Supplemental Information

Supplementary Tables

Supplementary Table 1

Frequency and types of BRCA mutations in the rucaparib-arm exceptional benefit and short-term subgroups.

	BRCA-mutant exceptional benefit subgroup (n=46)	**BRCA-mutant short-term subgroup (n=12)**	***p* value**	**Odds ratio (95% CI)**
Gene			0.106[a]	
BRCA1	21 (45.7)	9 (75.0)		0.3 (0.1–1.1)
BRCA2	25 (54.3)	3 (25.0)		3.6 (0.9–13.2)
Germline/somatic status			0.408[b]	
Germline	22 (47.8)	7 (58.3)		0.7 (0.2–2.4)
Somatic	18 (39.1)	5 (41.7)		0.9 (0.2–3.1)
Unknown	6 (13.0)	0		NA
Mutation type			>0.99[a]	
Short variant	41 (89.1)	11 (91.7)		0.7 (0.1–5.3)
Rearrangement/loss	5 (10.9)	1 (8.3)		1.3 (0.2–17.1)

BRCA, *BRCA1* or *BRCA2*; mut, mutated; NA, not applicable.

Data are n (%). Data for the placebo arm are available in Supplementary Table 3.

[a] Significance based on Fisher's exact test. [b]Significance based on chi-square test.

Supplementary Table 2

Genetic and epigenetic alterations in the placebo-arm exceptional benefit and short-term subgroups.

Alteration	Exceptional benefit subgroup (n=4)	Short-term subgroup (n=62)	*p* value	Odds ratio (95% CI)
BRCA mutant	3 (75.0)	26 (41.9)	0.312	4.2 (0.6–55.2)
BRCA wild-type + *RAD51C/D* mutation	0	0	NA	NA
BRCA wild-type + other HRR gene mutation	0	2 (3.2)	>0.99	NA
BRCA wild-type + LOH high	0	14 (22.6)	0.571	NA
BRCA wild-type + LOH low	1 (25.0)	15 (24.2)	>0.99	1.0 (0.1–7.5)
BRCA wild-type + high *BRCA1* methylation	0/1	5/29 (17.2)	>0.99	NA

BRCA, *BRCA1* or *BRCA2;* HRR, homologous recombination repair; LOH, loss of heterozygosity; NA, not applicable.

Statistical comparisons based on Fisher's exact test for all cases. Data are n (%) or n/N (%). Data for the rucaparib arm are available in Table 2 in the main text.

Supplementary Table 3

Frequency and types of BRCA mutations in the placebo-arm exceptional benefit and short-term subgroups.

	BRCA-mutant exceptional benefit subgroup (n=3)	**BRCA-mutant short-term subgroup (n=26)**	***p* value**	**Odds ratio (95% CI)**
Gene			>0.99[a]	
BRCA1	2 (66.7)	17 (65.4)		1.1 (0.1–16.9)
BRCA2	1 (33.3)	9 (34.6)		0.9 (0.1–9.0)
Germline/somatic status			0.8731[b]	
Germline	2 (66.7)	17 (65.4)		1.1 (0.1–16.9)
Somatic	1 (33.3)	7 (26.9)		1.4 (0.1–13.0)
Unknown	0	2 (7.7)		NA
Mutation type			>0.99[a]	
Short variant	3 (100)	23 (88.5)		NA
Rearrangement/loss	0	3 (11.5)		NA

BRCA, *BRCA1* or *BRCA2;* mut, mutated; NA, not applicable.

Data are n (%). Data for the rucaparib arm are available in Supplementary Table 1.

[a] Significance based on Fisher's exact test.

[b] Significance based on chi-square test.

Supplementary Table 4

Non-BRCA HRR gene mutations detected in the BRCA wild-type rucaparib-arm exceptional benefit and short-term subgroups.

Patient number	PFS (months)	Gene	Mutation	Germline/somatic status	Zygosity
Exceptional benefit subgroup					
1	46.7+	*RAD51C*	Splice site 572-1G>A	Somatic	Homozygous
2	38.6+	*RAD51C*	Splice site 706-2A>G	Germline	Homozygous
3	35.5+	*RAD51C*	Splice site 706-2A>G	NA	Homozygous
4	27.4+	*RAD51C*	R193*	Germline	Homozygous
5	54.3+	*RAD51D*	R120*	Germline	Homozygous
6	50.2+	*RAD51D*	R74*	Somatic	Homozygous
7	24.2	*FANCC*	Truncating rearrangement	NA	NA
Short-term subgroup					
8	2.9	*ATM*	R2832C	Germline	NA
		FANCM	L691fs*5	NA	NA
9[a]	9.0	*FANCA*	Duplication rearrangement	NA	NA
10	2.6	*FANCD2*	W1450*	NA	Heterozygous
11	2.7	*RAD54L*	H676fs*19	NA	Heterozygous
12	2.7	*ATR*	A1266fs*8	NA	Heterozygous

BRCA, *BRCA1* or *BRCA2*; HRR, homologous recombination repair; NA, not available; PFS, progression-free survival.

[a] This patient received rucaparib for 2 weeks then discontinued treatment but was included in the short-term subgroup as they had disease progression on their first scan, which was performed at 9 months after the first dose of rucaparib (protocol deviation).

Supplementary Table 5

Multivariate logistic regression model analysis of maximum likelihood estimates.

Parameter	Level	DF	Estimate	Standard error	Wald chi-square	Probability > chi-square
Intercept		1	−2.930	0.334	77.187	<0.0001
Treatment arm	Rucaparib	1	1.313	0.264	24.757	<0.0001
PPFI	>12 month	1	0.352	0.141	6.193	0.013
Measurable disease at baseline	No	1	0.237	0.144	2.724	0.099
Molecular characteristic	BRCA mutant	1	0.690	0.271	6.475	0.011
	BRCA wild-type/LOH high	1	−0.316	0.346	0.837	0.360
	BRCA wild-type/LOH unknown	1	0.177	0.444	0.159	0.690
	RAD51C/D mutation	1	1.817	0.558	10.594	0.001
	Other HRR gene mutation	1	−1.460	0.872	2.801	0.094

BRCA, *BRCA1* or *BRCA2*; DF, degrees of freedom; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; LOH, loss of heterozygosity; PPFI, penultimate platinum-free interval.

The following baseline characteristics were included in the model, only those that were identified as significant predictors are shown in the table: age, body mass index, race (White vs other or missing), ECOG PS, type of ovarian cancer, number of prior chemotherapy regimens, number of prior platinum-based chemotherapy regimens, measurable disease at baseline, stratification variables of penultimate platinum-free interval and best response to last chemotherapy treatment, and molecular classifications based on HRD-based molecular status (BRCA mutant, BRCA wild-type/high LOH, BRCA wild-type/low LOH, BRCA wild-type/unknown LOH), mutations in the *RAD51C* or *RAD51D* genes, mutations in other homologous-recombination-repair genes, and archival methylation status in BRCA–wild-type patients (high methylation, low methylation, unmethylated, or not available). Race was also identified as a borderline significant factor (p=0.114).

Supplementary Table 6

Odds ratio estimates for variables identified as significant predictors by multivariate logistics regression model comparing exceptional benefit patients to all remaining patients enrolled in ARIEL3.

Effect	Comparison	Point estimate	95% Wald Confidence Limit
Treatment arm	Rucaparib versus placebo	13.823	4.913–38.897
PPFI	>12 months versus 6–12 months	2.021	1.161–3.518
Measurable disease at baseline	No versus yes	1.606	0.915–2.820
Molecular characteristic	BRCA mutant versus BRCA wild-type/LOH low	4.944	2.286–10.691
	BRCA wild-type/LOH high versus BRCA wild-type/LOH low	1.807	0.717–4.557
	BRCA wild-type/LOH unknown versus BRCA wild-type/LOH low	2.96	0.941–9.316
	RAD51C/D mutation versus BRCA wild-type/LOH low	15.256	3.74–62.237
	Other HRR gene mutation versus BRCA wild-type/LOH low	0.576	0.068–4.858

BRCA, *BRCA1* or *BRCA2*; DF, degrees of freedom; HRR, homologous recombination repair; LOH, loss of heterozygosity; PPFI, penultimate platinum-free interval.

Supplementary Table 7

Summary of TEAEs in the overall ARIEL3 safety population and the exceptional benefit subgroup.

	Rucaparib arm		Placebo arm	
TEAEs, n (%)	**Exceptional benefit subgroup (n=79)**	**Overall[a] (N=372)**	**Exceptional benefit subgroup (n=4)**	**Overall[a] (N=189)**
Any TEAE	79 (100)	372 (100)	4 (100)	182 (96.3)
Grade ≥3 TEAE	59 (74.7)	231 (62.1)	3 (75.0)	31 (16.4)
TEAE leading to discontinuation[b]	16 (20.3)	64 (17.2)	0	3 (1.6)
TEAE leading to dose modification	66 (83.5)	271 (72.8)	1 (25.0)	20 (10.6)
TEAE leading to treatment interruption	62 (78.5)	248 (66.7)	1 (25.0)	19 (10.1)
TEAE leading to dose reduction	55 (69.6)	209 (56.2)	1 (25.0)	8 (4.2)

TEAE, treatment-emergent adverse event.

Data cutoff date is December 31, 2019.

[a] Dean et al. *Ann Oncol*. 2020;31(suppl 4):abst 821P.

[b] Excluding disease progression.

Supplementary Table 8

Most frequently occurring any grade (≥20% overall) and grade ≥3 TEAEs in the overall ARIEL3 safety population and the exceptional benefit subgroup

	Rucaparib arm				Placebo arm			
TEAEs, n (%)	**Exceptional benefit subgroup (n=79)**		**Overall (N=372)**		**Exceptional benefit subgroup (n=4)**		**Overall (N=189)**	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
At least one TEAE	79 (100)	59 (74.7)	372 (100)	231 (62.1)	4 (100)	3 (75.0)	182 (96.3)	31 (16.4)
Asthenia/Fatigue	64 (81.0)	10 (12.7)	267 (71.8)	29 (7.8)	4 (100)	1 (25.0)	85 (45.0)	5 (2.6)
Nausea	61 (77.2)	4 (5.1)	284 (76.3)	14 (3.8)	3 (75.0)	0	70 (37.0)	1 (0.5)
Abdominal pain	40 (50.6)	5 (6.3)	120 (32.3)	12 (3.2)	1 (25.0)	0	50 (26.5)	1 (0.5)
Anemia and/or low/decreased hemoglobin	36 (45.6)	20 (25.3)	147 (39.5)	83 (22.3)	0	0	9 (4.8)	1 (0.5)
Constipation	34 (43.0)	2 (2.5)	140 (37.6)	7 (1.9)	2 (50.0)	0	44 (23.3)	2 (1.1)
ALT/AST Increased	34 (43.0)	13 (16.5)	133 (35.8)	39 (10.5)	0	0	6 (3.2)	0
Diarrhea	34 (43.0)	1 (1.3)	129 (34.7)	3 (0.8)	2 (50.0)	0	43 (22.8)	2 (1.1)
Thrombocytopenia and/or low/decreased platelets	31 (39.2)	3 (3.8)	111 (29.8)	21 (5.6)	0	0	5 (2.6)	0
Decreased appetite	27 (34.2)	1 (1.3)	94 (25.3)	3 (0.8)	0	0	25 (13.2)	0
Vomiting	26 (32.9)	4 (5.1)	139 (37.4)	16 (4.3)	0	0	29 (15.3)	2 (1.1)
Dysgeusia	25 (31.6)	0	148 (39.8)	0	0	0	13 (6.9)	0
Neutropenia and/or low/decreased ANC	24 (30.4)	10 (12.7)	76 (20.4)	32 (8.6)	1 (25.0)	0	9 (4.8)	2 (1.1)

ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Visit cutoff date is December 31, 2019. Data are sorted by decreasing incidence in the rucaparib exceptional benefit subgroup. There were no TEAEs of myelodysplastic syndrome or acute myeloid leukemia reported.

Supplementary Table 9

Incidence of myelodysplastic syndrome/acute myeloid leukemia in the ARIEL3 patient population

MDS/AML, n (%)	Rucaparib arm			Placebo arm		
	All	BRCA mutant[a]	BRCA wild-type	All	BRCA mutant[a]	BRCA wild-type
Overall	14/375 (3.7)	9/130 (6.9)	5/245 (2.0)	4/189 (2.1)	3/66 (4.5)	1/123 (0.8)
Exceptional benefit subgroup	9/79 (11.4)	7/46 (15.2)	2/33 (6.1)	0/4 (0)	0/3 (0)	0/1 (0)
All others	5/296 (1.7)	2/84 (2.4)	3/212 (1.4)	4/185 (2.2)	3/63 (4.8)	1/122 (0.8)

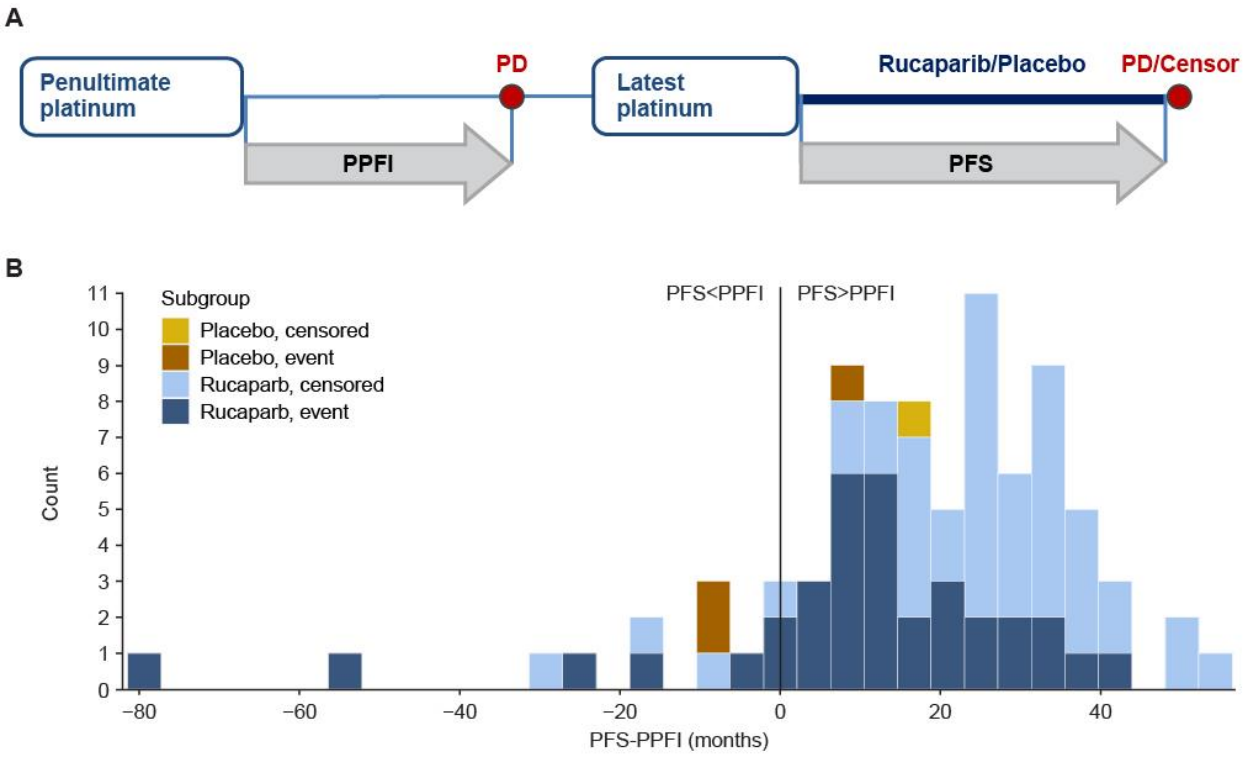
AML, acute myeloid leukemia; BRCA, *BRCA1* or *BRCA2*; MDS, myelodysplastic syndrome.

Visit cutoff date is December 19, 2020.

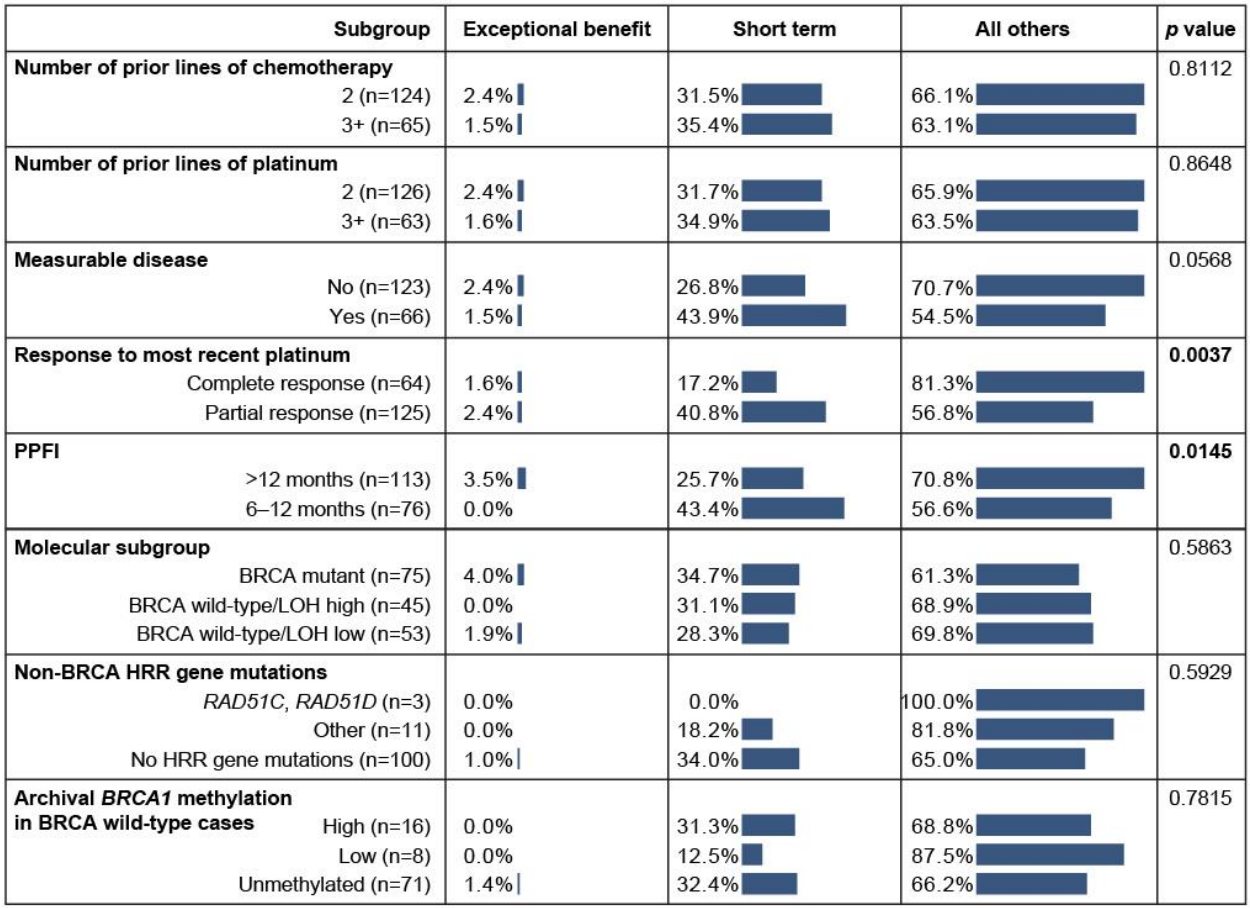
[a] Includes germline and somatic mutations.

Supplementary Figures

Supplementary Fig. 1. Analysis of PFS-PPFI differences in exceptional benefit patients. (A) A schematic showing simplified typical patient clinical history in ARIEL3 and the events that define the PPFI and PFS lengths. (B) Histogram showing the distributions of PFS-PPFI differences in ARIEL3 exceptional benefit patients. PD, progressive disease; PFS, progression-free survival; PPFI, penultimate platinum-free interval.

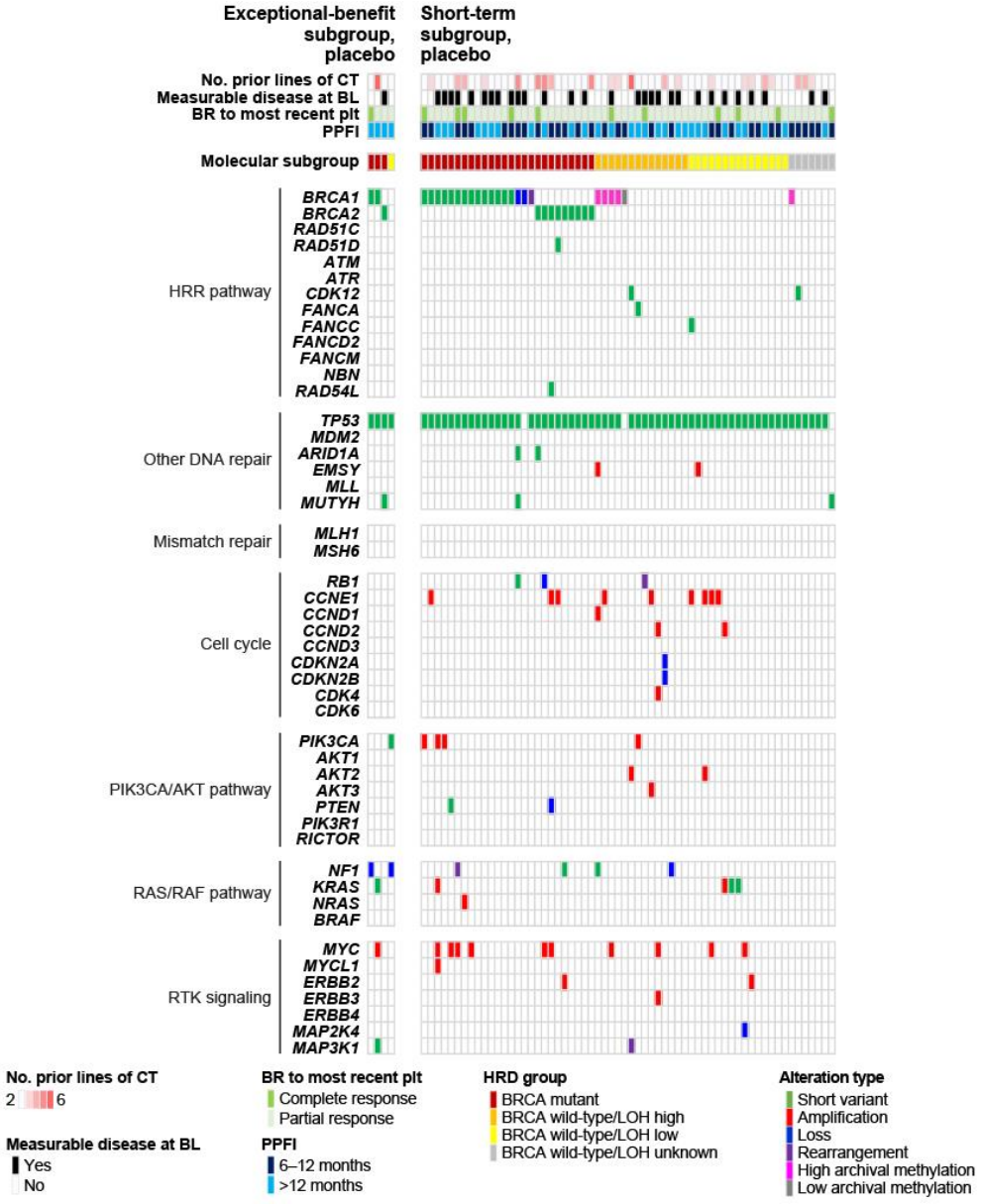


Supplementary Fig. 2. Frequencies of outcomes in placebo-arm patients with different baseline clinical and molecular characteristics. *p* values based on chi-square tests; bold denotes significant results ($p<0.05$). BRCA, *BRCA1* or *BRCA2*; HRR, homologous recombination repair; LOH, loss of heterozygosity; PPFI, penultimate platinum-free interval.



Subgroup	Exceptional benefit	Short term	All others	*p* value
Number of prior lines of chemotherapy				0.8112
2 (n=124)	2.4%	31.5%	66.1%	
3+ (n=65)	1.5%	35.4%	63.1%	
Number of prior lines of platinum				0.8648
2 (n=126)	2.4%	31.7%	65.9%	
3+ (n=63)	1.6%	34.9%	63.5%	
Measurable disease				0.0568
No (n=123)	2.4%	26.8%	70.7%	
Yes (n=66)	1.5%	43.9%	54.5%	
Response to most recent platinum				**0.0037**
Complete response (n=64)	1.6%	17.2%	81.3%	
Partial response (n=125)	2.4%	40.8%	56.8%	
PPFI				**0.0145**
>12 months (n=113)	3.5%	25.7%	70.8%	
6–12 months (n=76)	0.0%	43.4%	56.6%	
Molecular subgroup				0.5863
BRCA mutant (n=75)	4.0%	34.7%	61.3%	
BRCA wild-type/LOH high (n=45)	0.0%	31.1%	68.9%	
BRCA wild-type/LOH low (n=53)	1.9%	28.3%	69.8%	
Non-BRCA HRR gene mutations				0.5929
RAD51C, *RAD51D* (n=3)	0.0%	0.0%	100.0%	
Other (n=11)	0.0%	18.2%	81.8%	
No HRR gene mutations (n=100)	1.0%	34.0%	65.0%	
Archival *BRCA1* methylation in BRCA wild-type cases				0.7815
High (n=16)	0.0%	31.3%	68.8%	
Low (n=8)	0.0%	12.5%	87.5%	
Unmethylated (n=71)	1.4%	32.4%	66.2%	

Supplementary Fig. 3. Genetic and epigenetic alterations in exceptional benefit (left) and short-term (right) subgroup patients in the placebo arm. BL, baseline; BR, best response; BRCA, *BRCA1* or *BRCA2*; CT, chemotherapy; HRD, homologous recombination deficiency; HRR, homologous recombination repair; LOH, loss of heterozygosity; plt, platinum; PPFI, penultimate platinum-free interval.



Highlights (3–5 bullets; 125 characters max each [incl. spaces]):

- Clinical/molecular characteristics associated with exceptional benefit from rucaparib maintenance in ARIEL3 were explored.
- 21% of patients in the rucaparib arm derived exceptional benefit (PFS ≥2 years) compared with only 2% in the placebo arm.
- Clinical characteristics associated with exceptional outcomes on rucaparib were related to platinum sensitivity.
- *BRCA1*, *BRCA2*, *RAD51C,* and *RAD51D* mutations were associated with exceptional benefit from rucaparib.
- A diverse set of patients with high-grade ovarian carcinoma can derive exceptional benefit from rucaparib maintenance.