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Overall Survival Results From ARIEL4: A Phase 3 Study Assessing Rucaparib vs Chemotherapy in Patients With Advanced, Relapsed Ovarian Carcinoma and a Deleterious *BRCA1/2* Mutation

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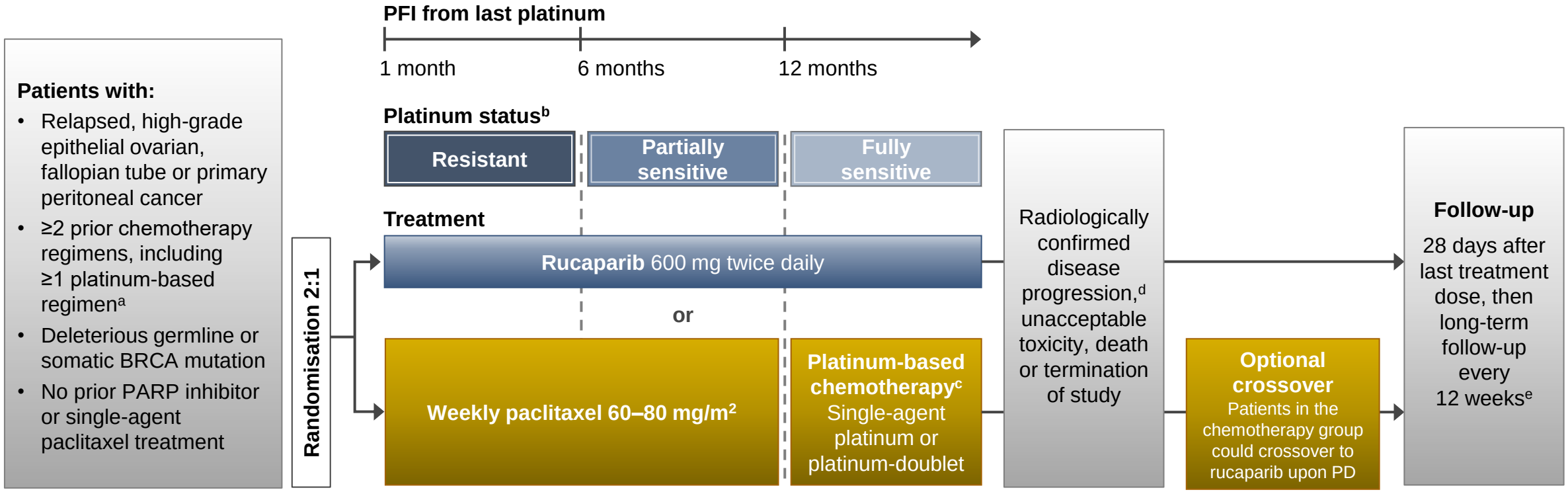
Background

- In the primary analysis of ARIEL4 (NCT02855944), rucaparib significantly improved the primary endpoint of investigator-assessed PFS vs standard-of-care chemotherapy in patients with relapsed, heavily pretreated, BRCA-mutated ovarian carcinoma[1]
- In the ITT population, median PFS was 7.4 months (95% CI, 6.7–7.9) in the rucaparib group (n=233) vs 5.7 months (95% CI, 5.5–6.7) in the chemotherapy group (n=116; HR 0.67 [95% CI, 0.52–0.86]; *P*=0.0017)[1]
- Here we present final OS data and other postprogression outcomes from the ARIEL4 study

Data cutoff: 30 September 2020.
BRCA, *BRCA1* or *BRCA2*; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.
1. Kristeleit et al. *Lancet Oncol*. 2022;23(4):465-478.

ARIEL4 Study Design



- Efficacy endpoints
  - Prespecified secondary endpoint: OS in the ITT population
  - Exploratory endpoints: OS in platinum-status subgroups; PFS2 in the ITT population and in platinum-status subgroups

[a]With treatment-free interval ≥6 months following first chemotherapy received. [b]Randomisation stratification factor. [c]At investigator's discretion. [d]Per RECIST. [e]Patients who discontinued for reasons other than PD were followed every 8 weeks. BRCA, *BRCA1* or *BRCA2*; ITT, intent-to-treat; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFI, progression-free interval; PFS, progression-free survival; PFS2, PFS from randomisation to progression on the subsequent line of therapy; RECIST, Response Evaluation Criteria in Solid Tumors, version 1.1.

Baseline Demographics and Disease Characteristics

- At data cutoff, 14/233 (6%) patients in the rucaparib-group and 0/116 patients in the chemotherapy-group were ongoing on assigned study treatment
- Following progression, 80/116 (69%) patients in the chemotherapy group crossed over to receive rucaparib
  - Of those, 41 (51%) patients had platinum-resistant disease, 25 (31%) had partially platinum-sensitive disease and 14 (18%) had fully platinum-sensitive disease
  - Overall, 313/349 (90%) patients who participated in ARIEL4 received rucaparib
- Death events occurred in 244/349 (70%) patients

	Platinum Resistant		Partially Platinum Sensitive		Fully Platinum Sensitive	
	Rucaparib (n=120)	CT (n=59)	Rucaparib (n=65)	CT (n=31)	Rucaparib (n=48)	CT (n=26)
Median age, y (range)	56.0 (38–81)	59.0 (42–85)	58.0 (42–74)	62.0 (45–73)	60.0 (41–75)	57.0 (38–77)
ECOG PS 0, n (%)	64 (53.3)	37 (62.7)	31 (47.7)	17 (54.8)	30 (62.5)	18 (69.2)
Median time since diagnosis, mo (range)	36 (13–146)	35 (14–119)	41 (17–169)	43 (16–111)	59 (29–185)	62 (24–140)
Prior chemotherapy regimens, n (%)						
2	63 (52.5)	30 (50.8)	37 (56.9)	19 (61.3)	34 (70.8)	19 (73.1)
3–5	49 (40.8)	26 (44.1)	28 (43.1)	11 (35.5)	11 (22.9)	7 (26.9)
≥6	8 (6.7)	3 (5.1)	0	1 (3.2)	3 (6.3)	0
Median number of prior platinum-based therapies, n (range)	2 (1–6)	2 (1–5)	2 (1–4)	2 (1–4)	2 (1–6)	2 (1–4)
Prior platinum-based regimens, n (%)						
1	2 (1.7)	1 (1.7)	9 (13.8)	4 (12.9)	1 (2.1)	1 (3.8)
2	80 (66.7)	36 (61.0)	40 (61.5)	18 (58.1)	36 (75.0)	20 (76.9)
≥3	38 (31.7)	22 (37.3)	16 (24.6)	9 (29.0)	11 (22.9)	5 (19.2)
Prior nonplatinum regimens immediately before randomisation, n (%)						
0	95 (79.2)	47 (79.7)	42 (64.6)	23 (74.2)	42 (87.5)	23 (88.5)
≥1	25 (20.8)	12 (20.3)	23 (35.4)	8 (25.8)	6 (12.5)	3 (11.5)

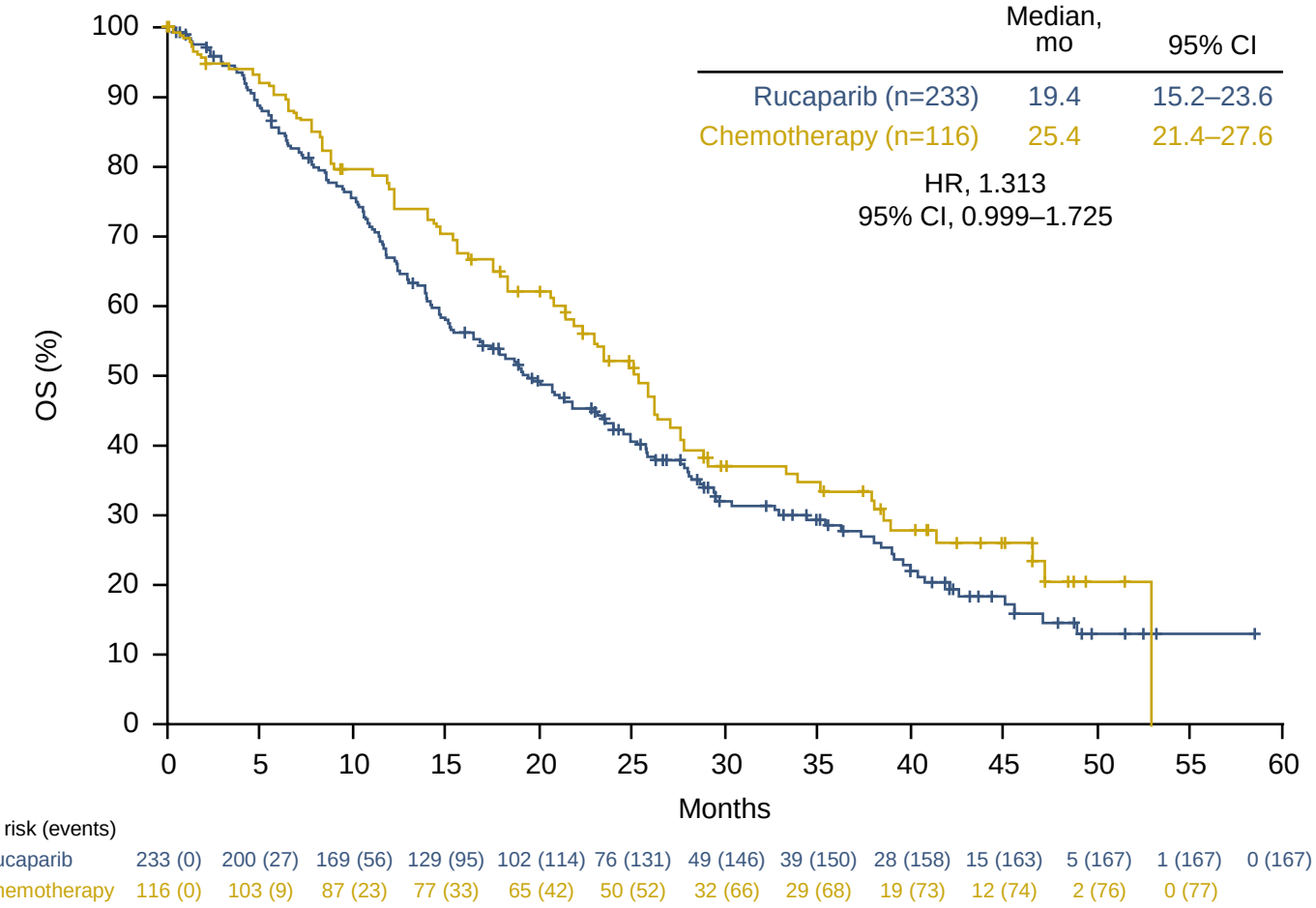
Data cutoff: 10 April 2022.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mo, months.

Crossover and Subsequent Treatments

	Platinum Resistant		Partially Platinum Sensitive		Fully Platinum Sensitive	
	Rucaparib (n=120)	Chemotherapy (n=59)	Rucaparib (n=65)	Chemotherapy (n=31)	Rucaparib (n=48)	Chemotherapy (n=26)
Median duration of randomised treatment, mo (range)[a]	5.6 (0–44)	4.4 (0–25)	7.6 (0–60)	4.5 (0–11)	13.7 (0–53)	3.4 (1–8)
Subsequent anticancer treatment reported, n (%)						
Yes	69 (57.5)	45 (76.3)	40 (61.5)	26 (83.9)	26 (54.2)	22 (84.6)
No	51 (42.5)	14 (23.7)	25 (38.5)	5 (16.1)	22 (45.8)	4 (15.4)
Type of first subsequent treatment, n (%)						
Crossover rucaparib	NA	41 (91.1)	NA	25 (96.2)	NA	14 (63.6)
Other PARPi	1 (1.4)	0	0	0	1 (3.8)	4 (18.2)
Platinum-based chemotherapy	29 (42.0)	1 (2.2)	27 (67.5)	1 (3.8)	20 (76.9)	2 (9.1)
Nonplatinum-based chemotherapy	36 (52.2)	2 (4.4)	11 (27.5)	0	5 (19.2)	1 (4.5)
Other[b]	3 (4.3)	1 (2.2)	2 (5.0)	0	0	1 (4.5)
Median duration of crossover rucaparib, mo (range)	NA	9.4 (2–39)	NA	9.7 (0–36)	NA	9.9 (1–37)
<6 months, n (%)	NA	14 (34.1)	NA	7 (28.0)	NA	2 (14.3)
≥6 months, n (%)		27 (65.9)		18 (72.0)		12 (85.7)

Data cutoff: 10 April 2022. Data are from the ITT population.
[a]Excludes patients who did not receive randomly allocated treatment. [b]Other treatments included monoclonal antibodies (excluding bevacizumab), hormonal therapies, investigational drugs.
ITT, intent-to-treat; mo, months; NA, not applicable; PARPi, poly(ADP-ribose) polymerase inhibitor.

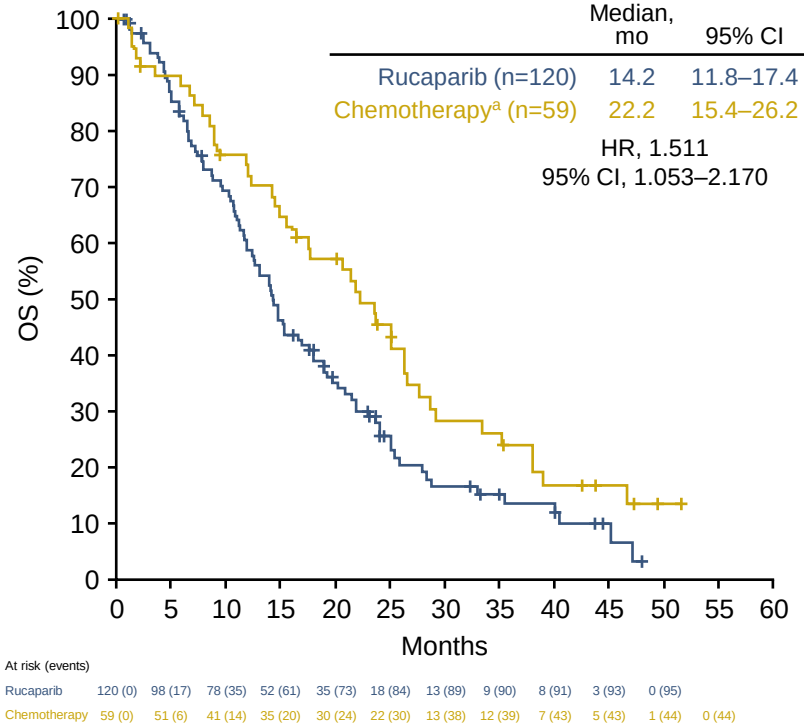
OS: ITT Population



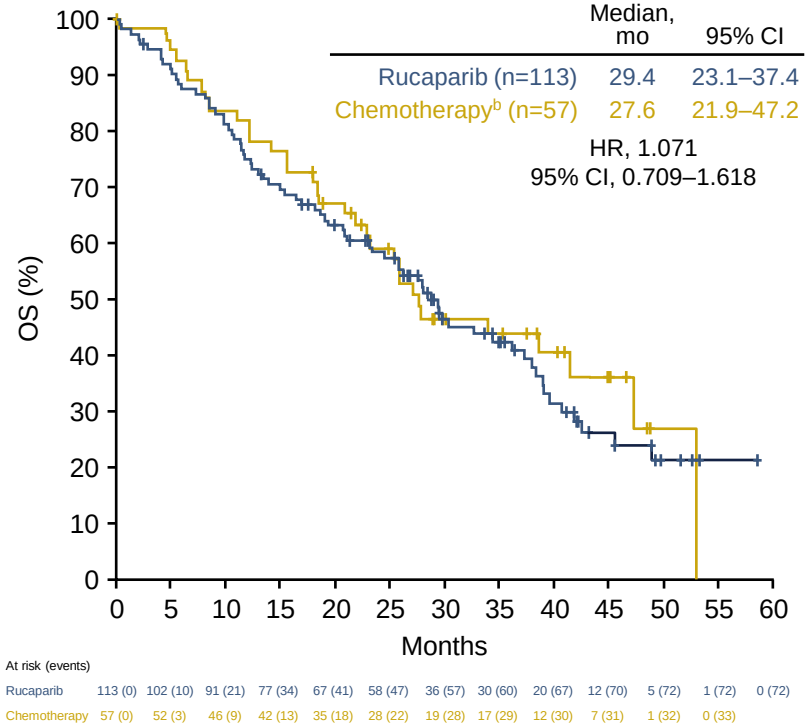
Data cutoff: 10 April 2022. HRs estimated with a Cox proportional hazards model.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival.

OS: Platinum Status Subgroups

Platinum Resistant



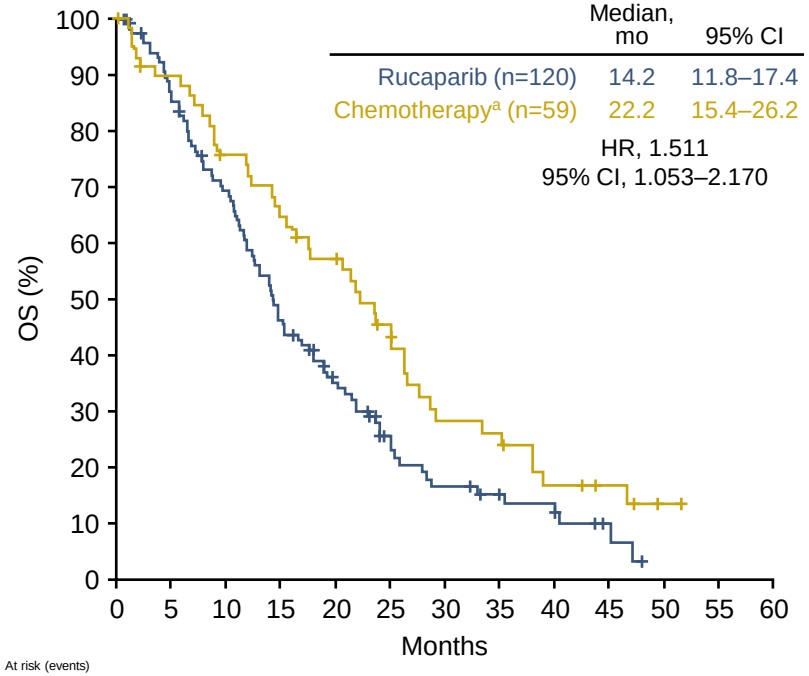
Platinum Sensitive



Data cutoff: 10 April 2022. HRs estimated with a Cox proportional hazards model. [a]Weekly paclitaxel. [b]Weekly paclitaxel for patients with partially platinum-sensitive disease; single-agent platinum or platinum doublet for patients with fully platinum-sensitive disease.
CI, confidence interval; HR, hazard ratio; mo, months; OS, overall survival.

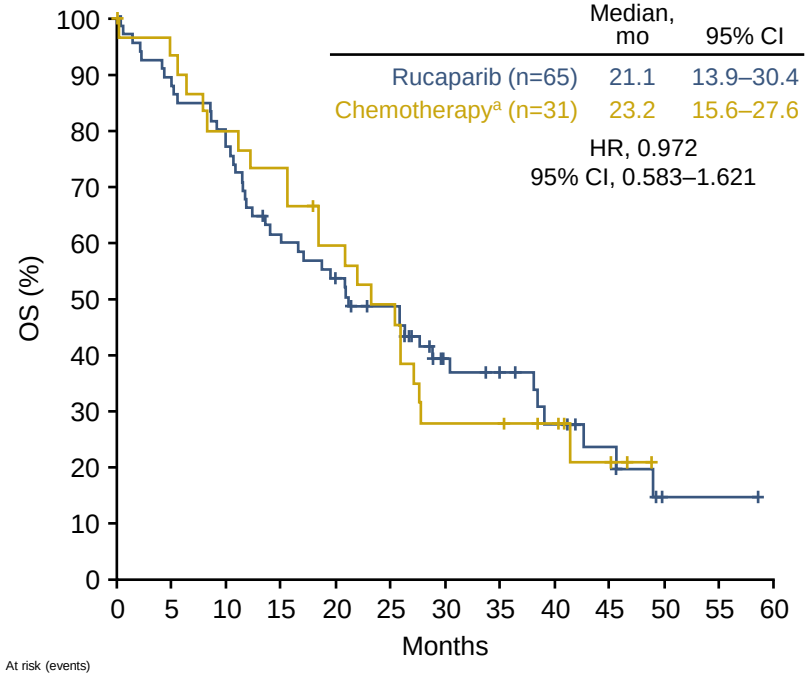
OS: Platinum Status Subgroups

Platinum Resistant



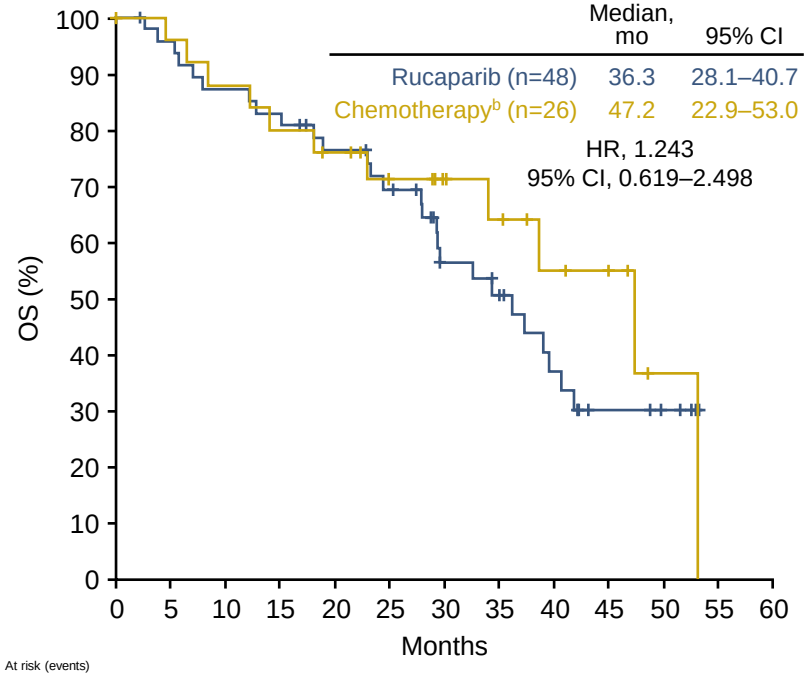
At risk (events)											
Rucaparib	120(0)	98 (17)	78 (35)	52 (61)	35 (73)	18 (84)	13 (89)	9 (90)	8 (91)	3 (93)	0 (95)
Chemotherapy	59 (0)	51 (6)	41 (14)	35 (20)	30 (24)	22 (30)	13 (38)	12 (39)	7 (43)	5 (43)	1 (44)	0 (44)

Partially Platinum Sensitive



At risk (events)												
Rucaparib	65 (0)	57 (8)	50 (15)	38 (26)	33 (30)	28 (33)	16 (38)	13 (39)	9 (42)	6 (43)	1 (45)	1 (45)	0 (45)
Chemotherapy	31 (0)	28 (2)	24 (6)	22 (8)	17 (12)	14 (15)	8 (21)	8 (21)	6 (21)	3 (22)	0 (22)	

Fully Platinum Sensitive

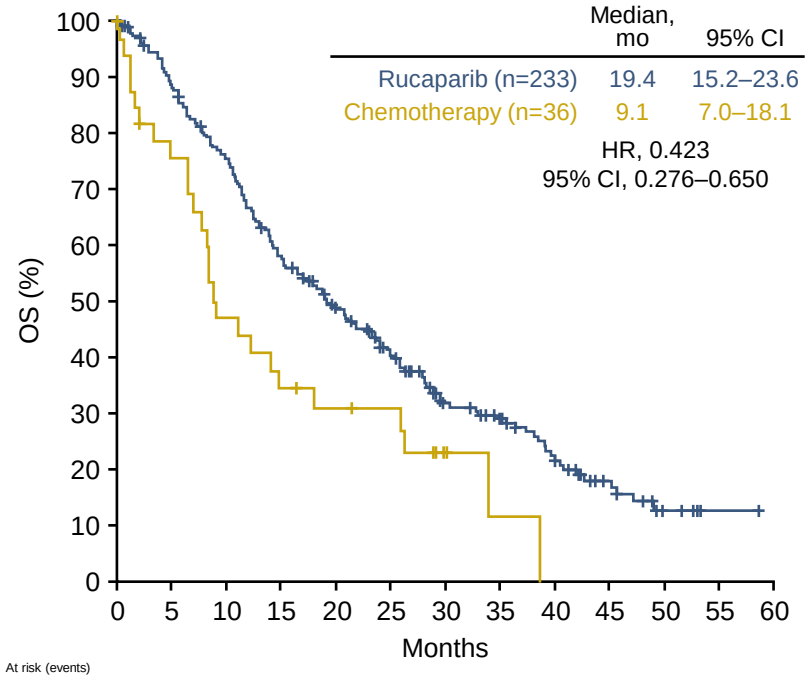


At risk (events)												
Rucaparib	48 (0)	45 (2)	41 (6)	39 (8)	34 (11)	30 (14)	20 (19)	17 (21)	11 (25)	6 (27)	4 (27)	0 (27)
Chemotherapy	26 (0)	24 (1)	22 (3)	20 (5)	18 (6)	14 (7)	11 (7)	9 (8)	6 (9)	4 (9)	1 (10)	0 (11)

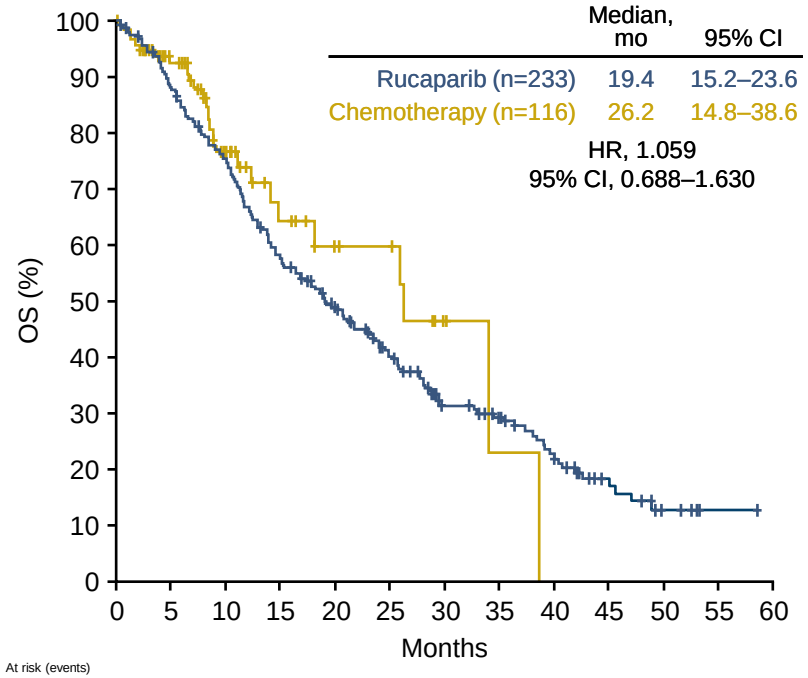
Data cutoff: 10 April 2022. HRs estimated with a Cox proportional hazards model. [a]Weekly paclitaxel. [b]Single-agent platinum or platinum doublet.
CI, confidence interval; HR, hazard ratio; mo, months; OS, overall survival.

OS: ITT Population – Adjustments for Crossover

Excluding Patients Who Crossed Over From Chemotherapy to Rucaparib



Censoring Data at Crossover From Chemotherapy to Rucaparib

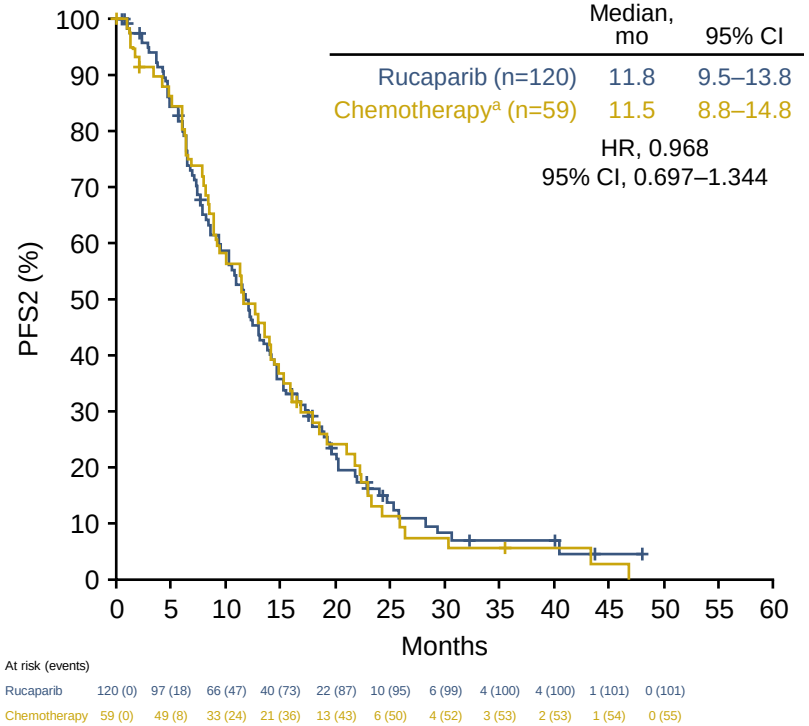


- OS with time-varying covariate adjustment (HR, 0.91; *P*=0.673) showed no difference between the treatment groups

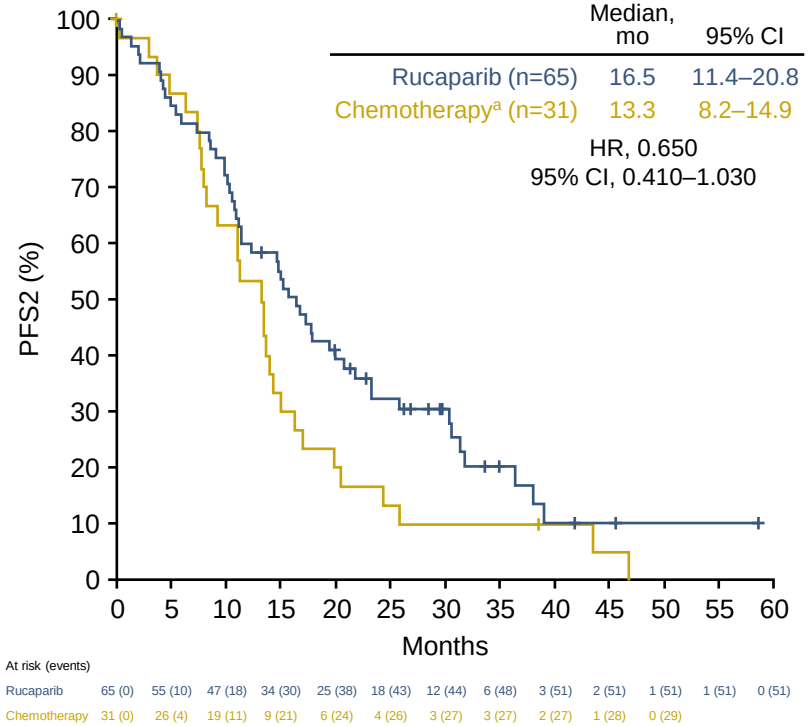
Data cutoff: 10 April 2022. HRs estimated with a Cox proportional hazards model.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival.

PFS2: Platinum Status Subgroups

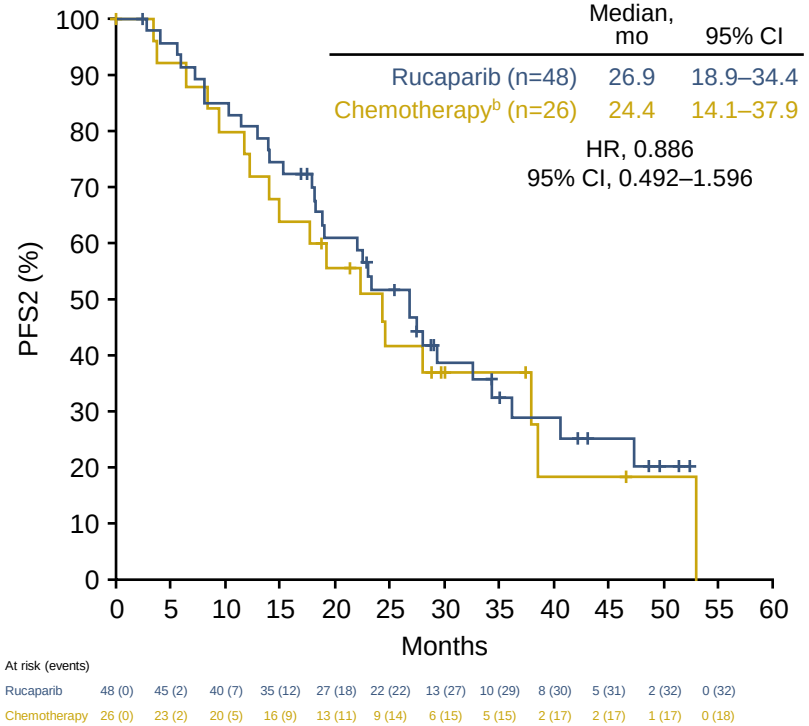
Platinum Resistant



Partially Platinum Sensitive

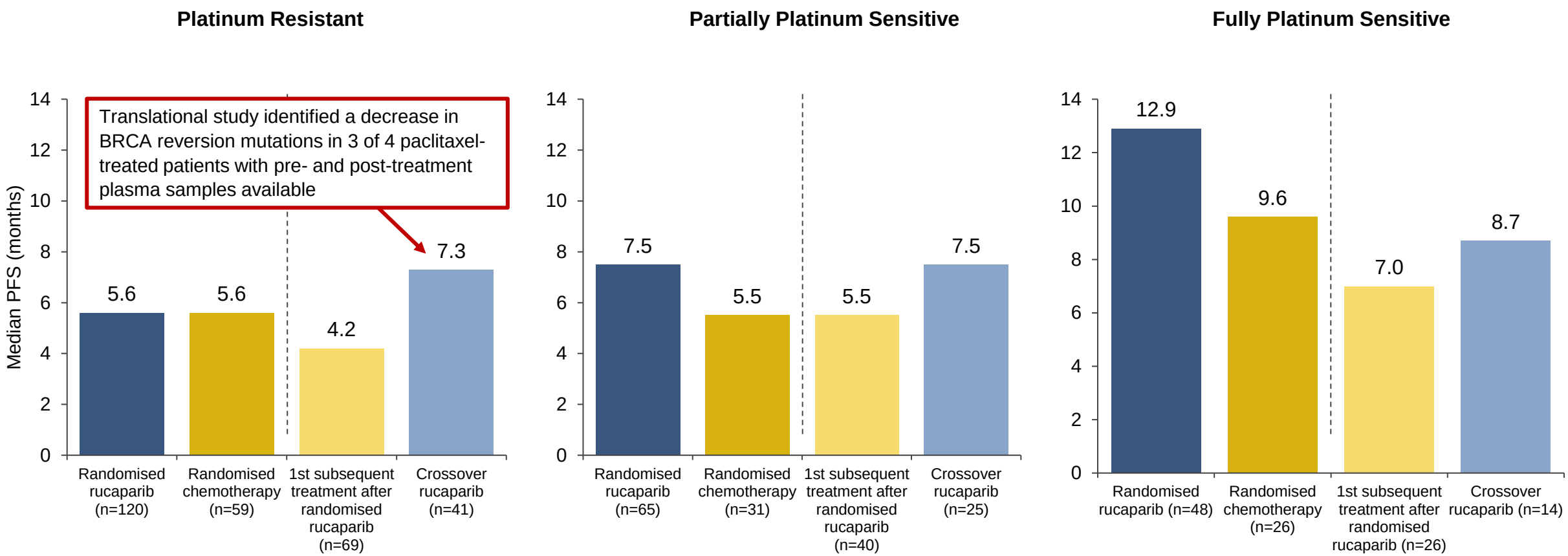


Fully Platinum Sensitive



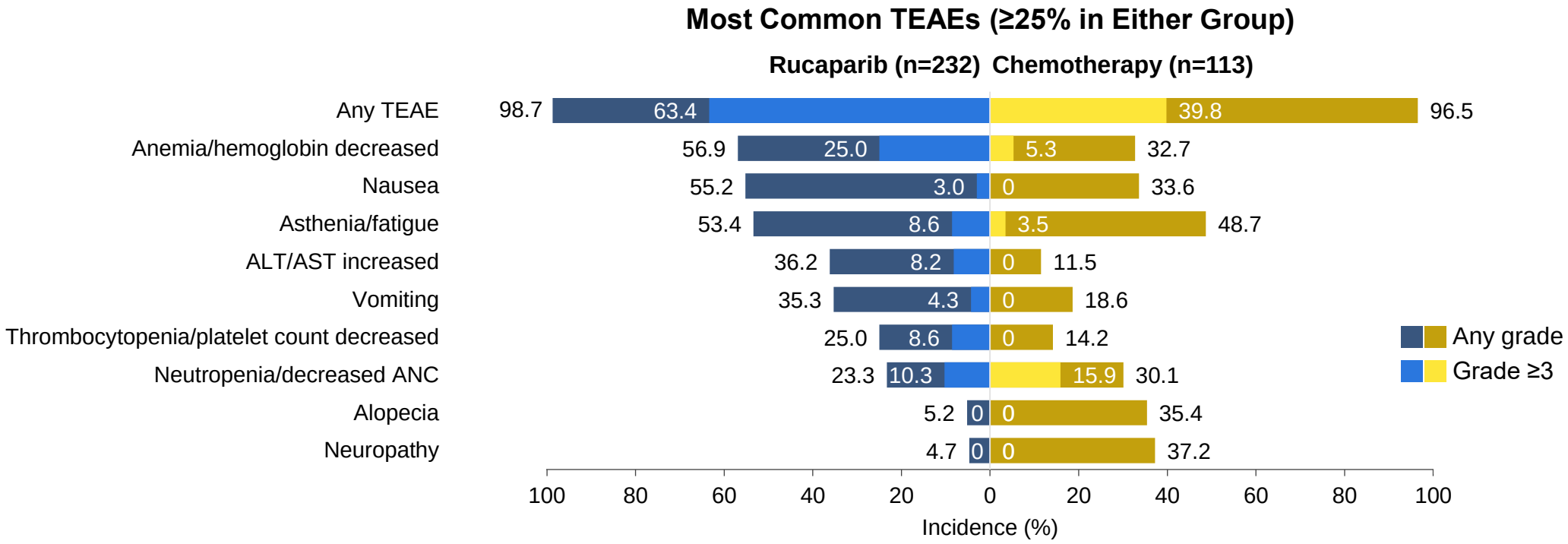
Data cutoff: 10 April 2022. HRs estimated with a Cox proportional hazards model. [a]Weekly paclitaxel. [b]Single-agent platinum or platinum doublet.
CI, confidence interval; HR, hazard ratio; mo, months; PFS2, progression-free survival from randomisation to progression on the subsequent line of therapy.

PFS During First Subsequent Anticancer Treatment: Platinum Status Subgroups



Data cutoff for PFS on randomised treatment: 30 September 2022; data cutoff for 1st subsequent treatment or crossover rucaparib: 10 April 2022. PFS events during 1st subsequent treatment after randomised rucaparib were reported by investigator and included non-radiological progression. BRCA, *BRCA1* or *BRCA2*; PFS, progression-free survival.

Summary of Safety



- MDS/AML was reported in 7 (3.0%) patients initially randomised to rucaparib (reported during long-term follow-up in 4 cases). No cases were reported among patients initially randomised to chemotherapy

Data cutoff for safety data: 10 April 2022. Data cutoff for MDS/AML: 23 March 2022. Neuropathy includes neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, and toxic neuropathy.
ALT, alanine aminotransferase; AML, acute myeloid leukemia; ANC, absolute neutrophil count; AST, aspartate aminotransferase; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

Conclusions

- In ARIEL4, rucaparib significantly improved PFS versus chemotherapy in the ITT population
- OS favored those randomised to chemotherapy vs rucaparib in the ITT population
  - OS was similar between treatment groups amongst patients with platinum-sensitive disease; the difference in OS in the ITT population was driven by the platinum-resistant subgroup
  - OS was confounded by the high rate of crossover from chemotherapy to rucaparib; 90% of patients received rucaparib after randomisation or crossover
  - Additionally, 98/233 (42.1%) of patients in the rucaparib arm did not receive subsequent anticancer treatment
- Further work is ongoing to understand the biological basis of resistance and the optimal sequence of therapy

ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.

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Backup

PARIS 2022 ESMO congress

Biological Hypothesis of Long PFS During Crossover Rucaparib Treatment in Platinum-Resistant Patients Randomised to Paclitaxel

- **Hypothesis**: In patients with platinum-resistant disease, tumour subclones harbouring cross-resistance mechanisms (eg, BRCA reversion mutations) may be selected against during paclitaxel treatment, resulting in these patients being more sensitive to subsequent PARPi treatment
- To test this hypothesis, we sequenced plasma samples collected pre- and post-paclitaxel treatment to assess BRCA reversion mutation frequency in circulating tumour DNA
- In the 4 patients with platinum-resistant disease who had BRCA reversion mutations detected in pre- and post-treatment and subsequently crossed over to rucaparib, 3 had a decrease in BRCA reversion mutation frequency (range, 20–91% decrease in variant allele frequency)
- This finding suggests that platinum-resistant subclones may be selected against during paclitaxel treatment

BRCA, *BRCA1* or *BRCA2*; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival.