Integrated Efficacy and Safety Analysis of the Poly(ADP-Ribose) Polymerase (PARP) Inhibitor Rucaparib in Patients with High-Grade Ovarian Carcinoma (HGOC)

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BACKGROUND

- Approximately 18% of epithelial ovarian cancers harbor a germline *BRCA1* or *BRCA2* mutation (*BRCA*^{mut}); 7% harbor a somatic *BRCA*^{mut}[1]
- The PARP inhibitor rucaparib has demonstrated antitumor activity in the treatment setting in *BRCA*^{mut} HGOC in two phase 2 studies, Study 10 (NCT01482715) and ARIEL2 (NCT01891344)[2,3]
- Data from these two studies supported the accelerated approval of rucaparib (600 mg twice daily [BID]) by the United States Food and Drug Administration as a monotherapy for patients with *BRCA*^{mut} HGOC who have received ≥2 prior chemotherapy regimens[4,5]
- Here we present an update of the integrated efficacy and safety analysis of the combined data from Study 10 and ARIEL2

METHODS

Integrated Analysis Datasets

- All patients who enrolled in Study 10 Parts 1, 2A, or 3, or in ARIEL2 Part 1 were included in the analysis; patients who enrolled in ARIEL2 Part 2 by 1 Oct 2015 were also included in the analysis
- Eligibility criteria for the integrated safety population and integrated efficacy population are outlined in **Figure 1**
- All patients initiated oral rucaparib (600 mg BID) and were treated until disease progression or other reason for discontinuation

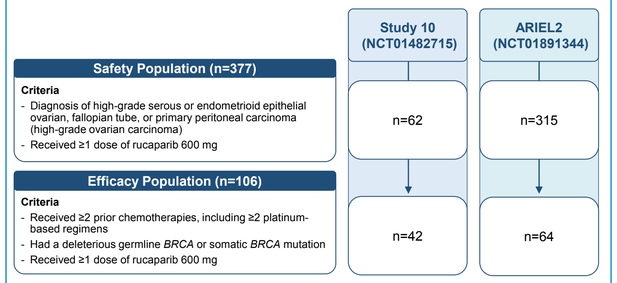
Integrated Efficacy Analysis Outcomes

- The primary outcome in the integrated efficacy analysis was investigator-assessed objective response rate (ORR) per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST), defined as the proportion of patients with a confirmed complete response or partial response on subsequent tumor assessment ≥28 days after the first response documentation
- Other integrated efficacy analyses included investigator-assessed best response in the sum of target lesions, duration of response, and progression-free survival (PFS)

Integrated Safety Analysis Outcomes

- Safety outcomes in the integrated analysis were adverse events (AEs) of any grade, grade ≥3 AEs, treatment-related AEs, AEs leading to dose modification (interruption and/or reduction), AEs leading to treatment discontinuation, and AEs leading to death

Figure 1. Efficacy and Safety Populations



Safety population visit cutoff date: 29 Apr 2016 (Study 10 Parts 1, 2A, and 3; ARIEL2 Parts 1 and 2).
Efficacy population visit cutoff date: 29 Apr 2016 (Study 10 Part 2A; ARIEL2 Parts 1 and 2).

RESULTS

Table 1. Patient Characteristics

Characteristic	Efficacy Population n=106	Safety Population n=377
Median age (range), years	59 (33–84)	62 (31–86)
ECOG Performance Status, n (%)		
0	65 (61.3)	233 (61.8)
1	41 (38.7)	144 (38.2)
Cancer type, n (%)		
Epithelial ovarian	91 (85.8)	305 (80.9)
Primary peritoneal	6 (5.7)	39 (10.3)
Fallopian tube	9 (8.5)	33 (8.8)
Histology, n (%)		
Serous	97 (91.5)	355 (94.2)
Endometrioid	3 (2.8)	9 (2.4)
Mixed	5 (4.7)	11 (2.9)
Other (including unknown)	1 (0.9)	2 (0.5)
BRCA mutation, n (%)		
Germline	88 (83.0)	108 (28.6)
Somatic	18 (17.0)	28 (7.4)
Origin uncertain	0	7 (1.9)
No mutation	0	234 (62.1)
BRCA gene mutation, n (%)		
BRCA1	67 (63.2)	89 (23.6)
BRCA2	39 (36.8)	54 (14.3)
No mutation	0	234 (62.1)
Median no. of prior chemotherapies (range)[a]	3 (2–6)	2 (1–7)
1 prior therapy, n (%)	0	127 (33.7)
2 prior therapies, n (%)	41 (38.7)	85 (22.5)
≥3 prior therapies, n (%)	65 (61.3)	165 (43.8)
Median no. of platinum-based therapies (range)[a]	2 (2–5)	2 (1–5)
1 prior platinum-based therapy, n (%)	0	131 (34.7)
2 prior platinum-based therapies, n (%)	60 (56.6)	144 (38.2)
≥3 prior platinum-based therapies, n (%)	46 (43.4)	102 (27.1)
PFI from latest platinum regimen, n (%)		
>12 months	23 (21.7)	129 (34.2)
6–12 months	55 (51.9)	152 (40.3)
<6 months	28 (26.4)	90 (23.9)
Missing	0	6 (1.6)
Platinum response (most recent therapy), n (%)		
Sensitive (PD ≥6 months after last platinum dose)	78 (73.6)	283 (75.1)
Resistant (PD <6 months after last platinum dose)	21 (19.8)	67 (17.8)
Refractory (progression on platinum, PFI <2 months)	7 (6.6)	26 (6.9)
Unknown	0	1 (0.3)

[a]Therapies given during the same time frame are considered 1 regimen; neoadjuvant and adjuvant treatments given before and after surgery constitute 1 regimen; maintenance treatments are considered to be part of the same regimen that preceded it.
Efficacy population visit cutoff date: 29 Apr 2016 (Study 10 Part 2A; ARIEL2 Parts 1 and 2).
Safety population visit cutoff date: 29 Apr 2016 (Study 10 Parts 1, 2A, and 3; ARIEL2 Parts 1 and 2).
ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PFI, progression-free interval.

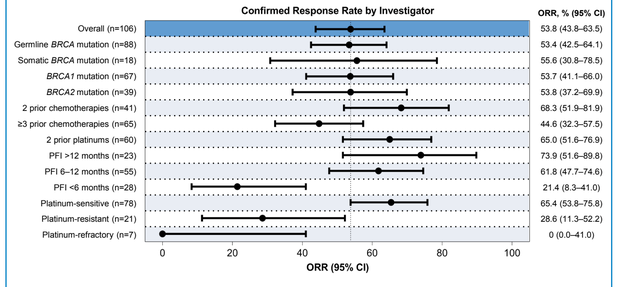
Integrated Efficacy Population

Table 2. Investigator-Assessed ORR in the Efficacy Population

Parameter	Study 10 n=42	ARIEL2 n=64	Efficacy Population n=106
	n (%) [95% CI]		
Investigator-assessed RECIST ORR (confirmed CR+PR)	25 (59.5) [43.3–74.4]	32 (50.0) [37.2–62.8]	57 (53.8) [43.8–63.5]
CR	4 (9.5)	5 (7.8)	9 (8.5)
PR	21 (50.0)	27 (42.2)	48 (45.3)
SD	12 (28.6)	24 (37.5)	36 (34.0)
PD	2 (4.8)	7 (10.9)	9 (8.5)
NE	3 (7.1)	1 (1.6)	4 (3.8)
Investigator-assessed RECIST/ GCIG CA-125 ORR	35 (83.3) [68.6–93.0]	39 (60.9) [47.9–72.9]	74 (69.8) [60.1–78.4]

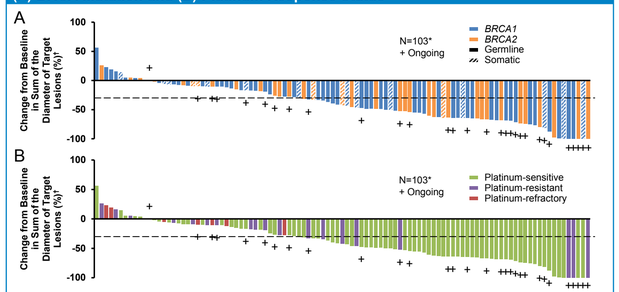
Efficacy population visit cutoff date: 29 Apr 2016 (Study 10 Part 2A; ARIEL2 Parts 1 and 2).
CA-125, cancer antigen 125; CI, confidence interval; CR, complete response; GCIG, Gynecologic Cancer InterGroup; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Figure 2. Investigator-Assessed ORR in Subgroups of the Efficacy Population



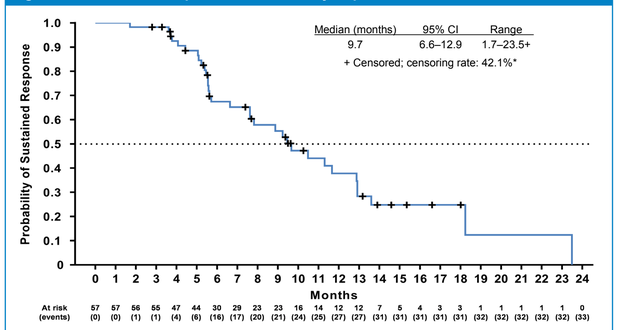
Efficacy population visit cutoff date: 29 Apr 2016 (Study 10 Part 2A; ARIEL2 Parts 1 and 2).
CI, confidence interval; ORR, objective response rate; PFI, progression-free interval.

Figure 3. Best Response for Target Lesions in the Efficacy Population by (A) *BRCA* Mutation and (B) Platinum Response Status



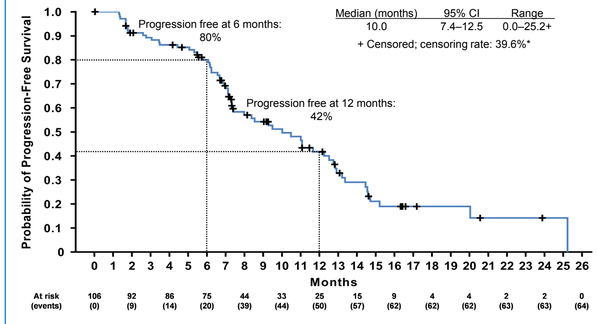
The majority of patients (88.3%) had a decrease in the sum of the diameter of target lesions from baseline, with most decreases being ≥30%.
*Three patients did not have a postbaseline scan. †For unconfirmed responses; includes the best percent change from baseline up to and including the first overall response of progressive disease.
Efficacy population visit cutoff date: 29 Apr 2016 (Study 10 Part 2A; ARIEL2 Parts 1 and 2).

Figure 4. Duration of Response in the Efficacy Population



*Of the 57 patients with a response, 24 did not have an event of disease progression or death at the data cutoff date; of these 24 patients, 16 were still on treatment and 8 discontinued treatment for reasons other than disease progression or death at the data cutoff date.
Efficacy population visit cutoff date: 29 Apr 2016 (Study 10 Part 2A; ARIEL2 Parts 1 and 2). Data were censored at the date of the last postbaseline scan for patients who had an ongoing response at the time of data cutoff.
CI, confidence interval.

Figure 5. Progression-Free Survival in the Efficacy Population



When stratified by response to most recent platinum-based therapy, median progression-free survival was 11.1 months (95% CI, 8.4–12.9) for patients who were platinum-sensitive (n=78), 7.4 months (95% CI, 5.8–NYR) for patients who were platinum-resistant (n=21), and 5.3 months (95% CI, 1.7–NYR) for patients who were platinum-refractory (n=7).

*Of 106 patients, 42 did not have an event of disease progression or death at the data cutoff date; of these 42 patients, 23 were still on treatment and 19 discontinued treatment for reasons other than disease progression or death at the data cutoff date.
Efficacy population visit cutoff date: 29 Apr 2016 (Study 10 Part 2A; ARIEL2 Parts 1 and 2). Data were censored at the last tumor assessment for patients without documented progression.
CI, confidence interval; NYR, not yet reached.

Integrated Safety Population

- Median duration of rucaparib treatment in the integrated safety population was 5.5 months (range, 0.1–28.0)
- Median dose intensity (actual dose received/first dose received) was 0.93 (range, 0.1–1.3)

Table 3. Safety Summary: All Ovarian Cancer Patients Who Received ≥1 Dose of Rucaparib 600 mg

Parameter	Ovarian Cancer Patients, n (%) n=377
Any AE	377 (100.0)
Treatment-related AE	360 (95.5)
Any grade ≥3 AE	232 (61.5)
Treatment-related grade ≥3 AE	178 (47.2)
AE leading to dose modification (interruption or reduction)	245 (65.0)
AE leading to dose interruption	222 (58.9)
AE leading to dose reduction	173 (45.9)
Treatment-related AE leading to dose reduction	167 (44.3)
AE leading to treatment discontinuation[a]	53 (14.1)
Treatment-related AE leading to discontinuation	30 (8.0)
Any AE leading to death	9 (2.4)
Malignant neoplasm progression	8 (2.1)
Nonprogression AE leading to death	1 (0.3)[b]

[a]Excludes patients who discontinued due to disease progression. [b]One patient, who had progressed radiologically, died of sepsis, which was assessed by the investigator as not related to rucaparib.
Safety population visit cutoff date: 29 Apr 2016 (Study 10 Parts 1, 2A, and 3; ARIEL2 Parts 1 and 2).
AE, adverse event.

- Primary reasons for dose reduction: anemia/decreased hemoglobin (17.2%), asthenia/fatigue (14.1%), and nausea (11.1%)
- Primary reasons for treatment discontinuation: asthenia/fatigue (2.4%), small intestinal obstruction (1.6%), nausea (1.3%), and thrombocytopenia/decreased platelets (1.3%)

Table 4. Treatment-Emergent Adverse Events: ≥20% Any Grade

Term	Ovarian Cancer Patients n=377	
	Any Grade, n (%)	Grade 3/4, n (%)
Nausea	290 (76.9)	19 (5.0)
Asthenia/fatigue[a]	290 (76.9)	42 (11.1)
Vomiting	174 (46.2)	15 (4.0)
Anemia[a]	165 (43.8)	94 (24.9)
ALT/AST increased[a]	156 (41.4)	41 (10.9)
Constipation	150 (39.8)	6 (1.6)
Decreased appetite	149 (39.5)	11 (2.9)
Dysgeusia	148 (39.3)	1 (0.3)
Diarrhea	130 (34.5)	9 (2.4)
Abdominal pain	120 (31.8)	13 (3.4)
Dyspnea	80 (21.2)	2 (0.5)
Thrombocytopenia[a]	80 (21.2)	18 (4.8)
Blood creatinine increased	79 (21.0)	2 (0.5)

[a]Combined terms.
Safety population visit cutoff date: 29 Apr 2016 (Study 10 Parts 1, 2A, and 3; ARIEL2 Parts 1 and 2).
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 5. Laboratory Abnormalities: Shifts from Baseline

Term	Ovarian Cancer Patients n=375[a]	
	Any Worsening Shift in Grade from Baseline, n (%)	Maximum Shift to Grade 3/4, n (%)
Increase in creatinine	347 (92.5)	5 (1.3)
Increase in ALT	280 (74.7)	47 (12.5)
Increase in AST	277 (73.9)	17 (4.5)
Decrease in hemoglobin	251 (66.9)	88 (23.5)
Decrease in lymphocytes[b]	169 (45.6)	26 (7.0)
Increase in cholesterol[c]	150 (41.0)	9 (2.5)
Decrease in platelets	147 (39.2)	24 (6.4)
Decrease in neutrophils	133 (35.5)	37 (9.9)

[a]Data shown for patients with both baseline and postbaseline results. [b]n=371. [c]n=366.
Safety population visit cutoff date: 29 Apr 2016 (Study 10 Parts 1, 2A, and 3; ARIEL2 Parts 1 and 2).
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- Elevations in creatinine likely result from potent inhibition by rucaparib of the renal transporters MATE1 and MATE2-K
- Alanine and aspartate aminotransferase levels normalized over time with continued treatment and were not accompanied by an elevation in bilirubin
- Acute myeloid leukemia and myelodysplastic syndrome were reported in 1 patient each (<1%) after 57 and 539 days of rucaparib treatment
  - Both patients had received prior platinum-based therapy and neither patient had a *BRCA*^{mut}

CONCLUSIONS

- Rucaparib is active in patients with germline or somatic *BRCA*^{mut} HGOC who have received ≥2 prior chemotherapies in the treatment setting
  - Response rates were highest in patients who had disease progression ≥6 months after last platinum (65.4%) or were limited to 2 prior lines of therapy (68.3%)
  - Response to rucaparib was durable (median duration of response, 9.7 months; 95% confidence interval, 6.6–12.9)
- Treatment-emergent AEs were managed with dose modification, including treatment interruption (58.9%) or dose reduction (45.9%)
- Rucaparib (600 mg BID) is approved in the United States as a monotherapy for patients with *BRCA*^{mut} HGOC who have received ≥2 prior chemotherapy regimens[5]
- Two randomized, phase 3 confirmatory trials are ongoing:
  - In the maintenance setting in patients with relapsed HGOC (ARIEL3; NCT01968213)
  - In the treatment setting in comparison to standard chemotherapy in patients with relapsed, *BRCA*^{mut} HGOC (ARIEL4; NCT02855944)

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ACKNOWLEDGMENTS

The authors would like to acknowledge all patients and their families and caregivers who are participating in the Study 10 and ARIEL2 trials, along with the investigators. Medical writing and editorial support funded by Clovis Oncology, Inc., were provided by Nathan Yardley, PhD, and Shannon Davis of Ashfield Healthcare Communications.