

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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Poster 096

BACKGROUND

- Approximately 18% of epithelial ovarian cancers harbor a germline *BRCA1* or *BRCA2* mutation (*BRCA*^{mut}); 7% harbor a somatic *BRCA*^{mut}
- 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}

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

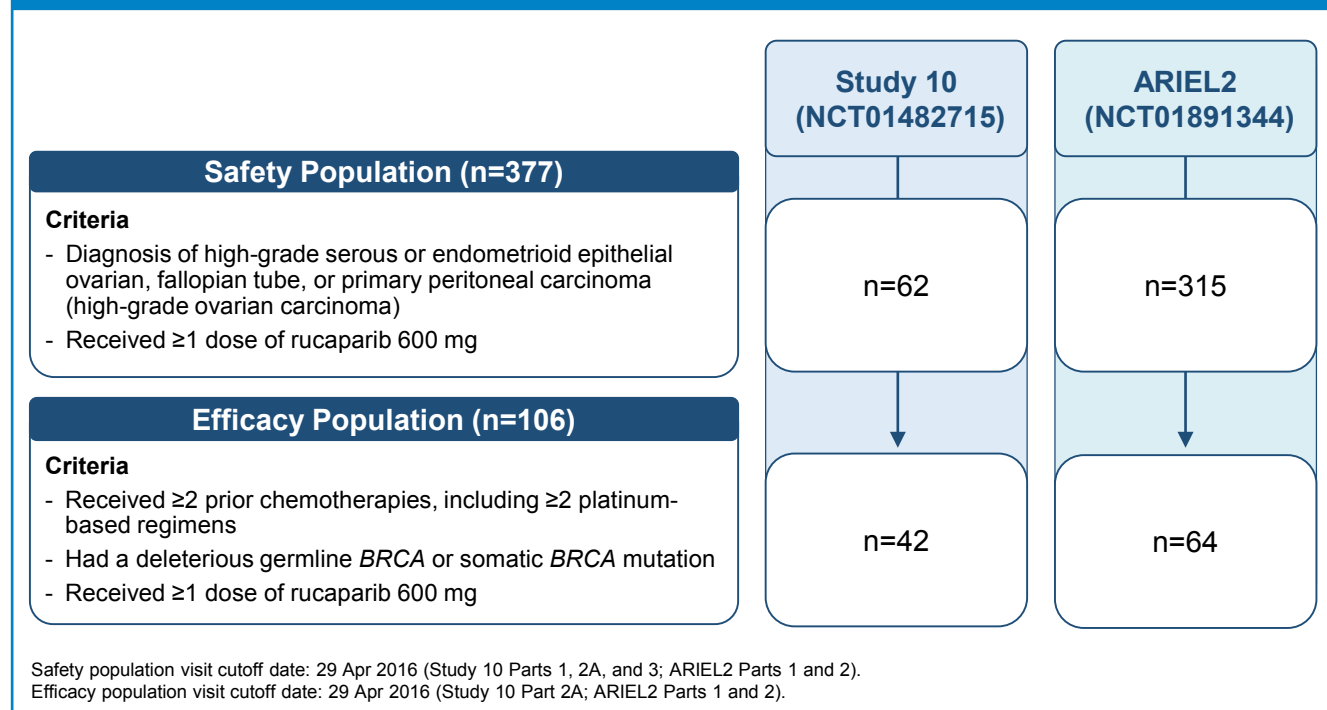
- The primary outcome in the integrated efficacy analysis was investigator-assessed objective response rate (ORR) per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST), defined as the proportion of patients with a confirmed complete response or partial response on subsequent tumor assessment ≥ 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

- 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

Figure 1. Efficacy and Safety Populations



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) |
| <i>BRCA</i> 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) |
| <i>BRCA</i> gene mutation, n (%) | | |
| <i>BRCA1</i> | 67 (63.2) | 89 (23.6) |
| <i>BRCA2</i> | 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) |

^aTherapies 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 |
|--|--------------------------|--------------------------|------------------------------|
| 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

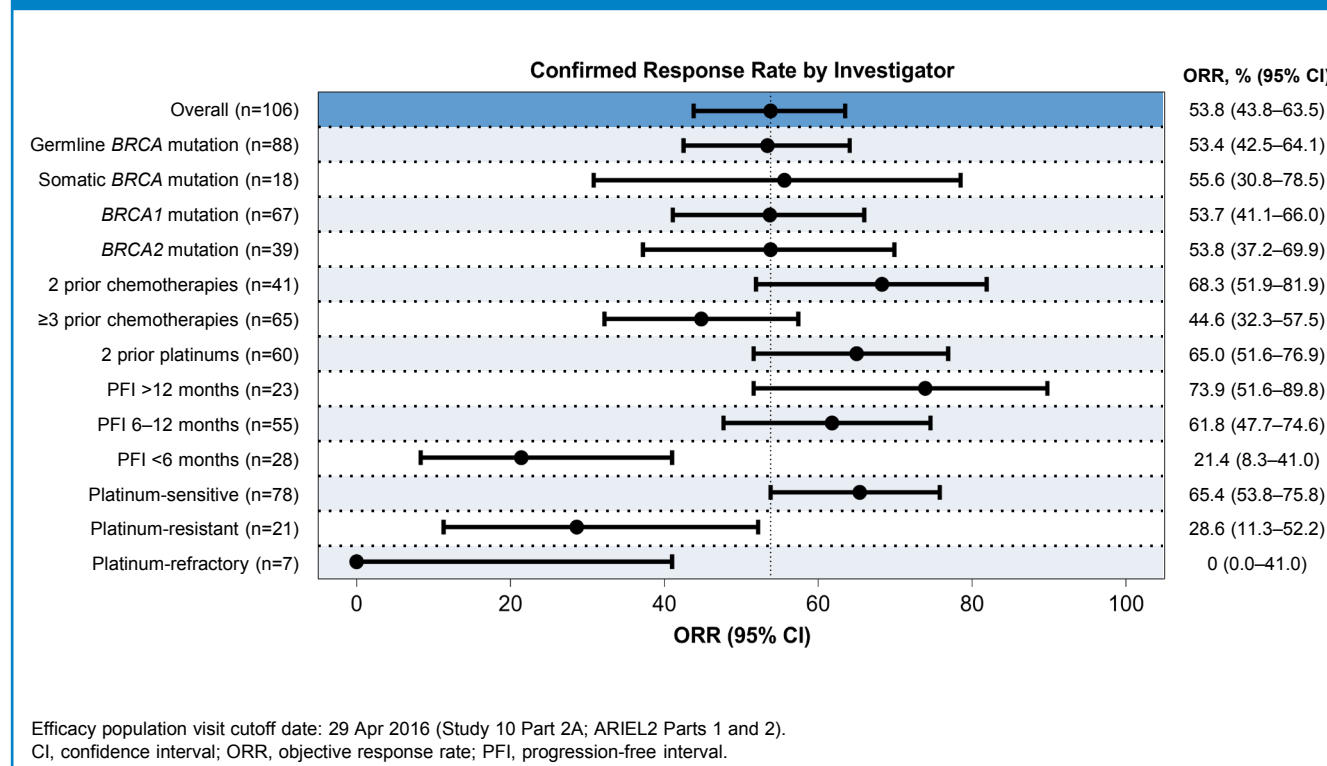


Figure 3. Best Response for Target Lesions in the Efficacy Population by (A) *BRCA* Mutation and (B) Platinum Response Status

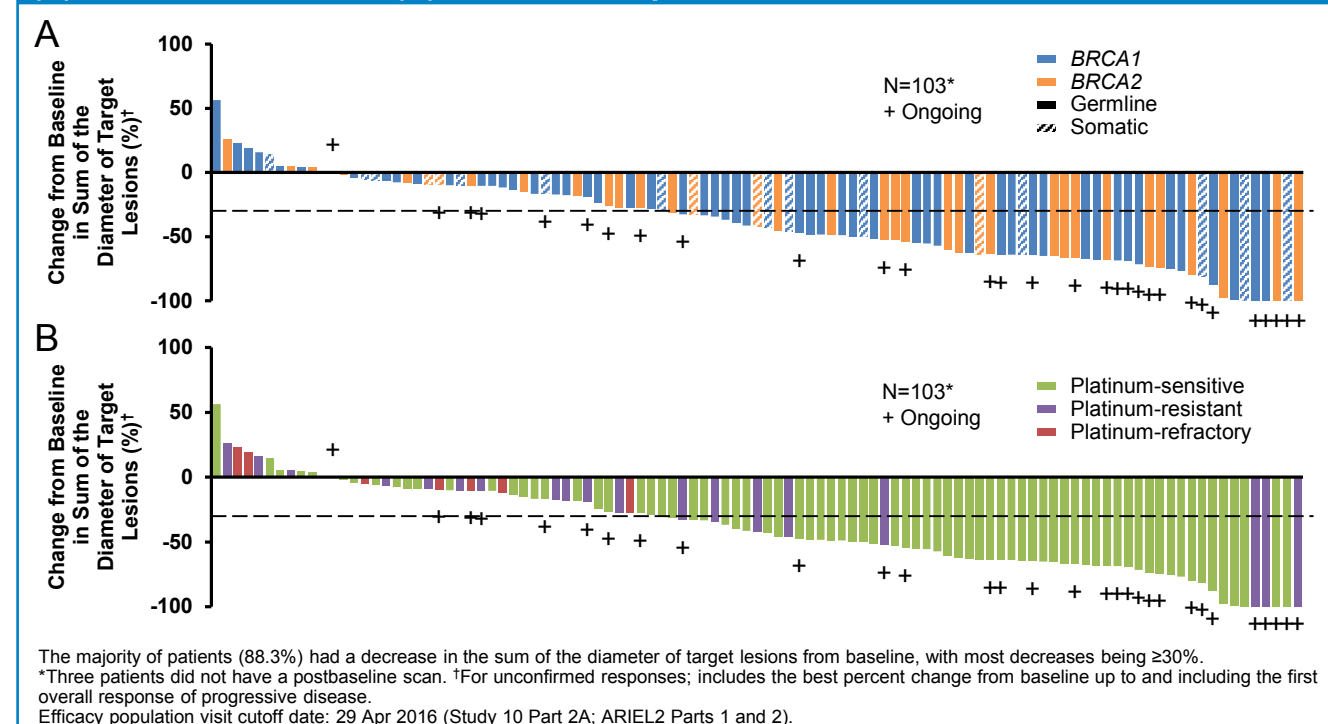


Figure 4. Duration of Response in the Efficacy Population

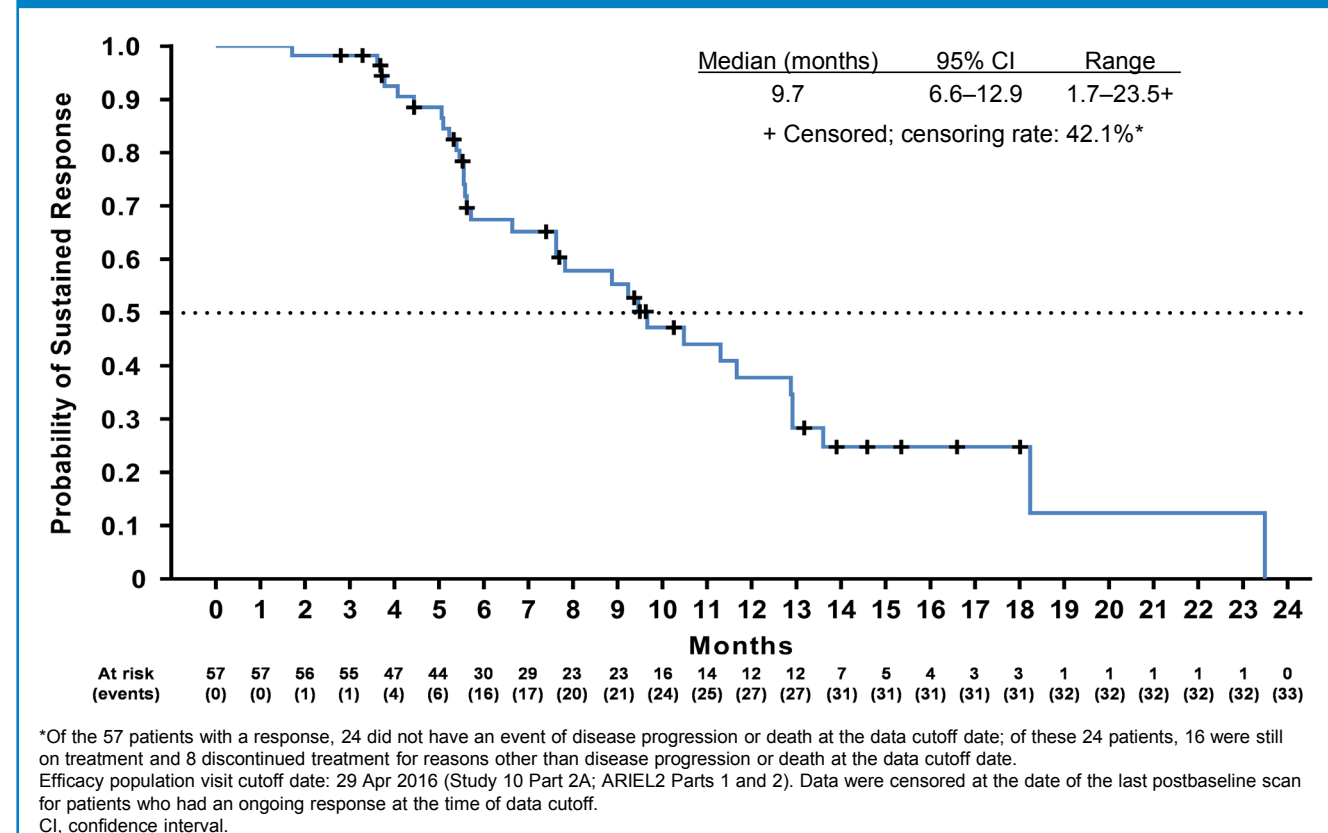
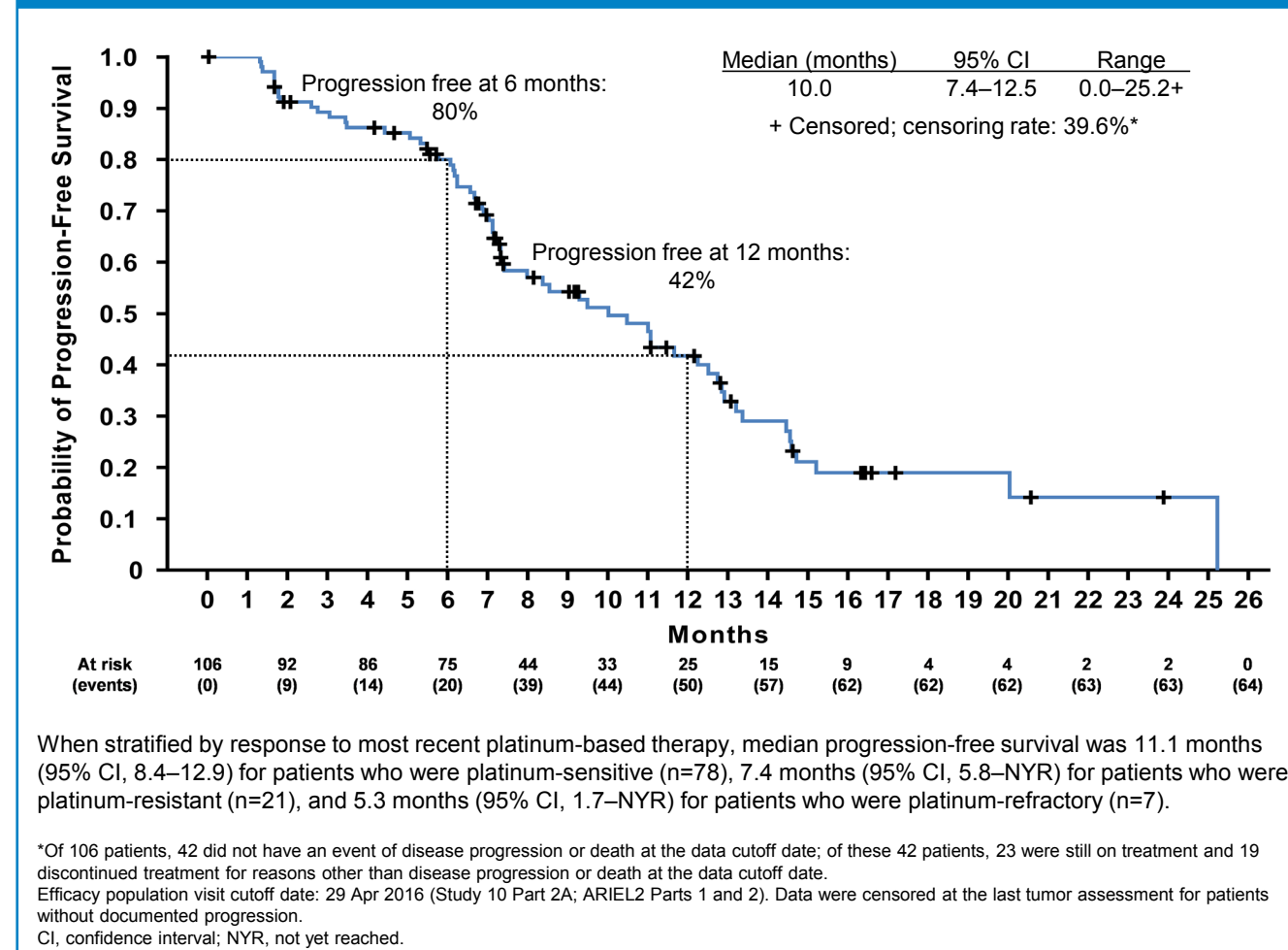


Figure 5. Progression-Free Survival in the Efficacy Population



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 (%) |
|---|--------------------------------|
| 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 |

- 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: $\geq 20\%$ 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) |

^aCombined 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) |

- 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 regimens⁵
- 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)

REFERENCES

- Pennington KP et al. Clin Cancer Res. 2014;20:764-75.
- Shapira-Frommer R et al. Eur J Cancer. 2015;51:3545; abstract 8560.
- Swisher EM et al. Lancet Oncol. 2017;18:75-87.
- Kristeleit RS et al. Ann Oncol. 2016;27(suppl 6):abstract 8560.
- Rubraca (rucaparib) tablets [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2016.

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