



Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic *BRCA1* or *BRCA2* mutation: Integrated analysis of data from Study 10 and ARIEL2

Amit M. Oza^{a,*}, Anna V. Tinker^b, Ana Oaknin^c, Ronnie Shapira-Frommer^d, Iain A. McNeish^e, Elizabeth M. Swisher^f, Isabelle Ray-Coquard^g, Katherine Bell-McGuinn^{h,1}, Robert L. Colemanⁱ, David M. O'Malley^j, Alexandra Leary^k, Lee-may Chen^l, Diane Provencher^m, Ling Maⁿ, James D. Brenton^o, Gottfried E. Konecny^p, Cesar M. Castro^q, Heidi Giordano^r, Lara Maloney^r, Sandra Goble^r, Kevin K. Lin^r, James Sun^s, Mitch Raponi^r, Lindsey Rolfe^r, Rebecca S. Kristeleit^t

^a Princess Margaret Cancer Centre, University Health Network, 610 University Avenue, Toronto M5G 2M9, Canada

^b Division of Medical Oncology, Vancouver Cancer Centre, British Columbia Cancer Agency, 600 West 10th Avenue, Vancouver V5N4E6, Canada

^c Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, 119-129, 08035 Barcelona, Spain

^d Sheba Medical Center, Emek HaEla St 1, 52621 Ramat Gan, Israel

^e Institute of Cancer Sciences, University of Glasgow, Wolfson Wohl Cancer Research Centre, Glasgow G61 1QH, UK

^f Department of Obstetrics and Gynecology, University of Washington, 1959 NE Pacific St, Seattle, WA 98195, USA

^g GINECO, Centre Léon Bérard and University Claude Bernard, 28 rue Laennec, 69373 Lyon, France

^h Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA

ⁱ The University of Texas MD Anderson Cancer Center, 1155 Herman Pressler Dr., CPB6.3590, Houston, TX 77030, USA

^j The Ohio State University, James Cancer Center, M210 Starling Loving, 320 W 10th Ave, Columbus, OH 43210, USA

^k GINECO, Gynecological Unit, Department of Medicine, Gustave Roussy Cancer Center and INSERM U981, 114 Rue Edouard-Vaillant, 94805 Villejuif, France

^l Department of Obstetrics, Gynecology, and Reproductive Sciences, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, 550 16th St., 7th Floor, San Francisco, CA 94143-1702, USA

^m Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Institut du cancer de Montréal, Department of Obstetrics and Gynecology, Université de Montréal, 1560 rue Sherbrooke Est, Montreal H2L 4M1, Canada

ⁿ Rocky Mountain Cancer Centers, 11750 W 2nd Pl #150, Lakewood, CO 80228, USA

^o Cancer Research UK Cambridge Institute, University of Cambridge, Li Ka Shing Centre, Cambridge, CB2 0RE, UK

^p David Geffen School of Medicine, University of California Los Angeles, 2825 Santa Monica Blvd, Suite 200, Santa Monica, CA 90404, USA

^q Massachusetts General Hospital Cancer Center, Harvard Medical School, 185 Cambridge St, 5th floor, Boston, MA 02114, USA

^r Clovis Oncology, Inc., 5500 Flatiron Parkway, Boulder, CO 80301, USA

^s Foundation Medicine, Inc., 150 Second St, Cambridge, MA 02141, USA

^t University College London Cancer Institute, 72 Huntley St, London WC1E 6BT, UK

HIGHLIGHTS

- Oral rucaparib (600 mg BID) is efficacious in advanced relapsed ovarian carcinoma.
- The objective response rate was 54% in *BRCA1/2*-mutated ovarian carcinoma.
- Median duration of response was 9.2 months (95% confidence interval, 6.6–11.6).
- Rucaparib had a manageable safety profile in women with advanced ovarian carcinoma.

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ABSTRACT

Objective. An integrated analysis was undertaken to characterize the antitumor activity and safety profile of the oral poly(ADP-ribose) polymerase inhibitor rucaparib in patients with relapsed high-grade ovarian carcinoma (HGOC).

Methods. Eligible patients from Study 10 (NCT01482715) and ARIEL2 (NCT01891344) who received a starting dose of oral rucaparib 600 mg twice daily (BID) with or without food were included in these analyses. The

* Corresponding author.

E-mail address: amit.oza@uhn.ca (A.M. Oza).

¹ Dr. Bell-McGuinn's current affiliation is Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA, but the current work was completed during her time with Memorial Sloan Kettering Cancer Center.

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Somatic, germline *BRCA* mutation

integrated efficacy population included patients with HGOC and a deleterious germline or somatic *BRCA1* or *BRCA2* (*BRCA1/2*) mutation who received at least two prior chemotherapies and were sensitive, resistant, or refractory to platinum-based chemotherapy. The primary endpoint was investigator-assessed confirmed objective response rate (ORR). Secondary endpoints included duration of response (DOR) and progression-free survival (PFS). The integrated safety population included patients with HGOC who received at least one dose of rucaparib 600 mg BID, irrespective of *BRCA1/2* mutation status and prior treatments.

Results. In the efficacy population ($n = 106$), ORR was 53.8% (95% confidence interval [CI], 43.8–63.5); 8.5% and 45.3% of patients achieved complete and partial responses, respectively. Median DOR was 9.2 months (95% CI, 6.6–11.6). In the safety population ($n = 377$), the most frequent treatment-emergent adverse events (AEs) were nausea, asthenia/fatigue, vomiting, and anemia/hemoglobin decreased. The most common grade ≥ 3 treatment-emergent AE was anemia/hemoglobin decreased. Treatment-emergent AEs led to treatment interruption, dose reduction, and treatment discontinuation in 58.6%, 45.9%, and 9.8% of patients, respectively. No treatment-related deaths occurred.

Conclusions. Rucaparib has antitumor activity in advanced *BRCA1/2*-mutated HGOC and a manageable safety profile.

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1. Introduction

The 17-member poly(ADP-ribose) polymerase (PARP) superfamily of nuclear enzymes includes PARP1, PARP2, and PARP3, which are activated by DNA damage and are key mediators in the repair of single-strand breaks [1]. Inhibition of PARP1, PARP2, and PARP3 results in collapsed DNA replication forks and development of double-strand breaks [2,3], which require repair through the *BRCA1*- and *BRCA2*-mediated homologous recombination repair pathway [4–6]. Defects in the homologous recombination repair pathway—for example, a deleterious *BRCA1* or *BRCA2* (*BRCA1/2*) mutation—cause homologous recombination deficiency (HRD) and can selectively sensitize tumors to PARP inhibition through synthetic lethality [1,7,8]. It is estimated that up to half of high-grade serous ovarian carcinomas may exhibit HRD, with 18% harboring a germline *BRCA1/2* mutation and 7% a somatic *BRCA1/2* mutation [9].

Rucaparib (formerly known as CO-338, AG-014447, and PF-01367338) is an oral, small molecule inhibitor of PARP1, PARP2, and PARP3 [10–12]. In preclinical studies, increased rucaparib-induced cytotoxicity was observed in tumor cell lines with a *BRCA1/2* mutation, epigenetically silenced *BRCA1*, or other DNA repair deficiency [13]. In mouse xenograft models, rucaparib has been shown to slow growth of tumors with a deficiency in *BRCA1/2* [13]. In vitro studies have shown that rucaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death [14]. Recently, two international clinical trials—Study 10 (CO-338-010, NCT01482715) [15] and ARIEL2 (CO-338-017, NCT01891344) [16]—demonstrated the antitumor activity of rucaparib in patients with relapsed high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal carcinoma (high-grade ovarian carcinoma [HGOC]) and a deleterious *BRCA1/2* mutation (germline in Study 10; germline or somatic in ARIEL2).

Here, we report integrated analyses of data from Study 10 and ARIEL2 that further characterize the antitumor activity and safety of rucaparib at a starting dose of 600 mg twice daily (BID) in patients with HGOC and a deleterious germline or somatic *BRCA1/2* mutation who received at least two prior chemotherapies.

2. Methods

2.1. Constituent study designs

Study 10 and ARIEL2 enrolled patients aged 18 years or older, with a life expectancy of at least 3 months, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and adequate organ function. All patients provided written informed consent.

Study 10 is a three-part, open-label, phase I/II study of oral rucaparib given until disease progression or unacceptable toxicity. Part 1 was conducted in patients with a relapsed advanced solid tumor (a known *BRCA1/2* mutation was not required) and established rucaparib 600 mg BID as the recommended dose for phase II and phase III evaluation. Part 1 also established that rucaparib could be taken with or without food. Part 2A enrolled patients with platinum-sensitive (disease progression ≥ 6 months after last dose of platinum) relapsed HGOC and a germline *BRCA1/2* mutation (detected by local testing) who had received two to four prior therapies. The primary endpoint in Part 2A was confirmed investigator-assessed objective response rate (ORR) per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST); secondary endpoints included duration of response (DOR), progression-free survival (PFS), and safety. Part 2B of the study enrolled patients with platinum-sensitive, -resistant, or -refractory HGOC with a germline or somatic *BRCA1/2* mutation who received three to four prior chemotherapy regimens. The primary endpoint in Part 2B is investigator-assessed ORR. No patients were enrolled in Study 10 Part 2B prior to the enrollment cutoff date of October 1, 2015; thus no data for patients enrolled in Part 2B are included in this analysis. Part 3 enrolled patients with a relapsed solid tumor and a germline or somatic *BRCA1/2* mutation (detected by local or central testing) for assessment of the pharmacokinetic and safety profiles of a higher dose tablet of rucaparib.

ARIEL2 is a two-part, phase II, open-label study of oral rucaparib 600 mg BID given until disease progression, unacceptable toxicity, or death in patients with relapsed HGOC. A known *BRCA1/2* mutation was not required in ARIEL2; tumor *BRCA1/2* status was determined centrally using the Foundation Medicine FoundationFocus™ CDx_{BRCA} assay (Foundation Medicine, Inc., Cambridge, MA, USA) [17] and germline testing of DNA extracted from blood was performed using BROCA-homologous recombination sequencing assay (University of Washington, Seattle, WA, USA) [16,18]. A somatic *BRCA1/2* mutation was defined as a mutation detected in the DNA extracted from tumor tissue but not from blood. For all mutations, biallelic inactivation of *BRCA1/2* genes was demonstrated through germline or somatic *BRCA1/2* mutation at one allele and loss of heterozygosity of the other allele. Part 1 enrolled patients with platinum-sensitive, relapsed HGOC who had received at least one prior platinum-based regimen and had platinum-sensitive disease. Part 2 is enrolling patients with relapsed HGOC who had received at least three, but not more than four, prior chemotherapies and had a treatment-free interval of >6 months following first-line chemotherapy. Patients in Part 2 could be platinum-sensitive (disease progression ≥ 6 months after last platinum), platinum-resistant (disease progression <6 months after last platinum, with best response other than progressive disease [PD]), or platinum-refractory (best response of PD on last platinum with progression-free interval [PFI] <2 months).

In both trials, treatment interruptions and dose reductions were permitted: for patients who received a 600 mg BID starting dose of

rucaparib in Study 10 Parts 1 and 2A or ARIEL2 Part 1, dose reduction steps were in 120 mg BID increments (e.g., 600 mg BID to 480 mg BID) down to 240 mg BID. In Study 10 Part 3 and ARIEL2 Part 2, dose reduction steps were in 100 mg BID increments down to 300 mg BID.

In both trials, patients with mild hepatic impairment (defined as alanine/aspartate aminotransferase [ALT/AST] > upper limit of normal [ULN] with total bilirubin ≤ ULN or any ALT/AST level with total bilirubin > 1.0–1.5 × ULN) were permitted to enroll. Patients with moderate (defined as ALT/AST level and total bilirubin > 1.5–3 × ULN) or severe (defined as any ALT/AST level and total bilirubin > 3 × ULN) hepatic impairment were excluded.

2.2. Integrated analysis datasets

The integrated efficacy population included patients from Study 10 (Part 2A only) and ARIEL2 (Parts 1 and 2) who met the following eligibility criteria: diagnosis of ovarian carcinoma (inclusive of primary peritoneal and fallopian tube carcinoma); received at least one dose of rucaparib 600 mg; received at least two prior chemotherapies, including at least two platinum-based therapies; and had a deleterious *BRCA1/2* mutation (germline *BRCA1/2* mutation in Study 10; germline or somatic *BRCA1/2* mutation in ARIEL2) (Fig. S1, Supplementary Data).

To enable a comprehensive evaluation of rucaparib safety in patients with ovarian carcinoma, the integrated safety population included Study 10 (Parts 1, 2A, and 3) and ARIEL2 (Parts 1 and 2) patients with a diagnosis of ovarian carcinoma (inclusive of primary peritoneal and fallopian tube carcinoma) who had taken at least one dose of rucaparib 600 mg. Patients were included in the integrated safety population irrespective of their *BRCA1/2* mutation status and number or type of prior therapies.

For both integrated analyses, the study enrollment cutoff date was October 1, 2015. The efficacy analysis visit cutoff dates were November 30, 2015 (Study 10 Part 2A), and February 29, 2016 (ARIEL2 Parts 1 and 2). The safety analysis visit cutoff dates were March 31, 2016 (Study 10 Parts 1, 2A, and 3) and April 29, 2016 (ARIEL2 Parts 1 and 2).

2.3. Integrated efficacy analysis outcomes

The primary outcome of interest in the integrated efficacy analysis was investigator-assessed ORR per RECIST, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) on subsequent tumor assessment at least 28 days after the first response documentation [19].

In Study 10 and ARIEL2, tumor assessments included clinical examination and appropriate imaging techniques (preferably computed tomography scans of chest, abdomen, and pelvis, with slice thickness per RECIST); other methods (e.g., magnetic resonance imaging) were utilized if required. In Study 10, assessments were performed at screening, at the end of every 6 weeks (± 7 days) of treatment until week 18, and every 9 weeks (± 7 days) thereafter; if an initial CR or PR was noted after week 18, confirmatory scans were performed 4 to 6 weeks later. In ARIEL2, assessments were performed at screening and at the end of every 8 weeks (± 4 days) of treatment, although for patients who had been on study for at least 18 months, the frequency of tumor assessments could be reduced to every 16 weeks (± 2 weeks).

Integrated subgroup analyses for ORR included the number of prior chemotherapies (2 or ≥ 3), the number of prior platinum-based therapies (2), PFI from the last platinum-based therapy (> 12, 6–12, or < 6 months), platinum response status following the last platinum-based therapy (sensitive, resistant, or refractory), age (< 65 or ≥ 65 years old), race (white, non-white, or unknown), ECOG PS (0 or 1), and treatment location (US or non-US).

Secondary endpoints included investigator-assessed ORR per Gynecological Cancer InterGroup (GCIG) combined RECIST and cancer antigen 125 (CA-125) criteria, investigator-assessed best response in the sum of target lesions, DOR, and PFS. An independent radiology review

Table 1

Baseline patient characteristics and prior chemotherapy in the integrated efficacy and safety populations.

	Integrated efficacy population (n = 106)	Integrated safety population (n = 377)
Median age (range), years	59 (33–84)	62 (31–86)
Race, n (%)		
White	83 (78.3)	302 (80.1)
Asian	7 (6.6)	22 (5.8)
Black or African American	4 (3.8)	8 (2.1)
Other	2 (1.9)	7 (1.9)
Missing	10 (9.4)	38 (10.1)
ECOG PS, n (%)		
0	65 (61.3)	233 (61.8)
1	41 (38.7)	144 (38.2)
Cancer type, n (%)		
Epithelial ovarian carcinoma	91 (85.8)	305 (80.9)
Fallopian tube carcinoma	9 (8.5)	33 (8.8)
Primary peritoneal carcinoma	6 (5.7)	39 (10.3)
Histological classification, n (%)		
Serous	97 (91.5)	355 (94.2)
Mixed ^a	5 (4.7)	11 (2.9)
Endometrioid	3 (2.8)	9 (2.4)
Clear cell carcinoma	1 (0.9)	1 (0.3)
Unknown	0	1 (0.3)
Median time since cancer diagnosis (range), months	51.7 (6.3–196.6)	42.7 (6.3–196.6)
<i>BRCA1/2</i> mutation type, n (%)		
Germline	88 (83.0)	108 (28.6)
Somatic	18 (17.0)	28 (7.4)
Mutation of uncertain origin	0	7 (1.9)
No mutation (<i>BRCA</i> wild-type)	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 number of prior chemotherapies (range)	3 (2–6)	2 (1–7)
1 prior chemotherapy, n (%)	0	127 (33.7)
2 prior chemotherapies, n (%)	41 (38.7)	85 (22.5)
≥ 3 prior chemotherapies, n (%)	65 (61.3)	165 (43.8)
Median number of platinum-based therapies (range)	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 last platinum-based therapy, n (%)		
> 12 months	23 (21.7)	129 (34.2)
6–12 months	56 (52.8)	152 (40.3)
< 6 months	27 (25.5)	90 (23.9)
Missing	0	6 (1.6)
Platinum response to last therapy, n (%)		
Sensitive ^b	79 (74.5)	283 (75.1)
Resistant ^c	20 (18.9)	67 (17.8)
Refractory ^d	7 (6.6)	26 (6.9)
Unknown	0	1 (0.3)

ECOG PS, Eastern Cooperative Group Oncology Performance Status; PFI, progression-free interval.

^a Additional details provided in Table S1, Supplementary Data.

^b Platinum sensitivity represents disease progression ≥ 6 months after last platinum.

^c Platinum resistance represents disease progression < 6 months after last platinum, with best response other than progressive disease.

^d Platinum-refractory patients had a best response of progressive disease on last platinum, with PFI < 2 months.

Table 2

Investigator-assessed confirmed objective response rate and duration of response (per RECIST) in the integrated efficacy population and individual study parts.

	Study 10 (n = 42)	ARIEL2 (n = 64)	Pooled efficacy population (n = 106)
Objective response rate, n (%) [95% CI] ^a	25 (59.5) [43.3–74.4]	32 (50.0) [37.2–62.8]	57 (53.8) [43.8–63.5]
Best overall response, n (%)			
Complete response	4 (9.5)	5 (7.8)	9 (8.5)
Partial response	21 (50.0)	27 (42.2)	48 (45.3)
Stable disease	12 (28.6)	24 (37.5)	36 (34.0)
Progressive disease	2 (4.8)	7 (10.9)	9 (8.5)
Not evaluable	3 (7.1)	1 (1.6)	4 (3.8)

CI, confidence interval; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

^a Objective response represents investigator-assessed confirmed complete response + partial response, per RECIST.

of ORR and DOR was also performed. The best response in the sum of target lesions was the percentage change from baseline in the sum of the diameter(s) of all target lesions. DOR was analyzed using Kaplan-Meier methodology; data were censored at the date of the last postbaseline scan for patients who had an ongoing response at the time of the visit cutoff. PFS was also analyzed using Kaplan-Meier methodology, with data censored at the last visit for patients without documented progression or death. Due to the lack of a comparator treatment arm, no statistical testing was performed and no multiplicity adjustment was required. Analyses are presented descriptively.

2.4. Integrated safety analysis outcomes

In both trials, safety assessments included adverse event (AE) monitoring and laboratory investigations. Verbatim AE terms were coded using the Medical Dictionary for Drug Regulatory Activities version 18.1 [20]. Severities of the AE and laboratory abnormalities were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [9]. Grade 3/4 AEs were

managed with dose modification (treatment interruption and/or dose reduction) or treatment discontinuation.

Safety outcomes of interest in the integrated analysis were treatment-emergent AEs of all grades, grade ≥3 treatment-emergent AEs, serious AEs, treatment-related AEs, AEs leading to dose modification (treatment interruption and/or dose reduction), AEs leading to treatment discontinuation, and AEs leading to death.

3. Results

3.1. Integrated efficacy population

The integrated efficacy population included 106 patients from Study 10 Part 2A (n = 42) and ARIEL2 Parts 1 and 2 (n = 64) (Fig. S1, Supplementary Data).

At baseline in the integrated efficacy population, median age was 59 (range, 33–84) years, all patients had an ECOG PS of 0 or 1 (61.3% and 38.7%, respectively), and 85.8% of patients had epithelial ovarian, 8.5% had fallopian tube, and 5.7% had primary peritoneal carcinoma (Table 1). All patients had a deleterious *BRCA1/2* mutation; 83.0% of patients had a germline *BRCA1/2* mutation, and 17.0% had a *BRCA1/2* mutation detected in tumor tissue but not in whole blood (i.e., somatic *BRCA1/2* mutation). The majority of patients had a *BRCA1* mutation (63.2%); the remainder had a *BRCA2* mutation (36.8%). Of the nine patients with nonserous ovarian cancer, five had a *BRCA1* mutation (2 with mixed, 2 with endometrioid, and 1 with clear cell histology), and four had a *BRCA2* mutation (3 with mixed and 1 with endometrioid histology). *BRCA1/2* mutation status in tumor was centrally confirmed retrospectively in 96.0% (64/67) of the patients for whom a tumor tissue sample was available for analysis with the companion diagnostic FoundationFocus CDx_{BRCA} assay. All patients received at least two prior lines of chemotherapy (median, 3; range, 2–6), inclusive of platinum-based therapies. 61.3% received three or more prior lines of chemotherapy, and 74.5% exhibited sensitivity to their last platinum-based therapy. The median PFI from the last platinum-based therapy was 8.0 (range, –0.7–116.4) months.

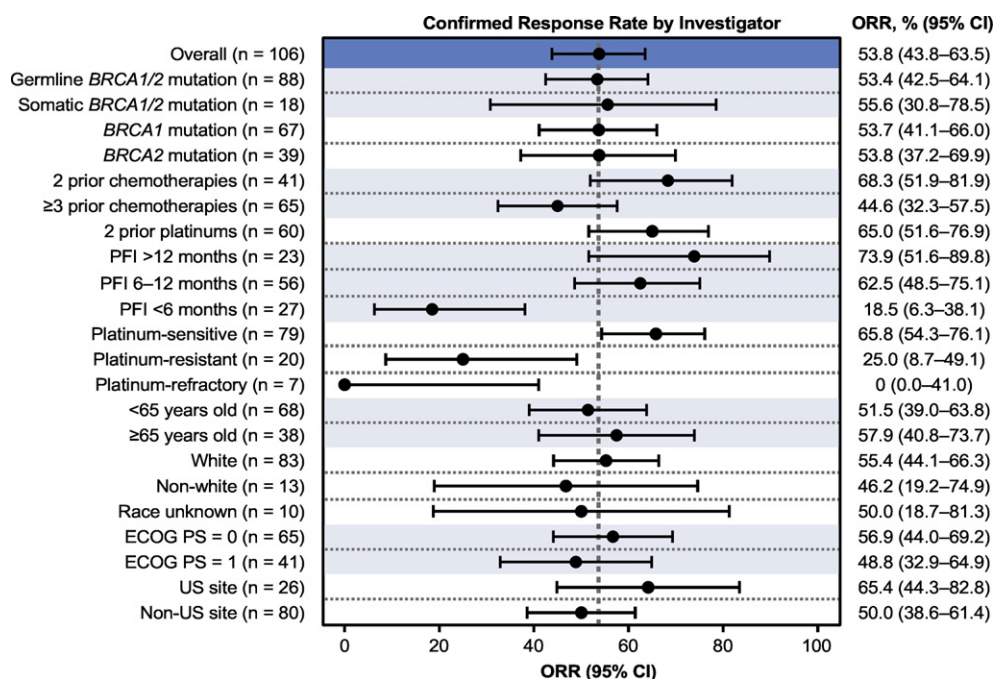


Fig. 1. Investigator-assessed confirmed ORR per RECIST in the integrated efficacy population, by subgroup. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, objective response rate; PFI, progression-free interval to last platinum-based therapy; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; US, United States.

3.2. Integrated efficacy findings

In the integrated efficacy population, the investigator-assessed confirmed ORR per RECIST was 53.8% (95% confidence interval [CI], 43.8–63.5) (Table 2; Fig. 1). Best overall investigator-assessed confirmed responses of CR and PR were achieved in 8.5% and 45.3% of patients, respectively; 34.0% of patients had stable disease and 8.5% had PD. The majority of patients (84.9%) had a decrease from baseline in the sum of the diameter of target lesions, with most decreases being $\geq 30\%$ (Fig. 2A). For the secondary endpoint of investigator-assessed confirmed response per combined RECIST and GCI CA-125 criteria, the ORR was 70.8% (95% CI, 61.1–79.2).

Findings from prespecified, exploratory subgroup ORR analyses in the integrated efficacy population are summarized in Fig. 1. The ORR was similar among patients in several of the subgroups, including patients with a germline or somatic *BRCA1/2* mutation and patients with a *BRCA1* or *BRCA2* mutation. The ORR was higher in patients who had received exactly two prior lines of chemotherapy (inclusive of platinum-based chemotherapy) than in patients who received three or more prior lines of chemotherapy. Patients with a PFI from their last platinum-based therapy >12 months had a higher ORR than those with a PFI of 6 to 12 months or <6 months. Patients who were sensitive to

their most recently administered platinum regimen had a higher ORR than those who were resistant or refractory to their most recent platinum regimen.

In the integrated efficacy population, the median duration of investigator-assessed confirmed response was 9.2 (range, 1.7–19.8; 95% CI, 6.6–11.6) months (Fig. 2B); 47.4% of patients with a response had not progressed at the time of the visit cutoff. Investigator-assessed PFS in the integrated efficacy population was 10.0 (range, 0.0–22.1; 95% CI, 7.3–12.5) months (Fig. S2A, Supplementary Data); 47.2% of patients had not progressed at the time of the visit cutoff. The PFS rate at 6 and 12 months was 79.0% and 41.0%, respectively (Fig. S2A, Supplementary Data). Investigator-assessed PFS was 11.1 (95% CI, 7.3–12.8) months in patients who were sensitive to their most recently administered platinum regimen ($n = 79$), and 7.4 (95% CI, 5.5–not reached) months in those who were resistant ($n = 20$) or refractory ($n = 7$) to their most recent platinum regimen, respectively (Fig. S2B, Supplementary Data).

According to the independent radiology review, the confirmed ORR per RECIST in the integrated efficacy population was 41.5% (95% CI, 32.0–51.5); 4.7% of patients achieved a CR and 36.8% achieved a PR. The median DOR according to the independent radiology review was 6.7 (range, 1.7–13.3; 95% CI, 5.5–11.1) months.

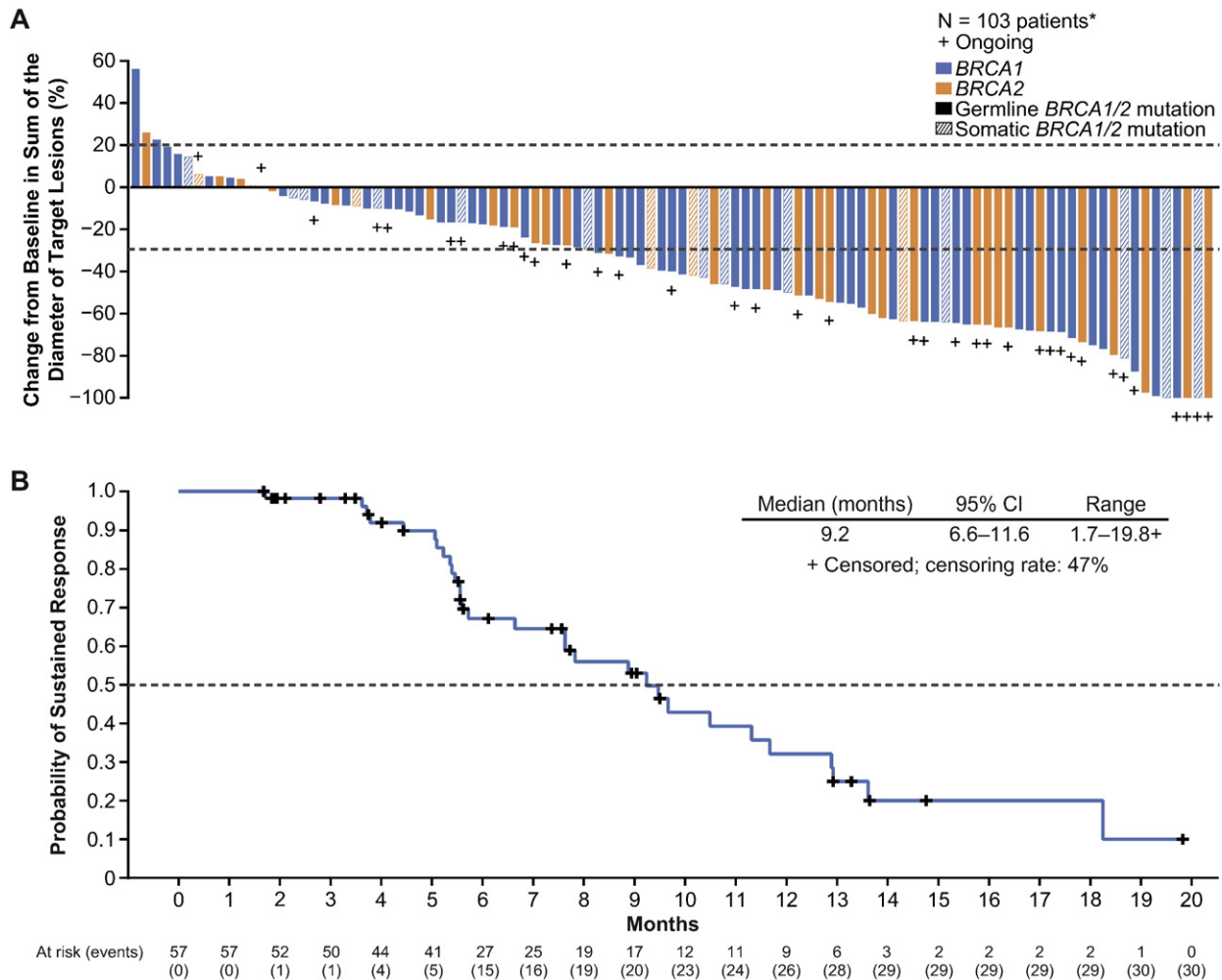


Fig. 2. (A) Best percentage change from baseline for target lesions and (B) duration of response, each by investigator assessment per RECIST in the integrated efficacy population. Best response for target lesions represents the largest percentage decrease from baseline in the sum of the longest diameter of target lesions; each bar represents a single patient; patients with zero change from baseline are shown as 0.5% for visual clarity; the upper dotted line indicates the threshold for progressive disease, a 20% increase in the sum of the longest diameter of the target lesions, whereas the lower dotted line indicates the threshold for partial response, a 30% decrease in the sum of the longest diameter of the target lesions; solid bars represent patients with a germline *BRCA1/2* mutation; striped bars represent patients with a somatic *BRCA1/2* mutation. Duration of response was analyzed by Kaplan-Meier methodology; data were censored at the date of the last postbaseline scan for patients who had an ongoing response at the time of the visit cutoff. CI, confidence interval; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1. *Three patients did not have a postbaseline scan.

3.3. Integrated safety population

The integrated ovarian carcinoma safety population included 377 patients from Study 10 Parts 1, 2A, and 3 ($n = 62$), and ARIEL2 Parts 1 and 2 ($n = 315$) (Fig. S1, Supplementary Data). The median duration of rucaparib treatment in the integrated safety population was 5.5 (range, 0.1–28.0) months.

At baseline in the integrated safety population, median age was 62 (range, 31–86) years. All patients had an ECOG PS of 0 or 1 (61.8% and 38.2%, respectively); 80.9% of patients had epithelial ovarian carcinoma (Table 1). Approximately one-third of patients (37.9%) had a deleterious *BRCA1/2* mutation (germline or somatic). All patients had received at least one prior line of chemotherapy; 43.8% had received three or more prior lines of chemotherapy (inclusive of platinum-based therapies), and 27.1% had received three or more platinum-based therapies.

3.4. Integrated safety findings

All patients in the integrated safety population had at least one treatment-emergent AE, and 60.7% had a grade ≥ 3 treatment-emergent AE. The most frequently reported treatment-emergent AEs were nausea (76.9%), asthenia/fatigue (76.7%), vomiting (46.2%), anemia/hemoglobin decreased (43.8%), and ALT/AST increased (41.4%) (Table 3). Median time to onset of anemia (preferred term only) was approximately 54 days. Common grade ≥ 3 treatment-emergent AEs included anemia/hemoglobin decreased (24.9%), asthenia/fatigue (10.9%), and ALT/AST increased (10.9%). Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) were reported as an AE in one patient each after 57 and 539 days of rucaparib treatment, respectively; both patients had received at least 12 cycles of prior platinum-based therapy, and neither patient had a *BRCA1/2* mutation. Immediately following the MDS and AML diagnosis, rucaparib treatment was discontinued.

The most frequently observed lab abnormalities were increase in creatinine (any worsening in grade, 92.0%; shift to grade 3/4, 1.3%), increase in ALT (any worsening in grade, 74.0%; shift to grade 3/4, 12.5%), increase in AST (any worsening in grade, 73.2%; shift to grade 3/4, 4.5%), and decrease in hemoglobin (any worsening in grade, 66.6%; shift to grade 3/4, 23.3%) (Table 3). Creatinine increases were observed within the first few weeks of rucaparib treatment and then stabilized with continued rucaparib treatment (Fig. 3A).

Elevations in ALT/AST were also observed within the first few weeks of rucaparib treatment (Fig. 3B). These elevations were mostly asymptomatic, reversible, and were rarely associated with increases in bilirubin (Fig. 3C); the elevations generally normalized over time with continued treatment and only resulted in treatment discontinuation in one patient (0.3%). At study entry, 32 patients had mild hepatic impairment, and 345 patients had no hepatic impairment. There was no difference in the incidence of all-grade treatment-emergent AEs between patients with or without mild hepatic impairment (100% in each group). The incidence of grade 3 or higher treatment-emergent AEs was reported in 59.4% and 60.9% of patients with or without mild hepatic impairment, respectively.

Treatment-emergent AEs led to treatment interruption in 58.6% of patients and dose reduction in 45.9% of patients (Table 3). AEs most frequently leading to dose modification (dose reduction or treatment interruption) included anemia/hemoglobin decreased (21.5%), asthenia/fatigue (20.7%), nausea (18.0%), vomiting (11.9%), ALT/AST increased (10.3%), and thrombocytopenia/platelets decreased (9.8%). Treatment-emergent AEs led to treatment discontinuation in 9.8% of patients (excluding those who discontinued because of disease progression) (Table 3). Treatment-emergent AEs leading to treatment discontinuation in five or more patients included asthenia/fatigue (2.4%) and nausea (1.3%).

An AE with an outcome of death occurred in 2.4% of patients (9 deaths). Of those deaths, 8 were associated with malignant neoplasm progression. The ninth patient died from sepsis and clinical progression,

which was assessed by the investigator to be unrelated to rucaparib treatment.

4. Discussion

Results from this integrated analysis demonstrate that oral rucaparib (600 mg BID) has antitumor activity in patients with HGOC and a deleterious germline or somatic *BRCA1/2* mutation who have received two or more prior chemotherapies. More than half (53.8%) of patients with HGOC achieved a CR (8.5%) or PR (45.3%). Responses to rucaparib were durable, with a median DOR of 9.2 months. Based on these results, single-agent rucaparib received accelerated approval from the United States Food and Drug Administration in December 2016 for treatment of women with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies.

Results of the integrated efficacy analysis also demonstrated antitumor activity in subgroups within the efficacy population. Notably, the ORR was higher in patients who had received only two prior chemotherapies (68.3%) than in those who received three or more prior chemotherapies (44.6%). The ORR was also higher in platinum-sensitive patients (65.8%) than in platinum-resistant (25.0%) or platinum-

Table 3

Safety summary: all patients with ovarian carcinoma who received ≥ 1 dose of rucaparib 600 mg BID.

Summary of AEs	Integrated ovarian carcinoma safety population ($n = 377$) ^a	
	n (%)	
AE leading to dose modification (dose reduction or treatment interruption)	233 (61.8)	
AE leading to dose reduction	173 (45.9)	
AE leading to treatment interruption	221 (58.6)	
AE leading to treatment discontinuation ^b	37 (9.8)	
AE leading to death	9 (2.4)	
Malignant neoplasm progression	8 (2.1)	
Nonprogression AE leading to death	1 (0.3)	
Individual AE occurring in $\geq 20\%$ of patients ^c	Any grade, n (%)	Grade 3/4, n (%)
Nausea	290 (76.9)	19 (5.0)
Asthenia/fatigue ^d	289 (76.7)	41 (10.9)
Vomiting	174 (46.2)	15 (4.0)
Anemia/hemoglobin decreased ^d	165 (43.8)	94 (24.9)
ALT/AST increased ^d	156 (41.4)	41 (10.9)
Constipation	150 (39.8)	6 (1.6)
Decreased appetite	148 (39.3)	10 (2.7)
Dysgeusia	148 (39.3)	1 (0.3)
Diarrhea	130 (34.5)	9 (2.4)
Abdominal pain	119 (31.6)	13 (3.4)
Dyspnea	81 (21.5)	2 (0.5)
Thrombocytopenia/platelet count decreased ^d	79 (21.0)	17 (4.5)
Blood creatinine increased	79 (21.0)	2 (0.5)
Laboratory abnormalities ^e	Any grade, n (%)	Grade 3/4, n (%)
Increase in creatinine	347 (92.0)	5 (1.3)
Increase in ALT	279 (74.0)	47 (12.5)
Increase in AST	276 (73.2)	17 (4.5)
Decrease in hemoglobin	251 (66.6)	88 (23.3)
Decrease in lymphocytes	168 (44.6)	26 (6.9)
Increase in cholesterol	150 (39.8)	9 (2.4)
Decrease in platelets	147 (39.0)	23 (6.1)
Decrease in neutrophils	132 (35.0)	37 (9.8)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

^a All data are from patients with ≥ 1 event.

^b Excludes patients who discontinued because of disease progression.

^c Other grade 3/4 AEs occurring in $\geq 3\%$ of patients were: neutropenia/neutrophil count decreased (8.2%); malignant neoplasm progression (5.0%); and small intestinal obstruction (3.7%).

^d To ensure full representation of similar AEs, certain terms were combined.

^e For laboratory abnormalities, "Any grade" represents any worsening shift from baseline, and "grade 3/4" represents a maximum shift to grade 3/4.

refractory (0.0%) patients; however, patients in all three subgroups appeared to derive some measure of clinical benefit as demonstrated by the median PFS in each subgroup (11.1, 7.4, and 5.3 months, respectively). Additionally, this analysis showed that the ORR was similar between patients with a germline or somatic *BRCA1/2* mutation and between patients with a *BRCA1* or *BRCA2* mutation.

Other PARP inhibitors, including olaparib, veliparib, and niraparib, have also been investigated in ovarian carcinoma in the treatment setting. In Study 42, olaparib had an ORR of 33.6%, a median DOR of 7.9 months, and median PFS of 6.7 months in patients with advanced ovarian carcinoma and a germline *BRCA1/2* mutation who had received at least three prior chemotherapies [21]. In a phase II trial, treatment

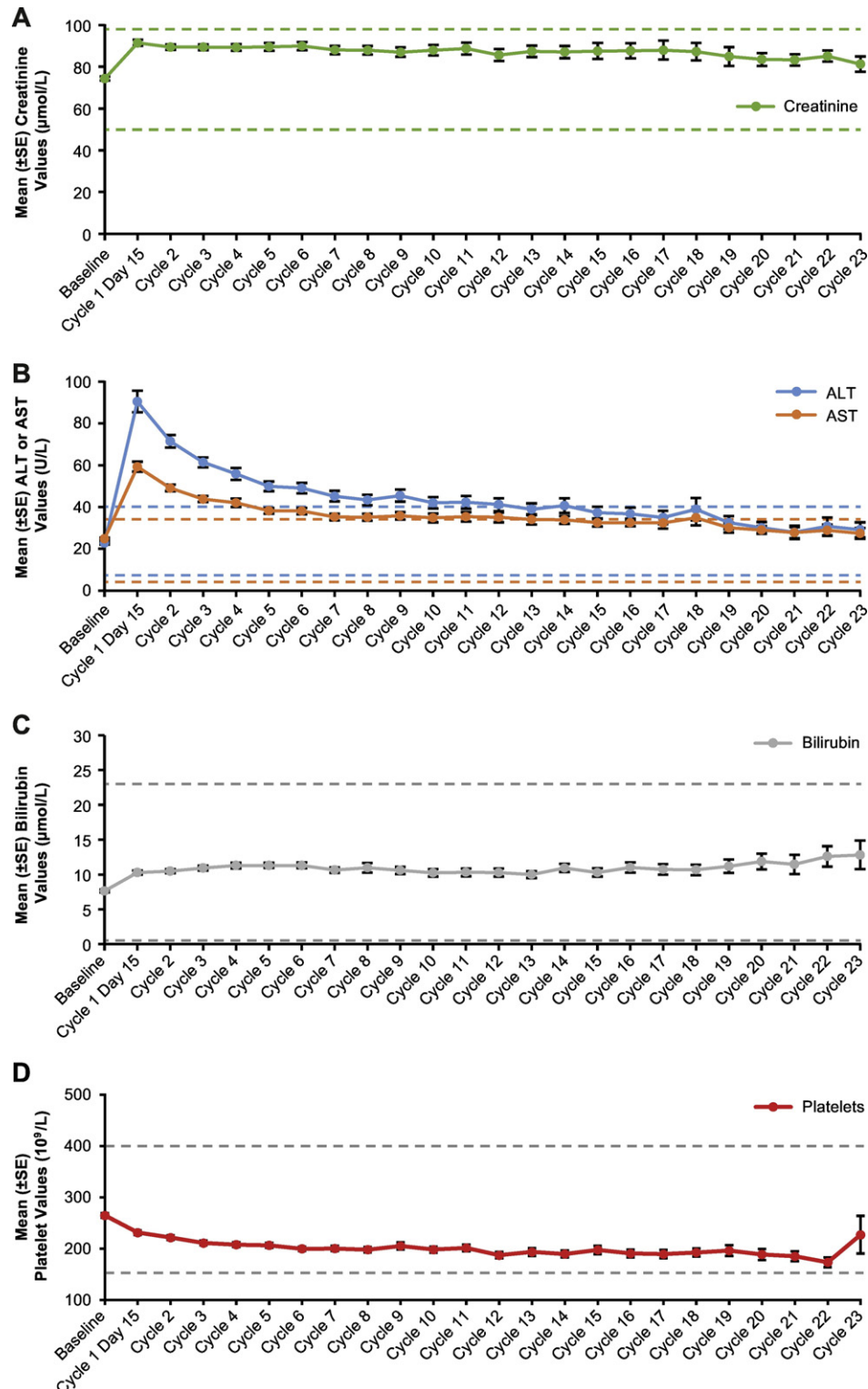


Fig. 3. Baseline and on-treatment values for (A) creatinine, (B) ALT/AST, (C) bilirubin, and (D) platelets in the integrated safety population. Dashed lines indicate the upper and lower limits of normal. ALT, alanine aminotransferase; AST, aspartate aminotransferase; SE, standard error.

with veliparib led to an ORR of 26.0% and a median PFS of 8.2 months in patients with recurrent ovarian carcinoma and a germline *BRCA1/2* mutation who had received up to three prior chemotherapies [22]. Niraparib is currently being evaluated in the treatment setting for patients with ovarian cancer who have received three to four prior chemotherapies (QUADRA; NCT02354586). At this time, we are not aware of any head-to-head trials of PARP inhibitors in the setting of HGOC; thus, direct comparisons cannot be made between agents in this class. If indirect comparisons were to be made, they would likely be confounded by differences in patient populations, tumor histologies and/or subtype, trial design, and study execution. Nevertheless, a common observation within clinical trials that have investigated PARP inhibitors is that patients with platinum-sensitive disease are more likely to respond to PARP inhibitors than patients with platinum-resistant or platinum-refractory disease [23,24]. In the United States, olaparib is approved as a monotherapy in the treatment setting for patients with HGOC and a germline *BRCA1/2* mutation who have received three or more prior chemotherapies. In the European Union, olaparib is approved as monotherapy for the maintenance treatment of patients with platinum-sensitive, relapsed, *BRCA*-mutated (germline and/or somatic), high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in remission (CR or PR) to platinum-based therapy. Niraparib and olaparib are approved in the United States as monotherapy for maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

The integrated safety analysis in patients with ovarian carcinoma demonstrated that rucaparib has a manageable safety profile. In the setting of these two trials, treatment-emergent AEs and lab abnormalities were managed with treatment interruption, treatment modification, and/or supportive care such as antiemetic medications for nausea or vomiting (e.g., 5-HT antagonist and a corticosteroid with or without a NK1 antagonist or palonosetron with dexamethasone) or red blood cell transfusions for anemia. Treatment discontinuations due to treatment-emergent AEs not related to disease progression were infrequent (9.8%). Furthermore, gastrointestinal side effects, asthenia/fatigue, and myelosuppression are consistent with toxicities already observed with the PARP inhibitor class of agents [21,22,24,25].

Creatinine increases observed with rucaparib were predominantly grade 1 or 2 and usually occurred within the first few weeks of rucaparib treatment and then stabilized. In the setting of these two trials, mild to moderate elevations in serum creatinine did not require dose modification. In vitro studies have shown that rucaparib potently inhibits MATE1 and MATE2-K and moderately inhibits OCT-1 [26], renal transporters that play a role in the secretion of creatinine into the proximal tubule and subsequent apical efflux into urine. Olaparib has been shown to inhibit MATE1, MATE2-K, and OCT2 in vitro [27]; veliparib also inhibits MATE1 and MATE2-K in vitro [28]. Increases in creatinine have also been observed following the use of olaparib in the setting of advanced ovarian cancer [29]. Thus, increases in blood creatinine observed following rucaparib treatment may be a PARP inhibitor class effect.

Observed ALT/AST elevations were transient and normalized over time with continued rucaparib treatment. Although no differences were observed in the rate of AEs in patients with or without mild hepatic impairment, a clinical pharmacokinetic study will be completed to determine the most appropriate starting dose for rucaparib in patients with moderate hepatic impairment.

A limitation of this integrated analysis is that these data were generated from two open-label, single-arm, nonrandomized phase II trials with unique study designs and overlapping patient populations. Furthermore, randomized data are not yet available for rucaparib in the treatment setting; however, a phase III trial is underway to further evaluate rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian carcinoma with a *BRCA1/2* mutation in the treatment setting (ARIEL4; NCT02855944). Rucaparib is also being compared with placebo in patients with ovarian carcinoma in a phase III trial in

the maintenance treatment setting (ARIEL3; NCT01968213). Both phase III trials will explore the use of biomarkers, including *BRCA1/2* mutations, for predicting response to rucaparib treatment in patients with HGOC.

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Competing interests

A.V. Tinker has served on an advisory board for and received grants from AstraZeneca. A. Oaknin has served on advisory boards for Roche, AstraZeneca, Pharmamar, and Clovis Oncology. I.A. McNeish has served on advisory boards for Clovis Oncology and AstraZeneca. E.M. Swisher reports a grant from the Department of Defense Ovarian Cancer Research Program. I. Ray-Coquard has served on an advisory board for AstraZeneca, Pharmamar, and Roche. K. Bell-McGuinn served on advisory boards for Clovis Oncology and AstraZeneca and is currently an employee of Eli Lilly and Company. R.L. Coleman reports grants from AstraZeneca, Genentech (Roche), Janssen, OncoMed, Millennium, Esperance, and AbbVie. D.M. O'Malley received research funding from Clovis Oncology; received institutional research support from Amgen, VentiRx, Regeneron, Immunogen, Array Biopharma, Janssen R&D, Clovis Oncology, EMD Serono, Ergomed, Ajinomoto, and Genentech (Roche); and served on a steering committee or advisory boards for Amgen, AstraZeneca, Janssen, Clovis Oncology, Genentech (Roche), and Eisai. A. Leary has served on an advisory board for Clovis Oncology, Pfizer, and Pharmamar, and reports institutional research grant support from GamaMabs and Merus. L.-M. Chen reports grants from Clovis Oncology and AstraZeneca, and has served on an advisory board for Genentech (Roche). J.D. Brenton has been advisor for and owns stock in Inivata, has served on a speakers' bureau for AstraZeneca, has received nonfinancial support from Clovis Oncology and Aprea AB, and has a pending patent for a diagnostic method of relevance to the current work. G.E. Konecny has served on speakers bureaus for AstraZeneca and Clovis Oncology; has received research funding from Amgen and Merck; and has received honorarium from Novartis. C.M. Castro has served as a scientific consultant for N-of-One and has served on an advisory board for Clovis Oncology. H. Giordano, L. Maloney, S. Goble, K. K. Lin, M. Raponi, and L. Rolfe are employees of Clovis Oncology. J. Sun is an employee of Foundation Medicine. R.S. Kristeleit served on an advisory board for Clovis

Oncology. A.M. Oza, R. Shapira-Frommer, D. Provencher, and L. Ma have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ygyno.2017.08.022>.

References

- [1] C.L. Scott, E.M. Swisher, S.H. Kaufmann, Poly (ADP-ribose) polymerase inhibitors: recent advances and future development, *J Clin Oncol* 33 (2015) 1397–1406.
- [2] T. Helleday, E. Petermann, C. Lundin, B. Hodgson, R.A. Sharma, DNA repair pathways as targets for cancer therapy, *Nat Rev Cancer* 8 (2008) 193–204.
- [3] T. Helleday, J. Lo, D.C. van Gent, B.P. Engelward, DNA double-strand break repair: from mechanistic understanding to cancer treatment, *DNA Repair* 6 (2007) 923–935.
- [4] A.R. Venkitesan, Cancer susceptibility and the functions of BRCA1 and BRCA2, *Cell* 108 (2002) 171–182.
- [5] M.E. Moynahan, A.J. Pierce, M. Jasin, BRCA2 is required for homology-directed repair of chromosomal breaks, *Mol Cell* 7 (2001) 263–272.
- [6] M.E. Moynahan, J.W. Chiu, B.H. Koller, M. Jasin, BRCA1 controls homology-directed DNA repair, *Mol Cell* 4 (1999) 511–518.
- [7] P.C. Fong, D.S. Boss, T.A. Yap, A. Tutt, P. Wu, M. Mergui-Roelvink, et al., Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers, *N Engl J Med* 361 (2009) 123–134.
- [8] H. Farmer, N. McCabe, C.J. Lord, A.N.J. Tutt, D.A. Johnson, T.B. Richardson, et al., Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy, *Nature* 434 (2005) 917–921.
- [9] K.P. Pennington, T. Walsh, M.I. Harrell, M.K. Lee, C.C. Pennil, M.H. Rendi, et al., Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas, *Clin Cancer Res* 20 (2014) 764–775.
- [10] Y. Drew, J. Ledermann, G. Hall, D. Rea, R. Glasspool, M.S. Highley, et al., Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer, *Br J Cancer* 114 (2016) 723–730.
- [11] E. Wahlberg, T. Karlberg, E. Kouznetsova, N. Markova, A. Macchiarulo, A.G. Thorsell, et al., Family-wide chemical profiling and structural analysis of PARP and tankyrase inhibitors, *Nat Biotechnol* 30 (2012) 283–288.
- [12] H.D. Thomas, C.R. Calabrese, M.A. Batey, S. Canan, Z. Hostomsky, S. Kyle, et al., Pre-clinical selection of a novel poly(ADP-ribose) polymerase inhibitor for clinical trial, *Mol Cancer Ther* 6 (2007) 945–956.
- [13] Y. Drew, E.A. Mulligan, W.T. Vong, H.D. Thomas, S. Kahn, S. Kyle, et al., Therapeutic potential of poly(ADP-ribose) polymerase inhibitor AG014699 in human cancers with mutated or methylated BRCA1 or BRCA2, *J Natl Cancer Inst* 103 (2011) 334–346.
- [14] J. Murai, S.Y. Huang, A. Renaud, Y. Zhang, J. Ji, S. Takeda, et al., Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib, *Mol Cancer Ther* 13 (2014) 433–443.
- [15] R. Kristeleit, G.I. Shapiro, H.A. Burris, A.M. Oza, P. LoRusso, M.R. Patel, et al., A phase I-II study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors, *Clin Cancer Res* 23 (2017) 4095–4106.
- [16] E.M. Swisher, K.K. Lin, A.M. Oza, C.L. Scott, H. Giordano, J. Sun, et al., Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 part 1): an international, multicentre, open-label, phase 2 trial, *Lancet Oncol* 18 (2017) 75–87.
- [17] Premarket Approval (PMA), FoundationFocus™ CDxBRCA assay, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P160018>, 2017.
- [18] T. Walsh, M.K. Lee, S. Casadei, A.M. Thornton, S.M. Stray, C. Pennil, et al., Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing, *Proc Natl Acad Sci U S A* 107 (2010) 12629–12633.
- [19] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), *Eur J Cancer* 45 (2009) 228–247.
- [20] E.G. Brown, L. Wood, S. Wood, The medical dictionary for regulatory activities (MedDRA), *Drug Saf* 20 (1999) 109–117.
- [21] S.M. Domchek, C. Aghajanian, R. Shapira-Frommer, R.K. Schmutzler, M.W. Audeh, M. Friedlander, et al., Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy, *Gynecol Oncol* 140 (2016) 199–203.
- [22] R.L. Coleman, M.W. Sill, K. Bell-McGuinn, C. Aghajanian, H.J. Gray, K.S. Tewari, et al., A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - an NRG Oncology/Gynecologic Oncology Group study, *Gynecol Oncol* 137 (2015) 386–391.
- [23] K.A. Gelmon, M. Tischkowitz, H. Mackay, K. Swenerton, A. Robidoux, K. Tonkin, et al., Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study, *Lancet Oncol* 12 (2011) 852–861.
- [24] U.A. Matulonis, R.T. Penson, S.M. Domchek, B. Kaufman, R. Shapira-Frommer, M.W. Audeh, et al., Olaparib monotherapy in patients with advanced relapsed ovarian cancer and a germline BRCA1/2 mutation: a multistudy analysis of response rates and safety, *Ann Oncol* 27 (2016) 1013–1019.
- [25] B. Kaufman, R. Shapira-Frommer, R.K. Schmutzler, M.W. Audeh, M. Friedlander, J. Balmaña, et al., Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation, *J Clin Oncol* 33 (2015) 244–250.
- [26] Rubraca (rucaparib), Tablets [Prescribing Information], Clovis Oncology, Inc., Boulder, CO, 2016.
- [27] A. McCormick, H. Swaisland, In vitro assessment of the roles of drug transporters in the disposition and drug-drug interaction potential of olaparib, *Xenobiotica* (2016) 1–47.
- [28] R. Kikuchi, Y. Lao, D.A. Bow, W.J. Chiou, M.E. Andracki, R.A. Carr, et al., Prediction of clinical drug-drug interactions of veliparib (ABT-888) with human renal transporters (OAT1, OAT3, OCT2, MATE1, and MATE2K), *J Pharm Sci* 102 (2013) 4426–4432.
- [29] Lynparza (olaparib), Capsules [Prescribing Information], AstraZeneca Pharmaceuticals, Wilmington, DE, 2016.