SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

Society of Gynecologic Oncology

Rucaparib vs Chemotherapy in Patients With Advanced, Relapsed Ovarian Cancer and a Deleterious BRCA Mutation: Efficacy and Safety From ARIEL4, a Randomized Phase 3 Study

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Presenting Author Disclosures

- Advisory boards: Clovis Oncology, Roche, and Tesaro

Introduction

- The PARP inhibitor rucaparib is approved as monotherapy treatment for patients with BRCA-mutated, relapsed OC who have received ≥2 prior lines of platinum-based chemotherapy[1,2]
  - Approval was based on data from 2 phase 1/2 studies[3,4]

- ARIEL4 (NCT02855944) is a phase 3 confirmatory study evaluating the efficacy and safety of rucaparib vs standard-of-care chemotherapy in patients with BRCA-mutated, relapsed OC
  - Designed in consultation with US FDA and EMA

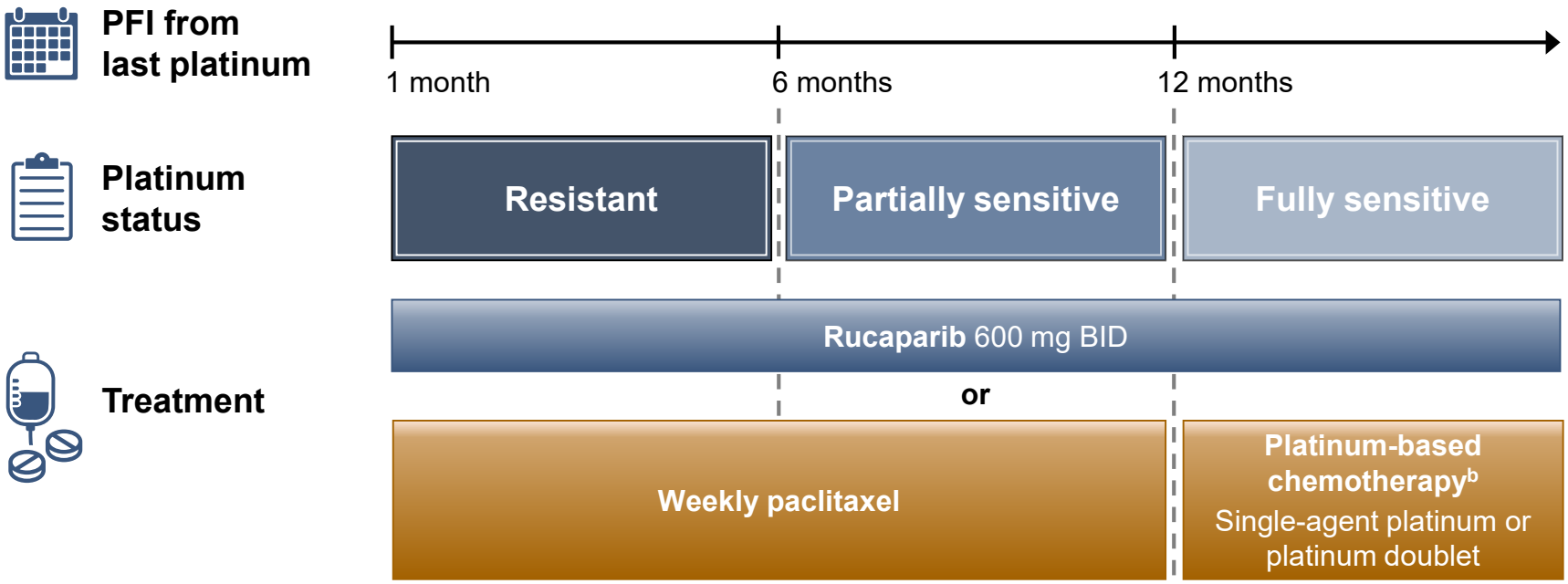
BRCA, *BRCA1* or *BRCA2;* OC, ovarian cancer; EMA, European Medicines Agency; FDA, Food and Drug Administration; OC, ovarian cancer; PARP, poly(ADP-ribose) polymerase; US, United States.

1. Rubraca (rucaparib) tablets [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2020; 2. Rubraca (rucaparib) tablets [summary of product characteristics]. Swords, Ireland: Clovis Oncology Ireland Ltd.; 2019. 3. Oza et al. *Gynecol Oncol*. 2017;147:267-75; 4. Kristeleit et al. *Int J Gynecol Cancer*. 2019;29:1396-404.

ARIEL4 Study Population

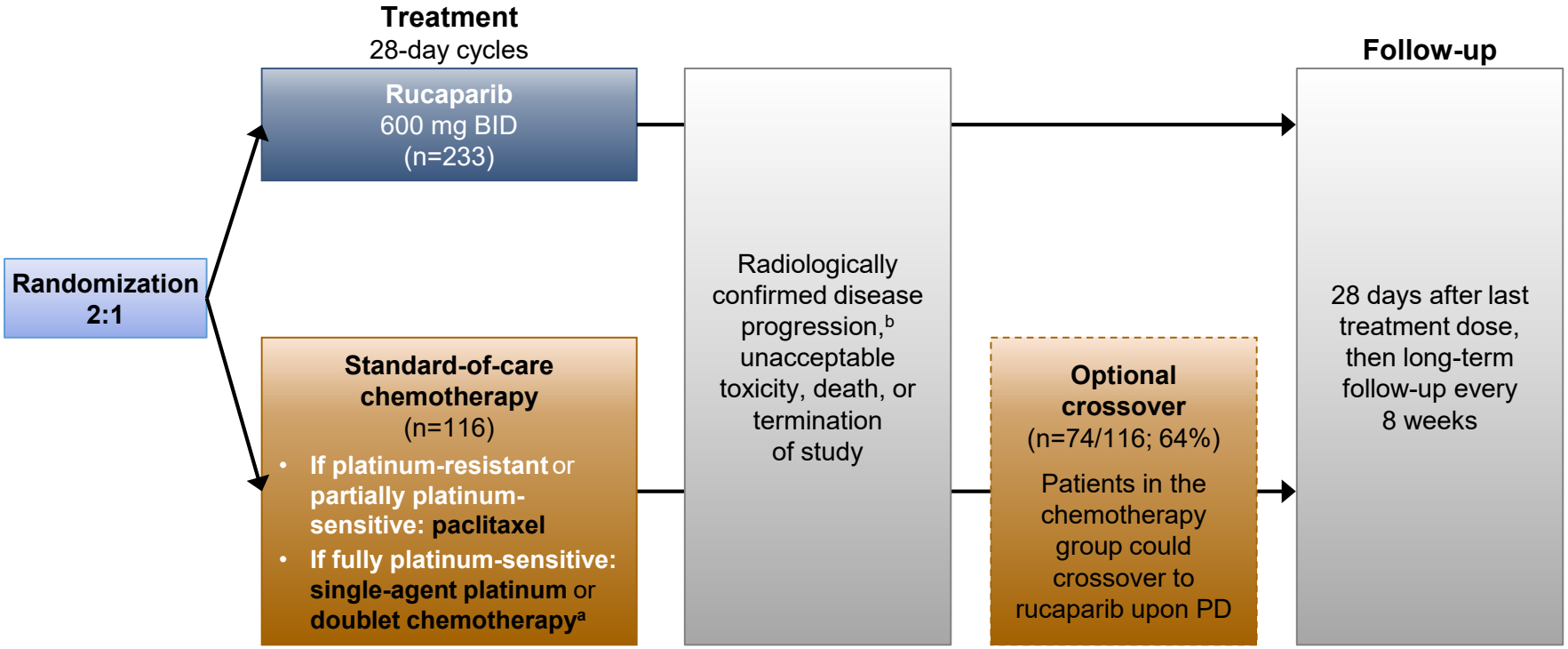
Patients with:

- Relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- ≥2 prior chemotherapy regimens, including ≥1 platinum-based regimen[a]
- Deleterious germline or somatic BRCA mutation
- No prior PARP inhibitor or single-agent paclitaxel treatment



[a]With treatment-free interval ≥6 months following first chemotherapy received. [b]At investigator's discretion.
BID, twice daily; BRCA, *BRCA1* or *BRCA2*; PARP, poly(ADP-ribose) polymerase; PFI, progression-free interval.

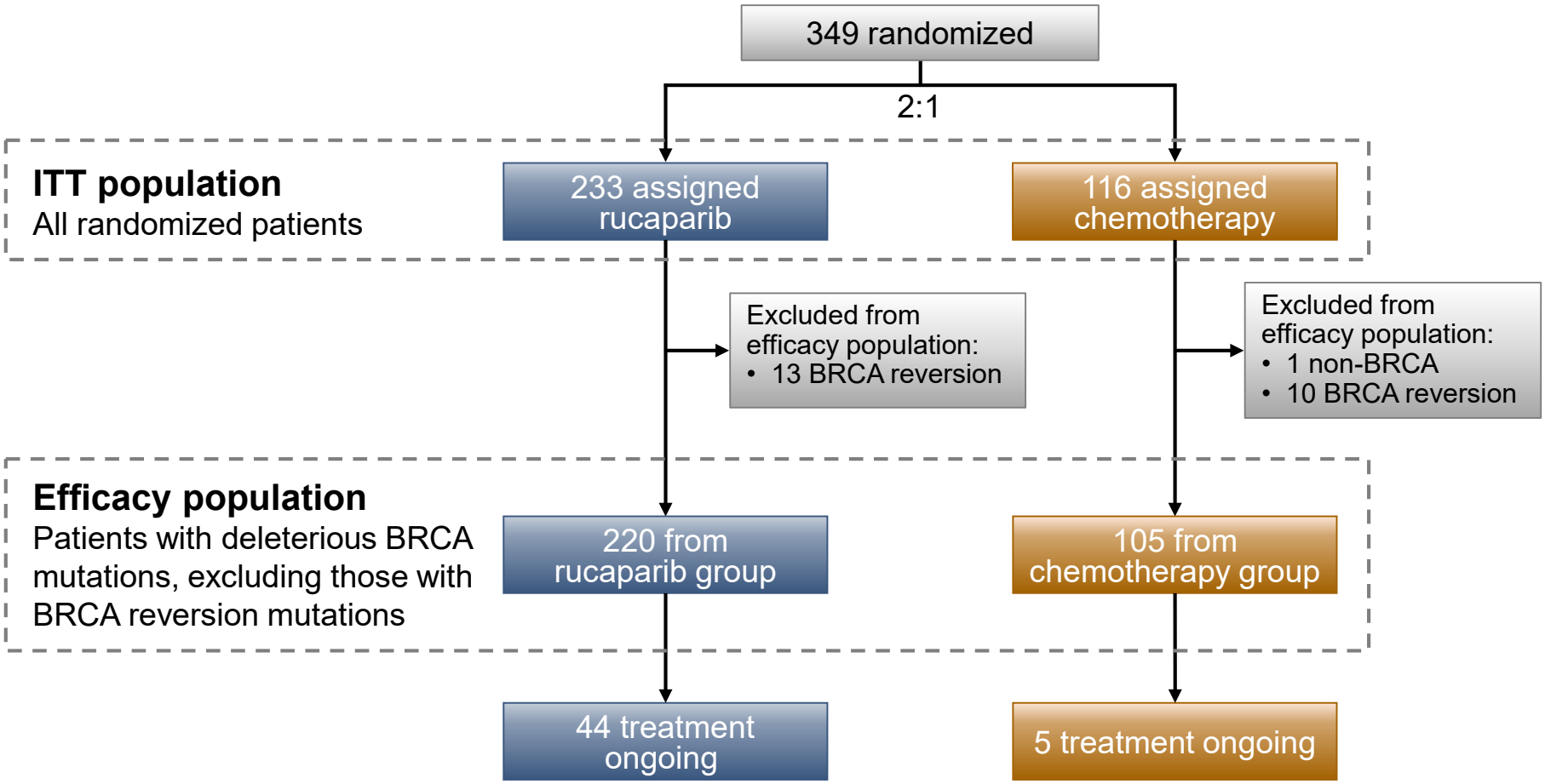
ARIEL4 Study Schema



Randomization stratification factor: Platinum status (platinum-resistant, partially platinum-sensitive, fully platinum sensitive)[c]

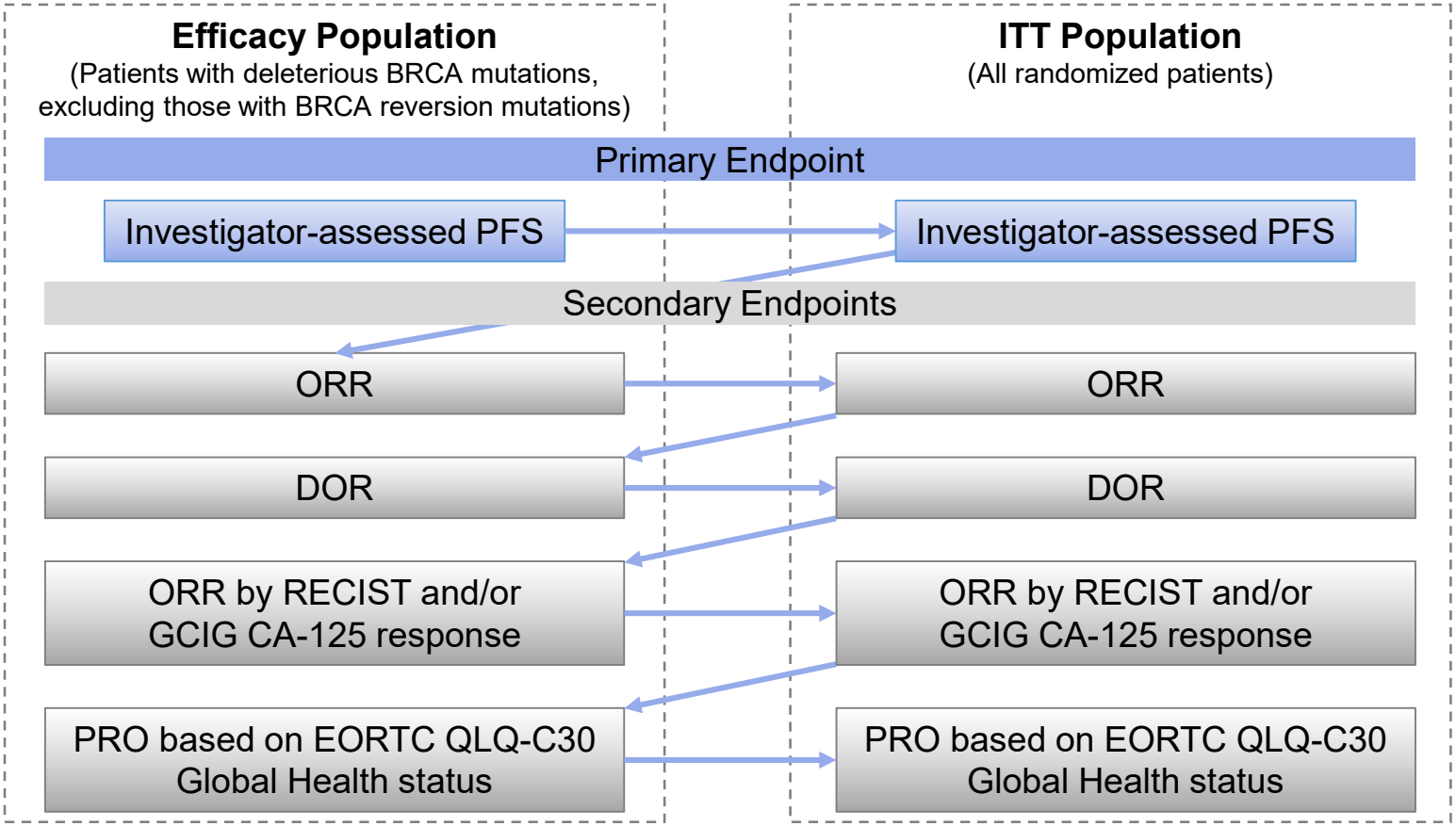
[a]At investigator's discretion. [b]Per RECIST. [c]Platinum resistant: PFI ≥1–<6 months, partially platinum sensitive: PFI ≥6–<12 months, fully platinum sensitive: PFI ≥12 months.
BID, twice daily; BRCA, *BRCA1* or *BRCA2;* PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFI, progression-free interval; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1.

Analysis Populations



Visit cutoff September 30, 2020.
BRCA reversion mutations restoring BRCA protein function have been associated with resistance to platinum and to PARP inhibitors.[1]
BRCA, *BRCA1* or *BRCA2;* ITT, intent to treat; PARP, poly(ADP-ribose) polymerase.
1. Lin KK, et al. *Cancer Discov*. 2019;9:210-9.

Statistical Analysis Plan for Efficacy Endpoints



- Overall survival is a standalone efficacy endpoint outside of the step-down analysis

BRCA, *BRCA1* or *BRCA2;* CA-125, cancer antigen 125; DOR, duration of response; EORTC QLQ, European Organization for Research and Treatment of Cancer quality of life questionnaire; GCIG, Gynecological Cancer Intergroup; ITT, intent to treat; ORR, objective response rate; PFS, progression-free survival; PRO, patient-reported outcomes; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1.

Baseline Patient Characteristics: ITT Population

	Rucaparib (n=233)	Chemotherapy (n=116)	Overall (N=349)
Median age, years (range)	58.0 (38–81)	58.5 (38–85)	58.0 (38–85)
Geographic region, n (%)			
Central/Eastern Europe	135 (57.9)	67 (57.8)	202 (57.9)
Northern/Southern Europe	59 (25.3)	35 (30.2)	94 (26.9)
Northern/South America	39 (16.7)	14 (12.1)	53 (15.2)
Median time since cancer diagnosis, months (range)	43 (13–185)	44 (14–140)	43 (13–185)
Diagnosis, n (%)			
Epithelial ovarian cancer	220 (94.4)	111 (95.7)	331 (94.8)
Fallopian tube cancer	7 (3.0)	3 (2.6)	10 (2.9)
Primary peritoneal cancer	6 (2.6)	2 (1.7)	8 (2.3)
Histology, n (%)			
Serous	208 (89.3)	105 (90.5)	313 (89.7)
Endometrioid	18 (7.7)	6 (5.2)	24 (6.9)
Other	7 (3.0)	5 (4.3)	12 (3.4)
ECOG PS, n (%)			
0	125 (53.6)	72 (62.1)	197 (56.4)
1	108 (46.4)	44 (37.9)	152 (43.6)
BRCA germline status, n (%)			
Germline	198 (85.0)	95 (81.9)	293 (84.0)
Somatic	35 (15.0)	19 (16.4)	54 (15.5)
Not available	0	2 (1.7)	2 (0.6)

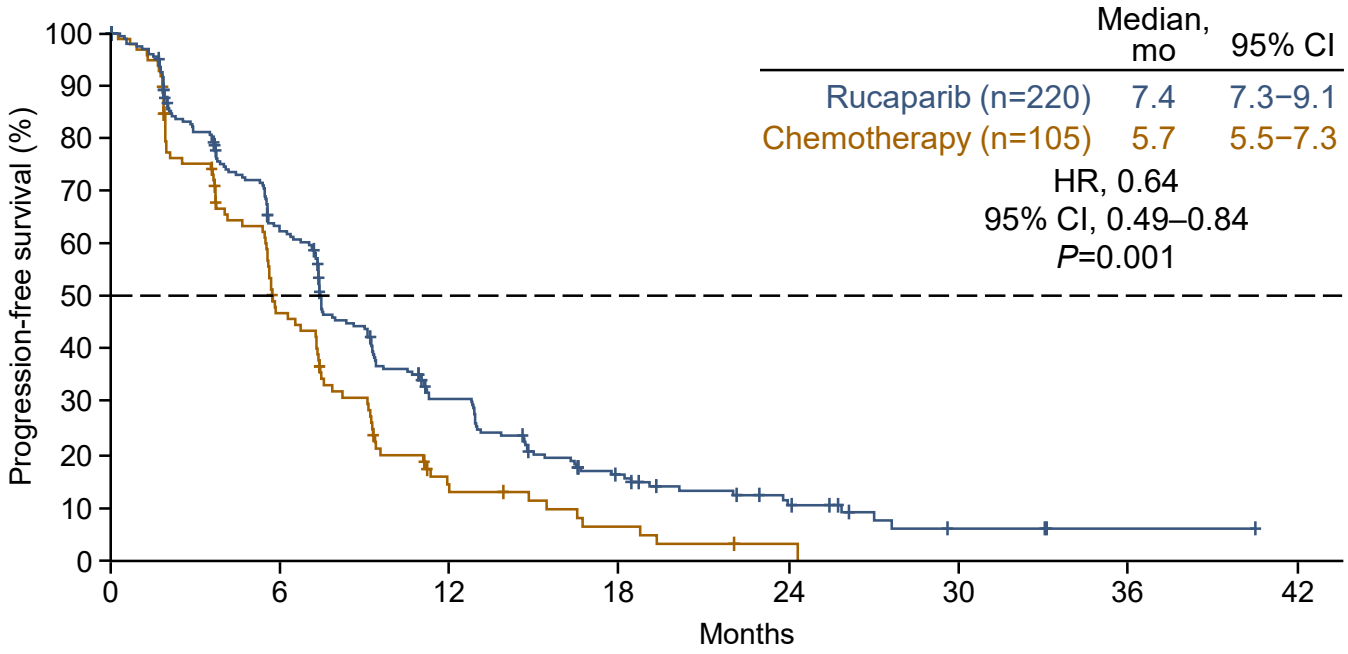
Visit cutoff September 30, 2020.
BRCA, *BRCA1* or *BRCA2;* ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent to treat.

Prior Anti-Cancer Treatment, Platinum Status, and Disease Burden: ITT Population

	Rucaparib (n=233)	Chemotherapy (n=116)	Overall (N=349)
Prior chemotherapy regimens, n (%)			
2	134 (57.5)	68 (58.6)	202 (57.9)
3–5	88 (37.8)	44 (37.9)	132 (37.8)
≥6	11 (4.7)	4 (3.4)	15 (4.3)
Prior platinum-based regimens, n (%)			
1	12 (5.2)	6 (5.2)	18 (5.2)
2	156 (67.0)	74 (63.8)	230 (65.9)
≥3	65 (27.9)	36 (31.0)	101 (28.9)
Prior nonplatinum regimens immediately before randomization, n (%)			
0	179 (76.8)	92 (79.3)	271 (77.7)
≥1	54 (23.2)	24 (20.7)	78 (22.3)
Median PFI after last dose of prior platinum regimen, months (range)	5.6 (1.1–67.4)	5.8 (1.0–90.1)	5.7 (1.0–90.1)
Platinum status, n (%)[a]			
Platinum resistant	120 (51.5)	59 (50.9)	179 (51.3)
Partially platinum sensitive	65 (27.9)	31 (26.7)	96 (27.5)
Fully platinum sensitive	48 (20.6)	26 (22.4)	74 (21.2)
Measurable disease at baseline, n (%)	224 (96.1)	106 (91.4)	330 (94.6)

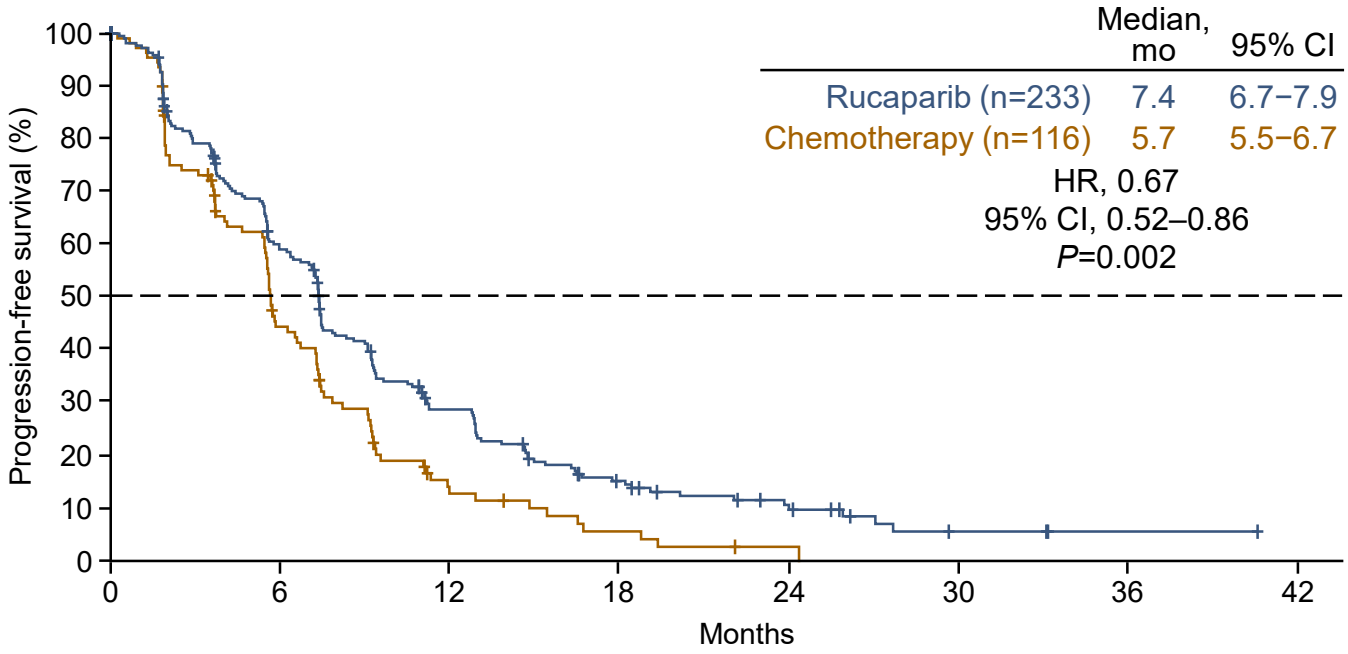
Visit cutoff September 30, 2020.
[a]Randomization stratification factor; platinum resistant: PFI ≥1–<6 months, partially platinum sensitive: PFI ≥6–<12 months, fully platinum sensitive: PFI ≥12 months.
ITT, intent to treat; PFI, progression-free interval.

Primary Endpoint – Investigator-assessed PFS: Efficacy Population



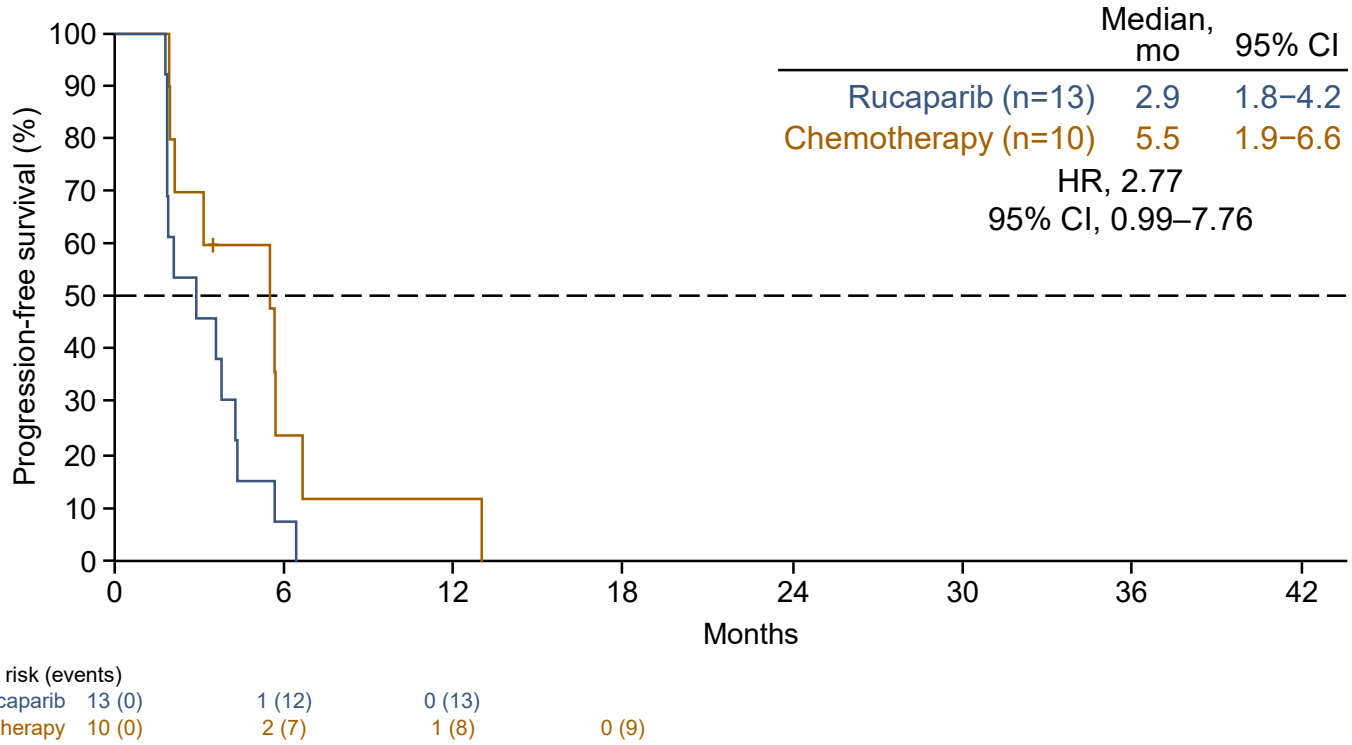
Visit cutoff September 30, 2020.
HR and associated *P* value calculated using a stratified Cox proportional hazards model.
HR, hazard ratio; PFS, progression-free survival.

Primary Endpoint – Investigator-assessed PFS: ITT Population



Visit cutoff September 30, 2020.
HR and associated *P* value calculated using a stratified Cox proportional hazards model.
HR, hazard ratio; ITT, intent to treat; PFS, progression-free survival.

Investigator-assessed PFS: BRCA Reversion Mutation Subgroup

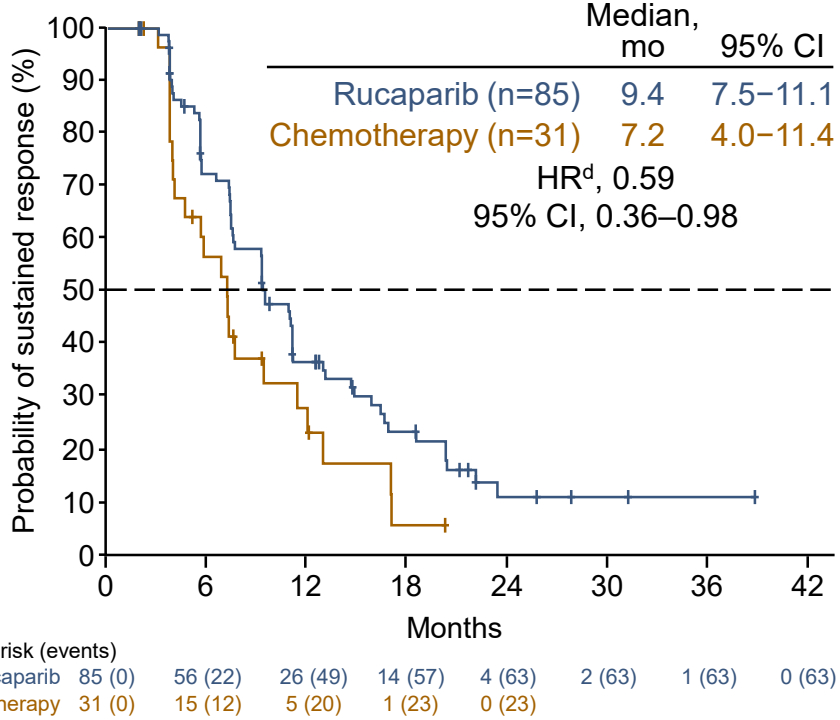


Visit cutoff September 30, 2020.
HR calculated using a stratified Cox proportional hazards model. *P* value was significant for treatment by BRCA reversion mutation (yes vs no) interaction test (*P*=0.0097).
BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; PFS, progression-free survival.

Secondary Endpoints – Response: Efficacy Population

	Rucaparib	Chemotherapy
RECIST ORR, n/N (%) [95% CI][a]	**85/211 (40.3) [33.6–47.2]**	**31/96 (32.3) [23.1–42.6]**
	P=0.13[b]	
Complete response	10 (4.7)	2 (2.1)
Partial response	75 (35.5)	29 (30.2)
Stable disease	77 (36.5)	38 (39.6)
Progressive disease	25 (11.8)	15 (15.6)
Not evaluable	24 (11.4)	12 (12.5)
RECIST and/or CA-125 response, n/N (%) [95% CI][c]	**110/217 (50.7) [43.8–57.5]**	**44/101 (43.6) [33.7–53.8]**

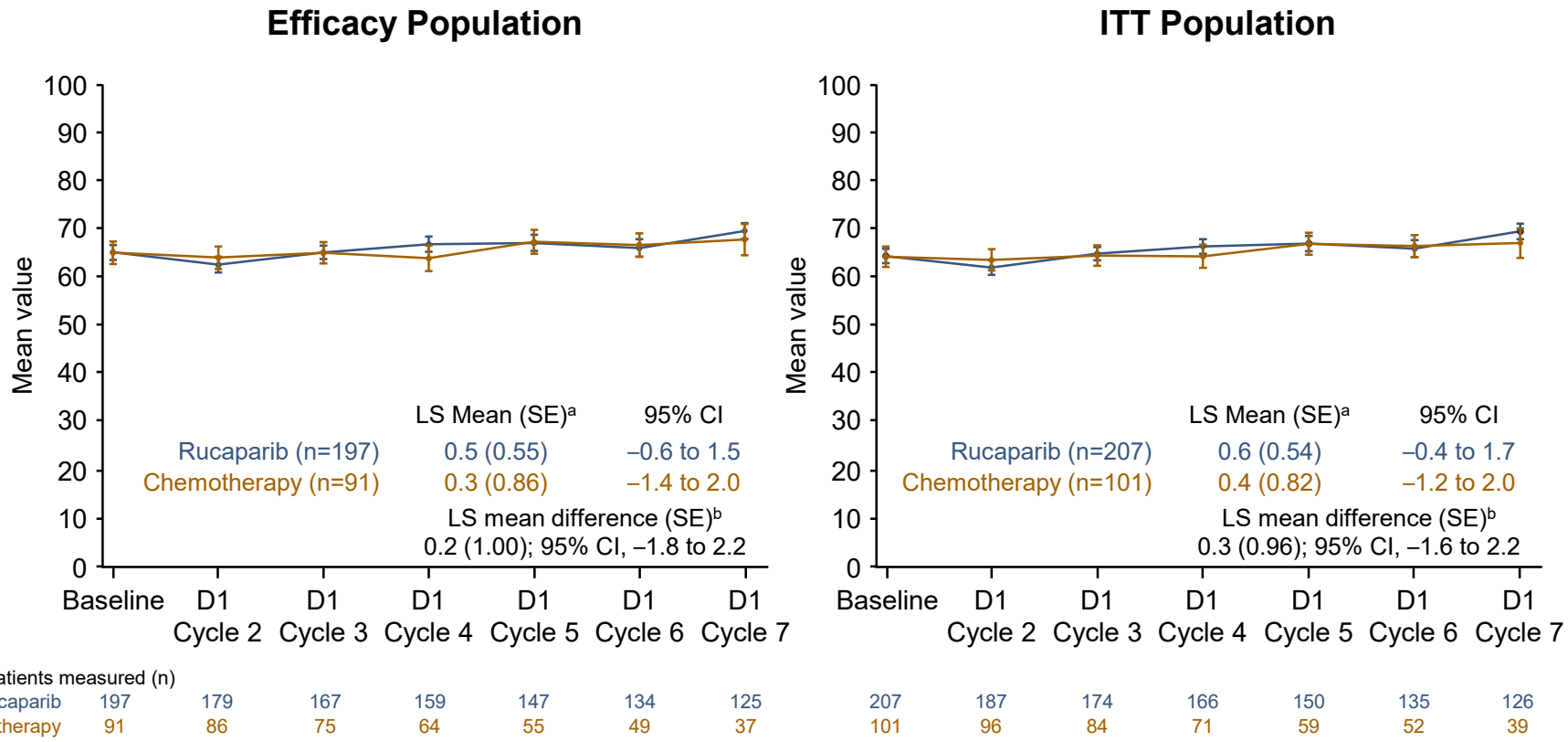
DOR



- Data were similar for the ITT population:
  - RECIST ORR: rucaparib, 37.9% (95% CI, 31.6–44.7) vs chemotherapy, 30.2% (95% CI, 21.7–39.9)
  - Median DOR: rucaparib, 9.4 months vs chemotherapy, 7.2 months (HR,[d] 0.56 [95% CI, 0.34–0.93])

Visit cutoff September 30, 2020.
[a]Patients with measurable disease at baseline. [b]Per Stratified Cochran-Mantel-Haenszel test. [c]Patients with measurable disease at baseline and/or evaluable by CA-125. [d]Per Cox proportional hazards model. CA-125, cancer antigen 125; DOR, duration of response; HR, hazard ratio; ITT, intent to treat; ORR, objective response rate; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1.

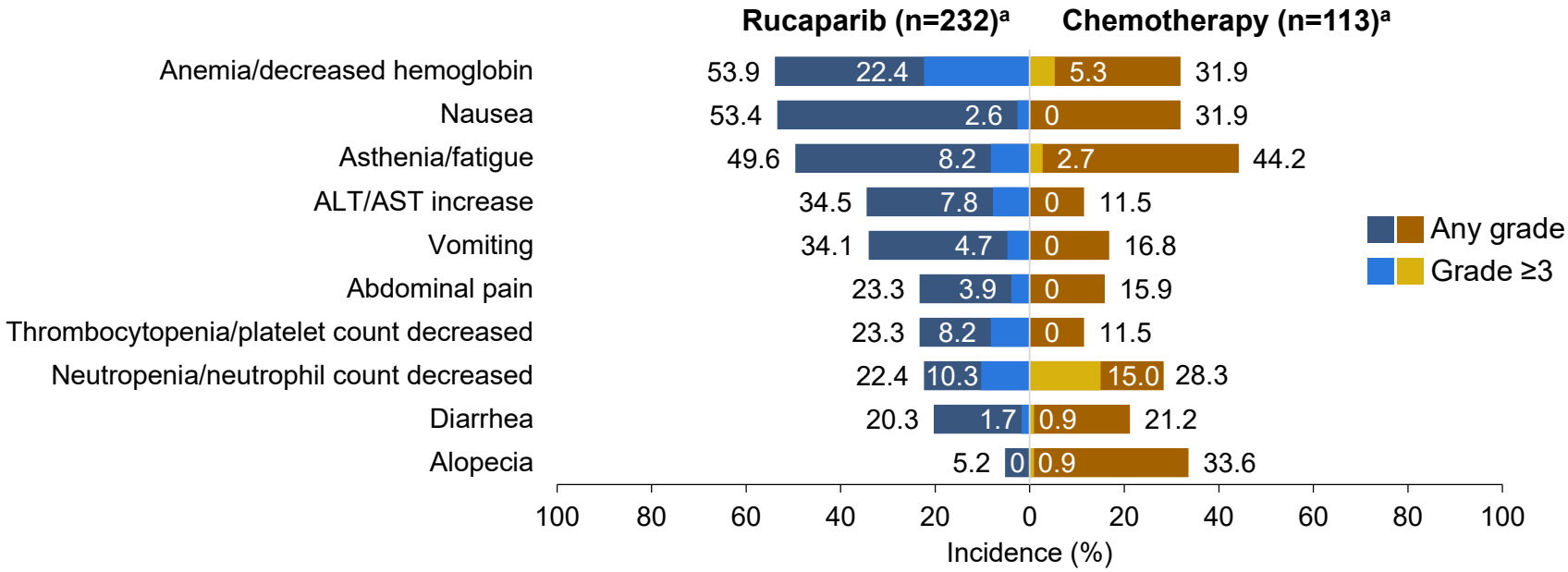
Secondary Endpoint – Change From Baseline in EORTC QLQ-C30 Global Health Status



Patients measured (n)														
Rucaparib	197	179	167	159	147	134	125	207	187	174	166	150	135	126
Chemotherapy	91	86	75	64	55	49	37	101	96	84	71	59	52	39

Visit cutoff September 30, 2020.
Data were analyzed using a repeated measures ANCOVA model, with the baseline value as a covariate, and treatment and randomization stratification as factors.
[a]LS mean change from baseline during first 6 cycles. [b]Rucaparib vs chemotherapy.
ANCOVA, analysis of covariance; D, day; EORTC QLQ, European Organization for Research and Treatment of Cancer quality of life questionnaire; ITT, intent to treat; LS, least square; SE, standard error.

Most Common TEAEs (≥20% in Either Group)



- Median treatment duration: rucaparib, 7.3 months (range <1–41); chemotherapy, 3.6 months (range <1–25)
- Nineteen (8.2%) patients in the rucaparib group and 14 (12.4%) in the chemotherapy group discontinued due to TEAE[b]
- MDS/AML was reported by 4 patients in the rucaparib group (1 during treatment, 3 during long-term follow-up) and no patients in the chemotherapy group

Visit cutoff September 30, 2020.
[a]Four patients (rucaparib, 1; chemotherapy, 3) discontinued before receiving study treatment and are excluded from the safety population. [b]Excluding disease progression. ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

Conclusions

- Patients with BRCA-mutated advanced, relapsed OC who received rucaparib had a significant improvement in PFS vs standard-of-care chemotherapy
- The rucaparib safety profile was consistent with that reported in prior studies
- This is the first prospective report from a randomized study demonstrating that the presence of a BRCA reversion mutation predicts for primary resistance to rucaparib
- Overall survival will be presented once death events are mature (at visit cutoff, 51% of death events had occurred)

BRCA, *BRCA1* or *BRCA2;* OC, ovarian cancer; PFS, progression-free survival.

Acknowledgments

ARIEL4 co-coordinating investigators: Rebecca Kristeleit, Guy's and St Thomas' NHS Foundation Trust, London, UK
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