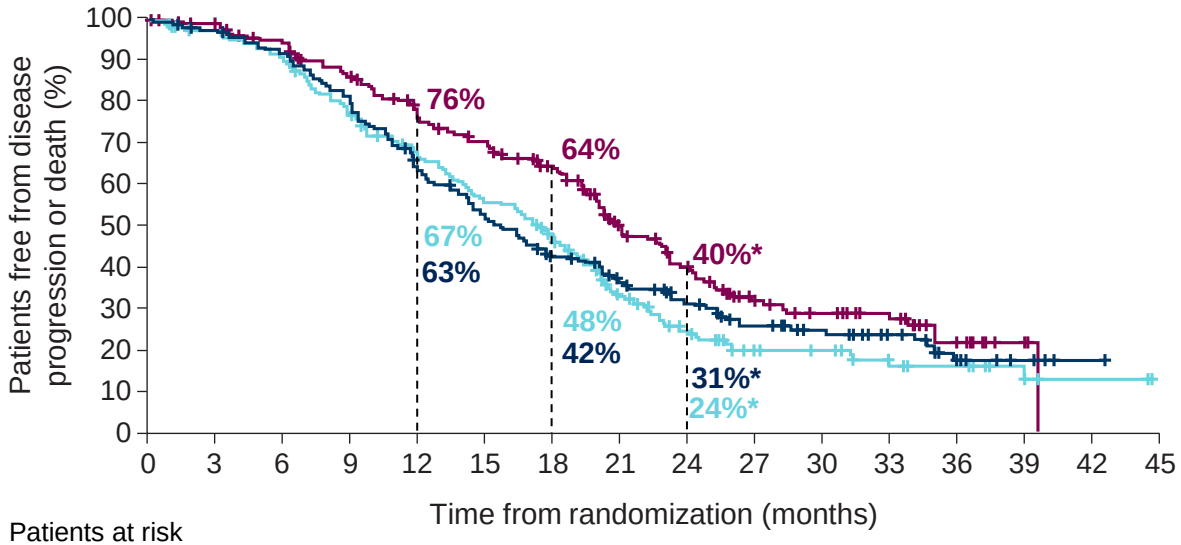


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

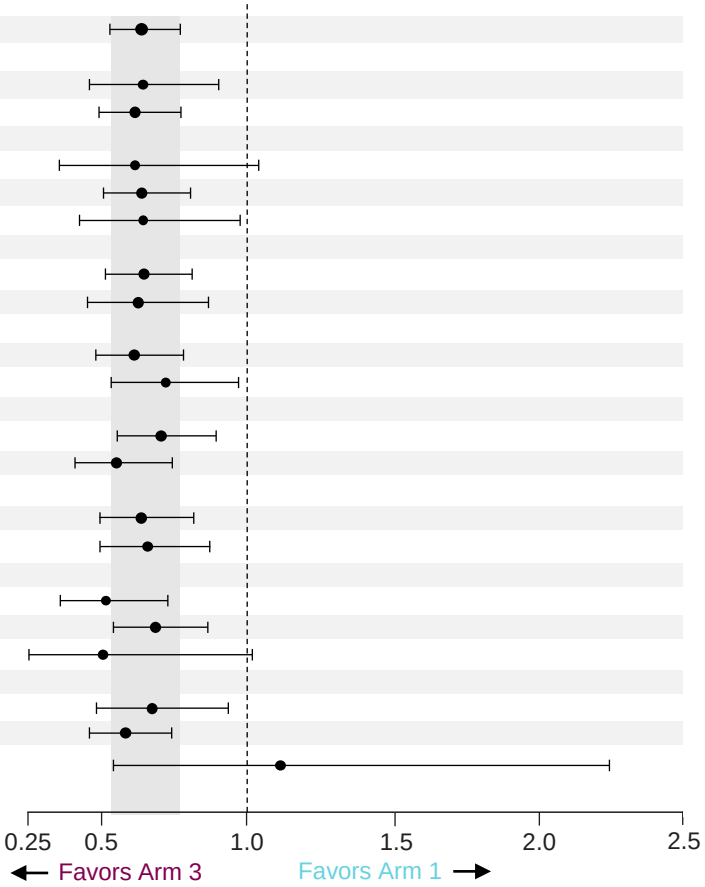
Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 2	199	189	177	153	120	97	76	59	45	33	25	17	8	4	1	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 2 PC + bev + durva N=199	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	142 (71)	127 (60)
Median PFS, months†	17.4	15.4	20.9
HR (95% CI) vs Arm 1		**0.94** (0.75–1.18)§	**0.68** (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

Subgroup analyses of PFS
Arm 3 vs Arm 1 (ITT population)

	Arm 3 PC + bev + durva + ola N=378	Arm 1 PC + bev N=378	
	Events, n/N (%)	Events, n/N (%)	HR (95% CI)
All patients	193/378 (51)	259/378 (69)	0.64 (0.53–0.77)
Time and outcome of cytoreductive surgery			
No macroscopic residual disease after upfront primary surgery	58/144 (40)	82/144 (57)	0.64 (0.46–0.90)
All others*	135/234 (58)	177/234 (76)	0.62 (0.49–0.77)
Geographic region			
North America	22/45 (49)	36/45 (80)	0.62 (0.36–1.04)
Europe	132/250 (53)	169/250 (68)	0.64 (0.51–0.80)
Rest of world	39/83 (47)	54/83 (65)	0.65 (0.43–0.98)
Age at screening			
<65 years	123/243 (51)	181/268 (68)	0.65 (0.51–0.81)
≥65 years	70/135 (52)	78/110 (71)	0.63 (0.45–0.87)
ECOG performance status			
0 (normal activity)	118/259 (46)	154/242 (64)	0.61 (0.48–0.78)
1 (restricted activity)	75/119 (63)	105/136 (77)	0.72 (0.53–0.97)
Stage of disease at diagnosis			
III	121/254 (48)	147/238 (62)	0.70 (0.55–0.89)
IV	72/124 (58)	112/140 (80)	0.55 (0.41–0.74)
Surgery status at study entry			
Upfront primary surgery	110/237 (46)	141/221 (64)	0.64 (0.50–0.82)
Planned IDS	83/141 (59)	118/157 (75)	0.66 (0.50–0.87)
Myriad HRD status			
HRD-positive	49/140 (35)	86/143 (60)	0.51 (0.36–0.72)
HRD-negative	127/211 (60)	157/216 (73)	0.68 (0.54–0.86)
HRD unknown	17/27 (63)	16/19 (84)	0.50 (0.25–1.01)
PD-L1 (TAP5) expression†			
TAP5 high	61/142 (43)	85/141 (60)	0.67 (0.48–0.93)
TAP5 low	118/215 (55)	156/201 (78)	0.58 (0.46–0.74)
TAP5 unknown	14/21 (67)	18/36 (50)	1.11 (0.54–2.24)



Consistency of treatment effect between subgroups estimated from an unstratified Cox proportional hazards model.
*Macroscopic residual disease after upfront surgery OR planned interval debulking surgery; †PD-L1 expression was centrally assessed by Ventana SP263 immunohistochemistry assay. Tumor area positivity PD-L1 expression (TAP5): high defined as ≥5%; low defined as <5%; unknown defined as samples where PD-L1 expression was not available. PD-L1, programmed death-ligand 1.

Safety summary

AEs, n (%)	Overall (chemotherapy phase + maintenance phase)			Maintenance phase		
	Arm 1 PC + bev N=376	Arm 2 PC + bev + durva N=373	Arm 3 PC + bev + durva + ola N=378	Arm 1 PC + bev N=331	Arm 2 PC + bev + durva N=323	Arm 3 PC + bev + durva + ola N=336
Any-grade AE	373 (99)	371 (99)	375 (99)	308 (93)	303 (94)	328 (98)
Grade ≥3 AE	231 (61)	245 (66)	269 (71)	88 (27)	113 (35)	164 (49)
AE with outcome of death	4 (1)	9 (2)	6 (2)	2 (1)	3 (1)	4 (1)
Serious AE (including outcome of death)	128 (34)	161 (43)	148 (39)	50 (15)	91 (28)	83 (25)
AE of special interest to olaparib						
MDS/AML*	1 (<1)	0	2 (1)	1 (<1)	0	1 (<1)
New primary malignancies*	1 (<1)	1 (<1)	4 (1)	1 (<1)	1 (<1)	3 (1)
Pneumonitis	3 (1)	5 (1)	7 (2)	1 (<1)	3 (1)	6 (2)
Any immune-mediated AEs†	132 (35)	209 (56)	200 (53)	94 (28)	139 (43)	141 (42)
AEs leading to dose modification‡,§	272 (72)	299 (80)	323 (85)	163 (49)	182 (56)	254 (76)
AEs leading to discontinuation‡	77 (20)	98 (26)	131 (35)	44 (13)	54 (17)	88 (26)
AEs leading to discontinuation of PC/bevacizumab	57 (15)	59 (16)	70 (19)	27 (8)	24 (7)	35 (10)
AEs leading to discontinuation of durvalumab/placebo	24 (6)	62 (17)	65 (17)	14 (4)	39 (12)	40 (12)
AEs leading to discontinuation of olaparib/placebo	15 (4)	19 (5)	62 (16)	14 (4)	19 (6)	61 (18)

Includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end of the safety follow-up period.

*Includes events from first dose of durvalumab/olaparib/placebo until end of study; †Investigator-assessed; ‡Based on action taken on AE CRF for at least one treatment. For durvalumab/placebo, dose modification includes skipped or delayed doses, or interruption of the infusion; §Either dose reduction or dose interruption. AE, adverse event; AML, acute myeloid leukemia; CRF, case report form; MDS, myelodysplastic syndrome.

Any AE with frequency of ≥20%*

AEs	Overall (chemotherapy phase + maintenance phase)			Maintenance phase		
	Arm 1 PC + bev N=376	Arm 2 PC + bev + durva N=373	Arm 3 PC + bev + durva + ola N=378	Arm 1 PC + bev N=331	Arm 2 PC + bev + durva N=323	Arm 3 PC + bev + durva + ola N=336
Nausea, %	31	30	57	15	17	52
Anemia,† %	29	32	55	5	10	41
Neutropenia,† %	44	45	51	8	8	23
Fatigue/asthenia,† %	40	38	49	19	20	32
Arthralgia, %	33	32	34	29	28	27
Constipation, %	26	25	30	11	10	15
Diarrhea, %	29	30	30	21	21	22
Thrombocytopenia,† %	19	20	28	3	5	17
Hypertension, %	34	30	26	24	18	14
Vomiting, %	16	16	26	10	11	22
Leukopenia,† %	18	18	24	5	4	13
Headache, %	21	20	22	19	16	18
Abdominal pain, %	18	22	21	12	15	13
Hypothyroidism, %	7	21	20	6	14	15
Myalgia, %	20	22	18	13	12	9

Includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end the safety follow-up period. *AEs of any grade with overall incidence of ≥20% in any arm and associated incidence in the maintenance phase, excluding alopecia; †Grouped-term.

Grade ≥3 AE with frequency of ≥5%*

Grade ≥3 AEs	Overall (chemotherapy phase + maintenance phase)			Maintenance phase		
	Arm 1 PC + bev N=376	Arm 2 PC + bev + durva N=373	Arm 3 PC + bev + durva + ola N=378	Arm 1 PC + bev N=331	Arm 2 PC + bev + durva N=323	Arm 3 PC + bev + durva + ola N=336
Neutropenia,† %	26	28	31	2	2	9
Anemia,† %	8	8	24	<1	<1	21
Leukopenia,† %	4	5	8	1	<1	2
Hypertension, %	11	9	7	8	6	4
Thrombocytopenia,† %	4	4	6	0	<1	3

Includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end the safety follow-up period.
*Grade ≥3 AEs with overall incidence of ≥5% in any arm and associated incidence in the maintenance phase; †Grouped-term.

Conclusions

- DUO-O met its primary endpoint at the planned PFS interim analysis, demonstrating statistically significant and clinically meaningful improvement in PFS with first-line chemotherapy + bevacizumab + durvalumab followed by maintenance bevacizumab + durvalumab + olaparib compared with control in patients with non-tBRCAm advanced OC
  - Non-tBRCAm HRD-positive: HR **0.49** (0.34–0.69); *P*<0.0001
  - Non-tBRCAm ITT: HR **0.63** (0.52–0.76); *P*<0.0001
- PFS benefit was observed across subgroups, including those patients with HRD-negative disease (HR **0.68** [0.54–0.86])
- A numerical, but not statistical, improvement in PFS was shown with chemotherapy + bevacizumab + durvalumab followed by maintenance bevacizumab + durvalumab, compared with control, in the non-tBRCAm ITT population at the time of the PFS interim analysis
- Safety was generally consistent with the known profiles of each individual agent
- The trial is ongoing – final PFS, OS and other key secondary results will be reported in due course

Scan for:
- Slides
- Plain-language infographic
- Patient lay summary (https://www.cancer.net/DUO-O)

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