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Authors

Kristeleit, Rebecca

Drew, Yvette

Oza, Amit

et al.

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ARTICLE

Clinical Studies

Efficacy and safety of rucaparib treatment in patients with BRCA-mutated, relapsed ovarian cancer: final results from Study 10

Rebecca S. Kristeleit[1,18]✉, Yvette Drew[2,19], Amit M. Oza[3], Susan M. Domchek[4], Susana Banerjee[5], Rosalind M. Glasspool[6,7], Judith Balmaña[8], Lee-may Chen[9], Manish R. Patel[10], Howard A. Burris[11], Tamar Safra[12], Jennifer Borrow[13], Kevin K. Lin[14], Sandra Goble[15], Lara Maloney[16] and Ronnie Shapira-Frommer[17]

BACKGROUND: Study 10, a four-part Phase 1/2 study, evaluated oral rucaparib monotherapy in patients with advanced solid tumours. Here we report the final efficacy and safety results in heavily pretreated patients with ovarian cancer who received rucaparib in Study 10 Parts 2A and 2B.

METHODS: Parts 2A and 2B (Phase 2 portions) enrolled patients with relapsed, high-grade, platinum-sensitive or platinum-resistant, BRCA-mutated ovarian cancer who had received 2–4 (Part 2A) or 3–4 (Part 2B) prior chemotherapies. Patients received oral rucaparib 600 mg twice daily (starting dose). The primary endpoint was the investigator-assessed objective response rate (ORR) by RECIST v1.1.

RESULTS: Fifty-four patients were enrolled: 42 in Part 2A (all had platinum-sensitive disease) and 12 in Part 2B (4 with platinum-sensitive disease; 8 with platinum-resistant disease). ORR was 59.3% (95% CI 45.0–72.4%). The median time to onset of the most common nonhaematological treatment-emergent adverse events (TEAEs) was typically early (<56 days) and was later for haematological TEAEs (53–84 days). The median duration of grade ≥3 TEAEs was ≤13 days.

CONCLUSIONS: In patients with relapsed, platinum-sensitive or platinum-resistant germline BRCA-mutant high-grade ovarian cancer who had received ≥2 prior chemotherapies, rucaparib had robust antitumour activity with a safety profile consistent with prior reports.

CLINICAL TRIAL REGISTRATION: NCT01482715.

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INTRODUCTION

Ovarian cancer is the eighth most common malignancy and the eighth leading cause of death from cancer among women globally, with an estimated 313,959 new cases and 207,252 deaths worldwide in 2020 [1]. More than half (~60%) of patients with ovarian cancer are diagnosed with advanced-stage disease; the prognosis for patients with advanced ovarian cancer remains poor, with a 5-year relative survival rate of 31% [2]. Despite initial therapy (typically surgical cytoreduction followed by platinum-based chemotherapy with or without taxane), most women with advanced ovarian cancer will relapse and require additional treatment [3–5]. Historically, treatment options for the recurrent disease have been selected according to definitions of platinum status based on duration of progression-free interval (PFI) (≤6 months, platinum-resistant; 6–12 months, partially platinum-sensitive; >12 months, fully platinum-sensitive) [4, 6]. However, platinum sensitivity is increasingly viewed as existing on a continuum in clinical practice [7]. Treatment with multiple lines

[1]UCL Cancer Institute, University College London, London, UK. [2]Northern Centre for Cancer Care, Newcastle Hospitals NHS Foundation and Newcastle University, Newcastle Upon Tyne, UK. [3]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. [4]Division of Hematology Oncology, Abramson Cancer Center, Basser Center for BRCA, University of Pennsylvania, Philadelphia, PA, USA. [5]Gynaecology Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK. [6]Beatson West of Scotland Cancer Center, National Health Service Greater Glasgow and Clyde and University of Glasgow, Glasgow, UK. [7]Scottish Gynaecological Cancer Trials Group, University of Glasgow, Glasgow, UK. [8]Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. [9]Division of Gynecologic Oncology, University of California, San Francisco, San Francisco, CA, USA. [10]Drug Development Unit, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL, USA. [11]Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN, USA. [12]Oncology Department, Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. [13]Clinical Operations, Clovis Oncology, Inc., Boulder, CO, USA. [14]Molecular Diagnostics, Clovis Oncology, Inc., Boulder, CO, USA. [15]Biostatistics, Clovis Oncology, Inc., Boulder, CO, USA. [16]Clinical Development, Clovis Oncology, Inc., Boulder, CO, USA. [17]Department of Oncology, Chaim Sheba Medical Center, Tel HaShomer, Israel. [18]Present address: Department of Oncology, Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, London, UK. [19]Present address: BC Cancer Centre, Vancouver, BC, Canada. ✉email: Rebecca.kristeleit@gstt.nhs.uk

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of platinum or nonplatinum agents is associated with dose-limiting toxicities, and these therapies eventually fail to provide clinical benefit. Therefore, alternative active and tolerable systemic therapies are urgently needed [8].

In recent years, poly(ADP-ribose) polymerase (PARP) inhibitors have emerged as a new class of targeted treatment for patients with recurrent ovarian cancer, and several are approved in the treatment and maintenance settings [9, 10]. Rucaparib is a potent and selective oral small-molecule inhibitor of the DNA repair molecules PARP1, PARP2 and PARP3 [11–13]. Rucaparib exerts its antitumour effect through synthetic lethality in the setting of homologous recombination deficiency (HRD). The enzymatic inhibition of PARP as well as trapping of PARP at sites of DNA damage lead to propagation of single-strand DNA breaks and an accumulation of DNA double-strand breaks that cannot be repaired due to HRD, leading to cell death [13–15]. Recent studies have shown that reversion mutations in genes involved in DNA repair, including *BRCA1* and *BRCA2*, can predict primary and acquired resistance to PARP inhibitors [16, 17].

Study 10 was a four-part Phase 1/2 study that evaluated oral rucaparib monotherapy in patients with advanced solid tumours, including patients with *BRCA1* or *BRCA2* (BRCA)-mutated ovarian cancer who had received multiple prior treatments [18]. The aim of the current report is to describe the final efficacy and safety results in heavily pretreated patients with relapsed platinum-sensitive or platinum-resistant ovarian cancer and a deleterious BRCA mutation treated with rucaparib in Parts 2A and 2B of Study 10. To better characterise the efficacy and safety effects of rucaparib, we present analyses of the association of rucaparib dosing with alanine transaminase (ALT) and serum creatinine measurements as well as time to first onset and duration of treatment-emergent adverse events (TEAEs) throughout the course of the study.

METHODS

Study design

Study 10 was an open-label, Phase 1/2 study that established and then evaluated the recommended Phase 2 dose of oral rucaparib monotherapy for efficacy, safety, and pharmacokinetics. The study was conducted at 18 sites (in the US, UK, Spain, Israel and Canada) between December 14, 2011 and March 27, 2019. The study had four parts (Part 1, Part 2A, Part 2B, and Part 3); patients could not enrol into multiple parts.

Part 2A (the first patient enrolled: February 5, 2014; last patient visit: March 27, 2019) and Part 2B (first patient enrolled: October 6, 2015; last patient visit: January 16, 2019) were Phase 2 portions of the study that evaluated the efficacy and safety of oral rucaparib 600 mg twice daily (BID) in patients with relapsed, high-grade ovarian cancer. In June 2016, enrolment into Study 10 was halted as the key objectives of the study had been met. Although enrolment of the Part 2B portion was not yet complete, the data generated in that portion of the study were complemented by data gathered in a similar patient population in ARIEL2. Parts 1 and 3 of the study have been published previously, as has the study design and primary analysis of Part 2A [18, 19].

The study was approved by an institutional review board at each study site and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation.

Patients

Eligible patients were aged ≥18 years, had an Eastern Cooperative Oncology Group performance status of 0–1, adequate haematological, hepatic, and renal function, and a life expectancy of ≥3 months. Patients in Parts 2A and 2B also had a known deleterious germline BRCA mutation (somatic BRCA mutations were also allowed for Part 2B, although no patients with somatic mutations were enrolled) and measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) [20]. Patients in Part 2A had a histologically confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer; had platinum-sensitive, relapsed disease confirmed by radiological assessment; and received 2–4 prior chemotherapies with a platinum-based regimen as their last treatment (PFI ≥ 6 months after the last platinum-based regimen). One nonplatinum regimen was required if 4 prior chemotherapy regimens were received; otherwise, ≤1 prior nonplatinum regimen was allowed. Patients in Part 2B had a histologically confirmed diagnosis of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer; had relapsed disease confirmed by radiological assessment; received 3–4 prior chemotherapies; and had a documented treatment-free interval of ≥6 months after the first chemotherapy regimen with no requirement for a specific platinum sensitivity or resistance status after the most recent platinum regimen. Key exclusion criteria in Parts 2A and 2B included the presence of another active cancer, prior treatment with a PARP inhibitor, untreated or symptomatic central nervous system metastases, impaired cardiac function or clinically significant cardiac disease, and hospitalisation for bowel obstruction within 3 months prior to enrolment (Part 2B only). Patients provided written consent before participating in the study.

Procedures

Patients received oral rucaparib 600 mg BID in continuous 21-day cycles until disease progression, unacceptable toxicity, or discontinuation. If a patient had disease progression but, in the opinion of the investigator, was still receiving benefit from rucaparib, then treatment could be continued. Treatment interruptions and dose reduction steps were permitted to manage toxicity, with dose reduction in 120 mg BID increments down to 240 mg for patients using 60- and 120-mg tablets or in 100 mg BID increments down to 200 mg BID for patients using 200- and 300-mg tablets.

Study visits were on days 1 and 15 of cycle 1, on day 1 of cycle 2 and each cycle thereafter, and at the end of treatment. In Parts 2A and 2B, patients were followed for safety for 28 days after the last dose of rucaparib. Long-term follow-up for survival, subsequent treatments and secondary malignancy was conducted for patients in Part 2B, who were followed every 12 weeks for 18 months, and every 16 weeks thereafter.

Outcomes

The primary efficacy endpoint was confirmed investigator-assessed objective response rate (ORR) by RECIST (defined as best confirmed response of complete response [CR] or partial response [PR]) [20]. Secondary efficacy endpoints included investigator-assessed duration of response (DOR), progression-free survival (PFS), overall survival (OS; Part 2B only), ORR by RECIST or response by Gynecologic Cancer InterGroup (GCIG) cancer antigen 125 (CA-125) criteria (defined as a 50% reduction from baseline in CA-125 measurement) [21], and safety. Post hoc analyses of the association of rucaparib dosing with ALT and serum creatinine measurements and time to first onset and duration of TEAEs throughout were also conducted.

Assessments

Tumour assessments consisted of clinical examination and imaging throughout the study, as described previously [18]. Tumour assessments were performed at screening (days −30 to −1); ≤7 days prior to cycles 3, 5, and 7; ≤7 days before every third cycle thereafter from cycle 10; and at the end of treatment visit. Confirmatory scans were performed at least 4–6 weeks later if a CR or PR was noted. In Part 2B, for patients who stopped treatment for reasons other than progression, tumour assessments were performed every 9 weeks until confirmed disease progression, death or subsequent treatment.

Throughout the study, patients were monitored for TEAEs, which were classified using the Medical Dictionary for Regulatory Activities Version 19.1 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. Other safety assessments included clinical laboratory evaluations (haematology and serum chemistry, including creatinine, ALT and aspartate transaminase (AST) levels).

Central assessment of BRCA mutations was performed using next-generation sequencing of tumour tissue by Foundation Medicine (Cambridge, MA, USA).

Statistical analyses

Approximately 41 and 40 evaluable patients were planned to be enrolled into Parts 2A and 2B of the trial, respectively. The sample size for Part 2A was based on a Simon 2-stage design. The sample size justification for Part

Table 1. Baseline patient demographics and disease characteristics.

Characteristic	Patients ($N = 54$)
Age, median (range), years	57 (42–84)
ECOG PS, *n* (%)	
0	30 (55.6)
1	24 (44.4)
BRCA gene mutation, *n* (%)	
BRCA1	39 (72.2)
BRCA2	15 (27.8)
Histologic classification, *n* (%)	
Serous	49 (90.7)
Mixed	3 (5.6)
Endometrioid	1 (1.9)
Other	1 (1.9)
PFI from last platinum therapy, *n* (%)	
<6 months	8 (14.8)
≥6–12 months	35 (64.8)
>12 months	11 (20.4)
Previous chemotherapies, median (range)	2.5 (2–4)
≥3 previous chemotherapies, *n* (%)	27 (50.0)
Previous platinum-based chemotherapies, median (range)	2 (1–4)
≥3 previous platinum-based chemotherapies, *n* (%)	23 (42.6)

ECOG PS Eastern Cooperative Oncology Group performance status, *PFI* progression-free interval.

Table 2. Response rates in patients with measurable disease at baseline.

Efficacy endpoint	Rucaparib ($N = 54$)
Confirmed RECIST ORR, *n/N* (%) [95% CI]	32/54 (59.3) [45.0–72.4]
Complete response, *n/N* (%)	5/54 (9.3)
Partial response, *n/N* (%)	27/54 (50.0)
Stable disease, *n/N* (%)	14/54 (25.9)
Progressive disease, *n/N* (%)	4/54 (7.4)
Not evaluable, *n/N* (%)	4/54 (7.4)
Confirmed RECIST and/or CA-125 response, *n/N* (%) [95% CI]	44/54 (81.5) [68.6–90.7]
Confirmed RECIST ORR by patient subsets, *n/N* (%) [95% CI]	
PFI from last platinum therapy	
<6 months	5/8 (62.5) [24.5–91.5]
≥6–12 months	19/35 (54.3) [36.6–71.2]
>12 months	8/11 (72.7) [39.0– 94.0]
Number of prior chemotherapy regimens	
2	16/27 (59.3) [38.8–77.6]
≥3	16/27 (59.3) [38.8–77.6]
BRCA gene with mutation	
BRCA1	24/39 (61.5) [44.6–76.6]
BRCA2	8/15 (53.3) [26.6–78.7]
BRCA mutation type	
Frameshift mutation	26/41 (63.4) [46.9–77.9]
Nonsense mutation	4/7 (57.1) [18.4–90.1]
Other mutation types	2/6 (33.3) [4.3–77.7]
BRCA Ashkenazi founder mutation[a]	
Yes	14/19 (73.7) [48.8–90.9]
No	18/35 (51.4) [34.0–68.6]

CA-125 cancer antigen 125, *CI* confidence interval, *ORR* objective response rate, *PFI* progression-free interval, *RECIST* Response Evaluation Criteria In Solid Tumours version 1.1.
[a]Ashkenazi Jews founder mutations were defined as: *BRCA1* E23fs*17 and Q1756fs*74; *BRCA2* S1982fs*22.

2B was based on an ORR ≥20% in this population being considered worthy of further exploration.

Efficacy and safety data from Parts 2A and 2B were combined for this post hoc analysis. The primary endpoint of ORR and the secondary endpoint of ORR and/or CA-125 response were summarised as percentages with 95% confidence interval (CI) using Clopper–Pearson methodology. Kaplan–Meier methodology was used to estimate time-to-event distributions, including DOR, PFS and OS. PFS was calculated as 1 + the number of days from the first rucaparib dose to disease progression or death due to any cause, whichever occurred first. Patients were censored at their last scan if they did not have disease progression. OS was defined as 1 + the number of days from the first rucaparib dose to death due to any cause. Patients who were still alive were censored at the last visit or last date known to be alive from follow-up.

The time to first TEAE was defined as 1 + the number of days from first rucaparib dose to start of the event. The duration of first TEAE was calculated using Kaplan–Meier methodology and included resolved and ongoing events; patients with ongoing events without a known end date were censored at the date of the last dose plus 28 days. A TEAE overlapping by ≤2 days was considered as the same continuous event. TEAEs occurring after the first event were not included in the time to first TEAE or the duration of first TEAE calculation. All other safety analyses are reported descriptively.

RESULTS

Patient characteristics

A total of 54 patients were enrolled in Parts 2A and 2B of the study: 42 in Part 2A and 12 in Part 2B. Baseline patient characteristics and prior therapies are presented in Table 1. The median patient age was 57 years (range, 42–84). All patients had a documented germline BRCA mutation; 72.2% had a *BRCA1* mutation, and 27.8% had a *BRCA2* mutation. Tumour tissue was available from 24 (44.4%) patients for central assessment of BRCA mutations; no BRCA reversion mutations were detected in these samples, which were predominantly archival and not obtained immediately before treatment. Patients had received a median of 2.5 prior chemotherapies, with 50.0% receiving ≥3 prior chemotherapies. All patients had received prior platinum therapy; 46 (85.2%) patients were platinum-sensitive (PFI ≥ 6 months): 35 (64.8%) patients had a PFI ≥ 6–12 months, and 11 (20.4%) patients had a PFI > 12 months. Eight (14.8%) patients (all in Part 2B) were platinum-resistant (PFI < 6 months).

Response rates

Among all patients in Parts 2A and 2B, investigator-assessed ORR by RECIST was 59.3% (95% CI 45.0–72.4; Table 2), with confirmed complete and partial responses reported for 5 (9.3%) and 27 (50.0%) patients, respectively (Table 2). The median duration of response was 8.9 months (95% CI 6.6–12.9) in 32 patients who had a response to rucaparib (Supplementary Fig. 1); of these patients, 29 (90.6%) achieved a response by the second scan (at ~14 weeks), including 17 (53.1%) who had responded by the first assessment (at ~8 weeks). The RECIST/GCIG CA-125 response rate was 81.5% (95% CI 68.6–90.7%; Table 2).

Subgroup analysis showed that ORR by RECIST was consistent among patients with platinum-resistant disease (PFI of <6 months following most recent platinum therapy; 5/8 [62.5%]) and patients with platinum-sensitive disease (PFI ≥ 6–12 months or >12 months; 19/35 [54.3%] and 8/11 [72.7%], respectively; Table 2). The ORR was the same in patients with 2 prior chemotherapy regimens (16/27 [59.3%]) and in those with ≥3 prior chemotherapy regimens (16/27 [59.3%]). Objective responses were also observed in patients with *BRCA1* (24/39 [61.5%]) and *BRCA2* (8/15 [53.3%]) mutations (Table 2

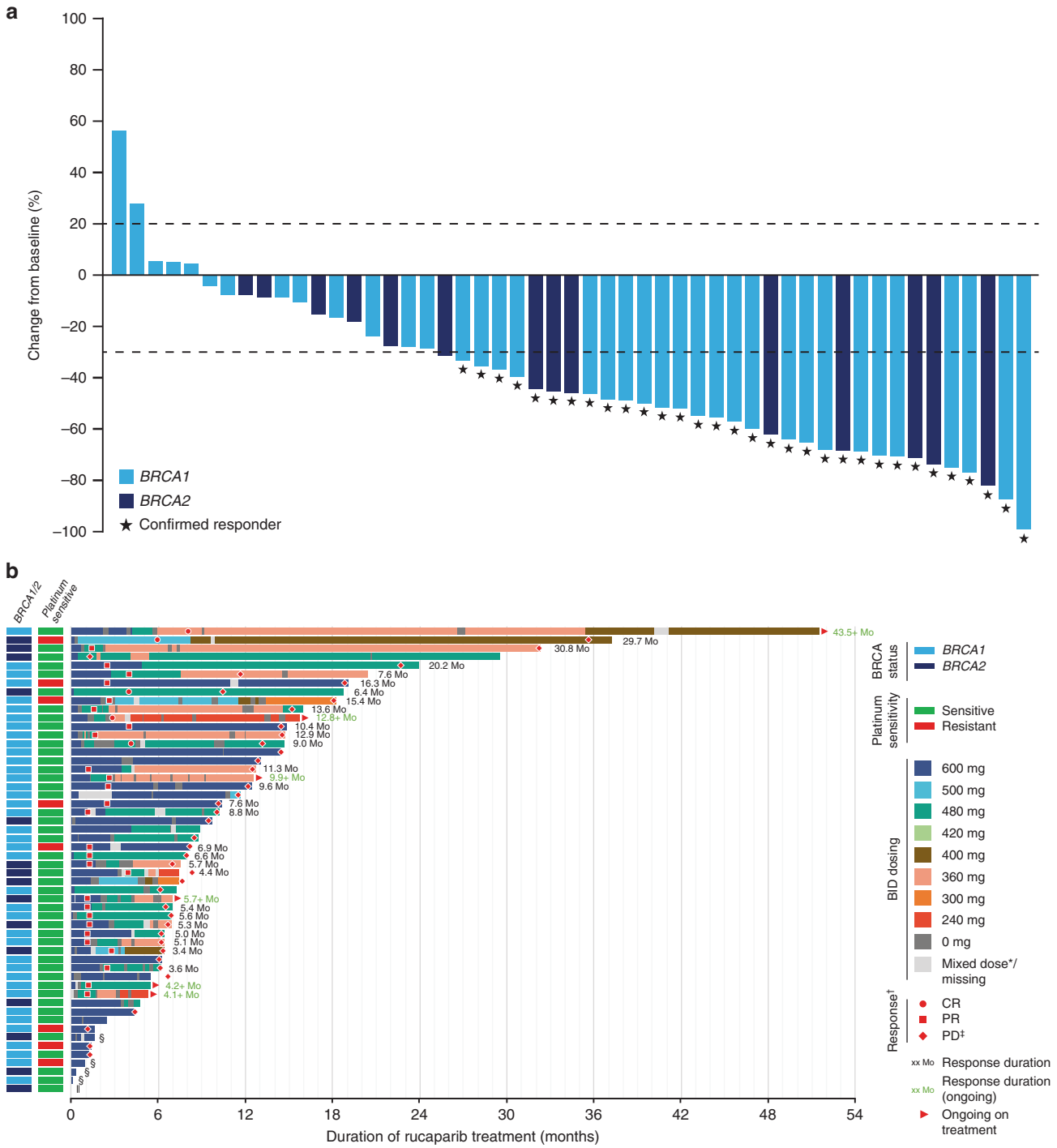

Fig. 1 Response to rucaparib according to RECIST ($N = 54$). a Best overall change from baseline in target lesions in patients with *BRCA1* or *BRCA2* mutations and evaluable target lesions. The best percentage change from baseline up to and including the first overall response of PD was included in the analysis. Each bar represents a single patient. **b** Individual time on treatment, RECIST responses, and dosage history. Dose modifications of ≥3 days are shown; reported dose is the lowest dose administered on any given day, starting from the first day of any dose reduction until the first day of completing a new dose. *Inconsistent dosing for ≥3 days. †Patients without a CR, PR, or PD achieved SD. ‡Patients without PD were censored at their last postbaseline scan. §Four patients were not evaluable for response. ‖Dosing information not available. BID twice daily, CI confidence interval, CR complete response, PD progressive disease, PR partial response, RECIST Response Evaluation Criteria in Solid Tumours version 1.1, SD stable disease.

and Fig. 1a); frameshift mutations (26/41 [63.4%]), nonsense mutations (4/7 [57.1%]), and other mutation types (2/6 [33.3%]); and patients with and without Ashkenazi Jews founder mutations (14/19 [73.7%] and 18/35 [51.4%], respectively; Table 2).

The time on treatment and individual pattern of response for each patient according to the dose of rucaparib is represented in Fig. 1b. Responses to rucaparib were observed and maintained, irrespective of whether patients had received rucaparib dose reductions or interruptions.

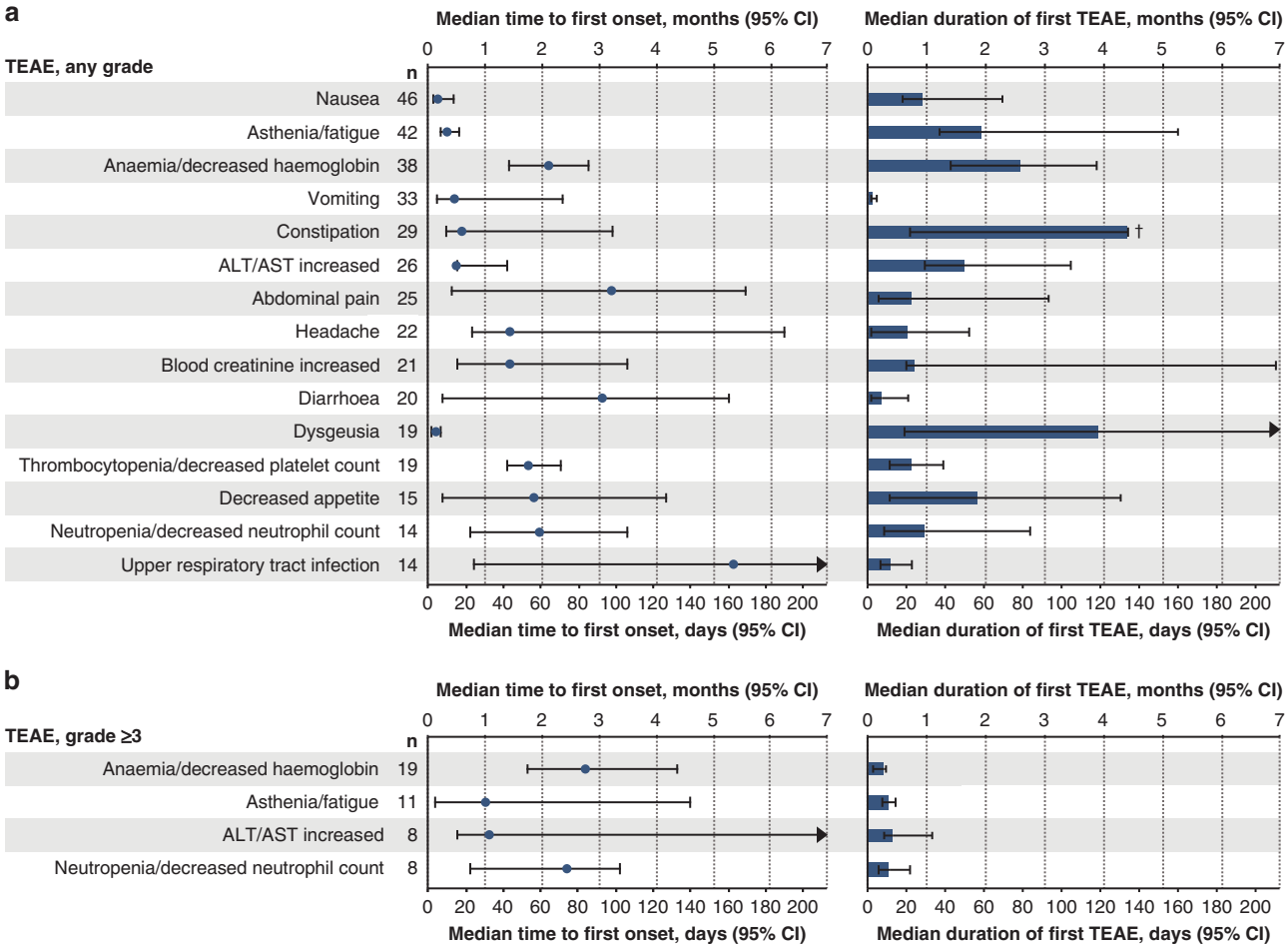

Fig. 2 Median time to first onset and median duration of first TEAE. a Most frequently reported any-grade TEAEs (≥25%). **b** Most frequently reported grade ≥3 TEAEs (≥10%). In both panels, n represents the number of patients experiencing a TEAE with or without a known end date. Median duration of first TEAE calculated using Kaplan–Meier methodology and included resolved and ongoing events censored at date of last dose + 28 days, collapsing events within 2 days. †95% CI upper limit not reached. ALT alanine transaminase, AST aspartate transaminase, CI confidence interval, NC not calculable, TEAE treatment-emergent adverse event.

Survival

In the overall population, median PFS was 8.5 months (95% CI 6.7–11.7; Supplementary Fig. 2). Median OS for Part 2B patients ($n = 12$) was 25.1 months (95% CI 5.5–not reached). Three patients without a documented event of death were censored on the date of their last visit.

Safety

Median total duration of rucaparib treatment was 7.7 months (range, 0.1–51.6). All patients experienced at least one TEAE; 41/54 (75.9%) experienced at least one grade ≥3 TEAE (Supplementary Table 1). No cases of treatment-emergent myelodysplastic syndrome or acute myeloid leukaemia were reported in patients during the study, including the 28-day safety follow-up after the last dose. TEAEs led to treatment interruption in 36/54 (66.7%) patients and to dose reduction in 34/54 (63.0%) patients. TEAEs (excluding disease progression) led to discontinuation of rucaparib in 8/54 (14.8%) patients. Three patients discontinued rucaparib due to TEAEs that were considered to be treatment-related: one patient with anaemia, thrombocytopenia, and asthenia; one patient with nausea and fatigue; and one patient with hyperventilation. Treatment-related serious TEAEs reported were anaemia (3/54 [5.6%]) and B-cell type acute leukaemia, febrile neutropenia, nausea, neutropenia, and urinary tract infection (1/54 each [1.9%]). TEAEs with an outcome of death occurred in 5/54 (9.3%) patients, of which four deaths were associated with malignant neoplasm progression of their underlying ovarian cancer and were not considered related to rucaparib. One patient died due to B-cell type acute leukaemia, which was assessed by the investigator as possibly related to rucaparib; although there is no known mechanism by which a PARP inhibitor could cause a lymphocytic-type acute leukaemia, the temporal association with treatment precluded ruling out a causal relationship.

The most common any-grade nonhaematological TEAEs (reported in ≥35% of patients) were nausea, asthenia/fatigue, vomiting, constipation, ALT/AST increased, abdominal pain, headache, blood creatinine increased, diarrhoea, and dysgeusia (Supplementary Table 1). In general, median time to first onset of TEAEs occurred within 56 days from starting rucaparib, although diarrhoea, abdominal pain, and upper respiratory tract occurred later (Fig. 2a). For most of the frequently occurring nonhaematological TEAEs, median duration of the first event was <30 days (e.g., nausea, 28 days [95% CI 18–69]; vomiting, 2 days [95% CI 2–4]; abdominal pain, 22 days [95% CI 5–93]). Other common nonhaematological TEAEs had a median duration of first event ≥50 days (eg, asthenia/fatigue, 58 days [95% CI 37–160]; constipation, 134 days [95% CI 22–not reached]; ALT/AST increased, 50 days [95% CI 29–105]; Fig. 2a).

The most common any-grade haematological TEAE was anaemia/decreased haemoglobin (38/54 [70.4%]), followed by thrombocytopenia/decreased platelet count (19/54 [35.2%]), and

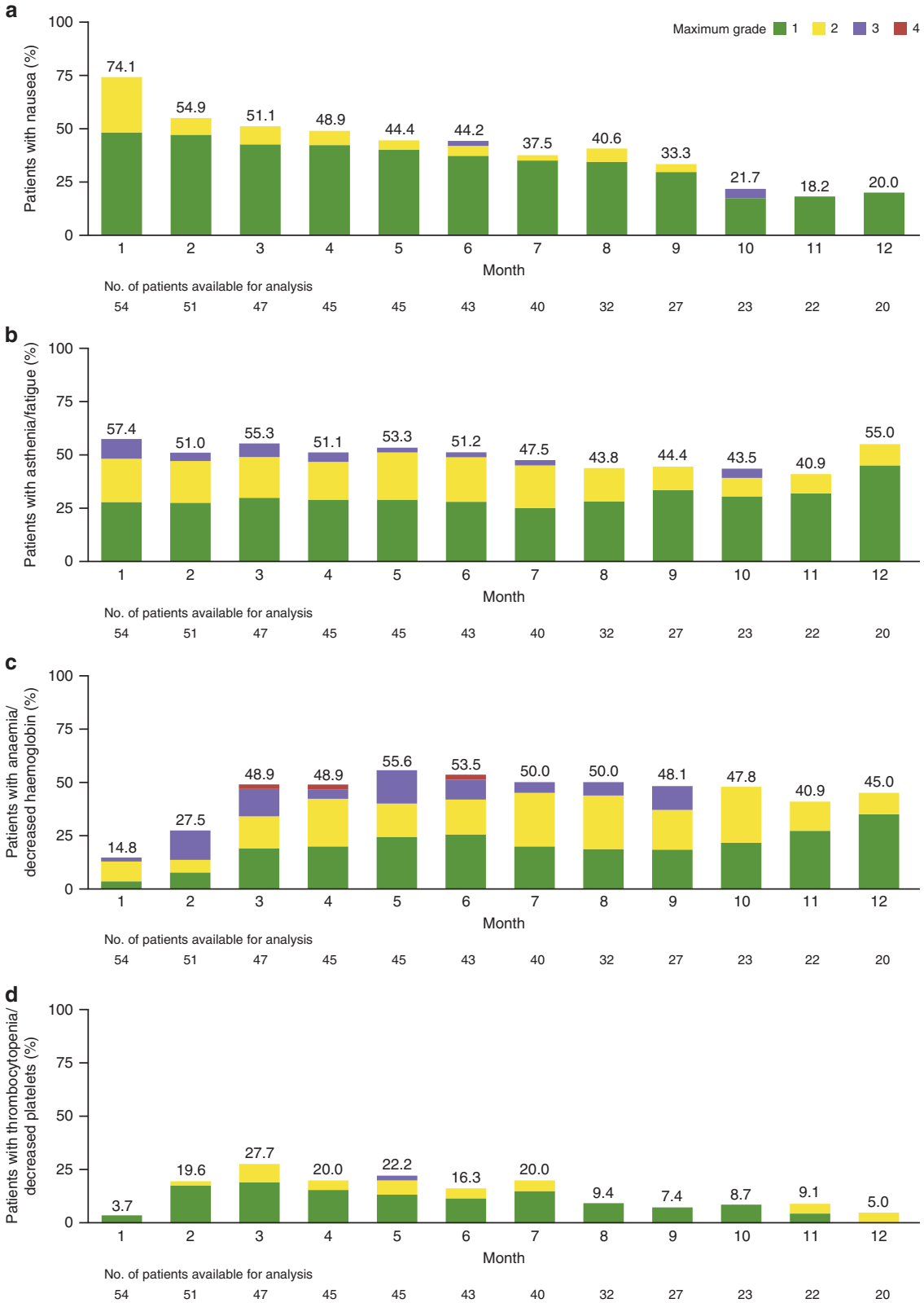

Fig. 3 Prevalence of most common nonhaematological and haematological TEAEs by treatment month. a Nausea. **b** Asthenia/fatigue. **c** Anaemia/decreased haemoglobin. **d** Thrombocytopenia/decreased platelets. Prevalence is defined as the proportion of patients experiencing a particular TEAE during each month and was based on the number of patients treated for that month. A treated patient is defined as receiving ≥1 dose of rucaparib or placebo during the month. TEAE treatment-emergent adverse event.

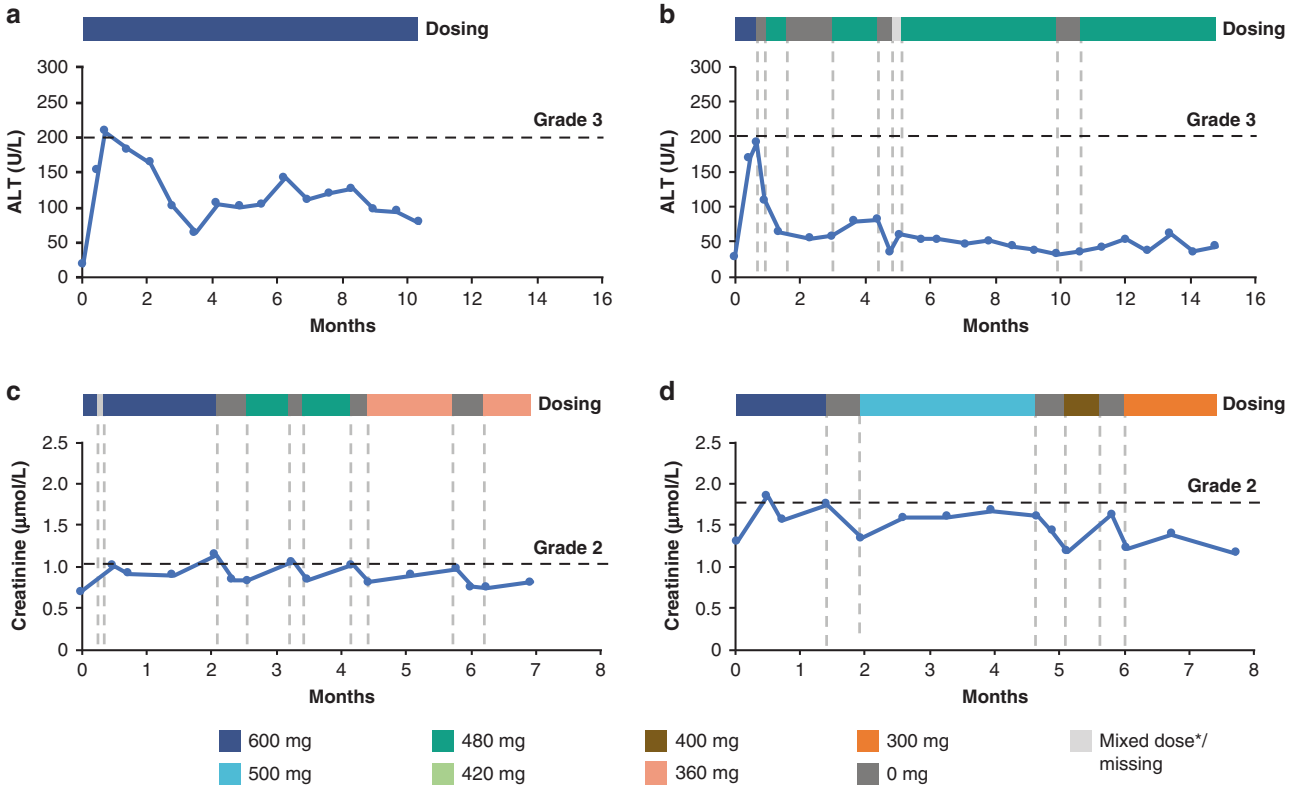

Fig. 4 Examples of individual patient laboratory values according to the rucaparib dose received. a Patient with grade 3 ALT elevation with no rucaparib dose reduction. **b** Patient with grade 3 ALT elevation with rucaparib dose reduction. **c**, **d** Patients with grade 2 creatinine elevations with rucaparib dose interruptions. Treatment interruptions of <3 days are not presented. *Inconsistent dosing for ≥3 days. ALT alanine aminotransferase.

neutropenia/decreased neutrophil count (14/54 [25.9%]) (Supplementary Table 1). The median time to first onset of these TEAEs was 53–64 days after treatment initiation (Fig. 2a). For these most frequently reported haematological TEAEs, median duration of first event ranged from 22 days (thrombocytopenia/decreased platelet count) to 78 days (anaemia/decreased haemoglobin; Fig. 2a).

The most common grade ≥3 TEAEs (occurring in ≥10% of patients) were anaemia/decreased haemoglobin (19/54 [35.2%]), followed by asthenia/fatigue (11/54 [20.4%]), ALT/AST increased (8/54 [14.8%]) and neutropenia/decreased neutrophil count (8/54 [14.8%]; Supplementary Table 1). Median time to first onset of grade ≥3 asthenia/fatigue and ALT/AST increased was 31 and 33 days after treatment initiation, respectively, while median time to first onset of grade ≥3 neutropenia/decreased neutrophil count and anaemia/decreased haemoglobin was 74 and 84 days after treatment initiation, respectively (Fig. 2b). For the most frequently occurring grade ≥3 TEAEs, the median duration of first event was 8–13 days (Fig. 2b), which was shorter than the median duration of the corresponding any-grade TEAEs (29–78 days; Fig. 2a).

When examining the prevalence of the two most common any-grade nonhaematological TEAEs (nausea and asthenia/fatigue) and haematological TEAEs (anaemia/decreased haemoglobin and thrombocytopenia/decreased platelet count) over the first 12 months of treatment (Fig. 3), events were predominantly grade 1 or 2. Prevalence of any-grade nausea tended to decline, with an incidence of 74.1% in month 1 to 20.0% in month 12. Although the prevalence of any-grade asthenia/fatigue did not decrease notably over the 12-month period (month 1, 57.4%; month 12, 55.0%), the proportion of patients with grade ≥2 asthenia/fatigue decreased from 29.6% at month 1 (11/54 patients with grade 2 and 5/54 patients with grade 3 events) to 10.0% at month 12 (2/20 patients with grade 2 events). Prevalence of any-grade anaemia/decreased haemoglobin increased from 14.8% in month 1 to a plateau at or near 50.0% over months 3–10 and decreased thereafter. Prevalence of any-grade thrombocytopenia/decreased platelets peaked at month 3 of treatment (27.7%), thereafter, gradually decreasing over the rest of the 12-month period to 5.0% at month 12.

Transient elevations in ALT and AST occurred relatively early after initiation of treatment (middle of cycle 1), normalised with continued treatment (Supplementary Fig. 3a, b), and were not associated with other signs of drug-induced liver toxicity. Elevations in creatinine were also observed within the first few weeks of rucaparib treatment and then stabilised with continued treatment (Supplementary Fig. 3c). Examples of individual patient laboratory values for ALT and creatinine are shown in Fig. 4. Grade 3 increased ALT was transient and subsequently decreased irrespective of rucaparib dose (no dose reduction, Fig. 4a; dose reduction, Fig. 4b). Grade 2 elevations in creatinine were reversible with rucaparib treatment interruption (Fig. 4c, d).

DISCUSSION

In Study 10 Parts 2A and 2B, we assessed the efficacy and safety of rucaparib in patients with relapsed, platinum-sensitive or platinum-resistant germline BRCA-mutant high-grade ovarian cancer who had received ≥2 prior chemotherapies. This analysis provides an additional 40 months of follow-up for patients who remained on rucaparib treatment beyond that reported previously for patients with platinum-sensitive ovarian cancer in Part 2A study (data cutoff November 30, 2015) [18]. Data for patients with platinum-resistant ovarian cancer from Part 2B of the study are also presented for the first time. These combined data have allowed us to provide a comprehensive analysis of rucaparib safety, including median time to first onset of frequently occurring

TEAEs, median duration of first TEAE, and their prevalence throughout the study. Further, we also characterised the relationship between rucaparib dosing and liver transaminase and serum creatinine measurements.

We recognise that the landscape for available therapies for ovarian cancer is ever changing. Although data are beginning to emerge [22, 23], it remains an open question how exposure to PARP inhibitors earlier in the course of disease may affect their utility if used again to treat more advanced disease. Nonetheless, our analysis demonstrates rucaparib's activity in patients with relapsed, platinum-sensitive or platinum-resistant germline BRCA-mutant high-grade ovarian cancer who were PARP inhibitor-naïve, including in patients who were heavily pretreated, with an investigator-assessed ORR of 59.3%. Responses were robust irrespective of the rucaparib dose received. Although all subgroups revealed some patients with antitumour activity, several subgroups had small numbers of patients (e.g., those with platinum-resistant disease), which limits the conclusions that can be made from these observations.

Our findings are consistent with those from previous studies that have shown that PARP inhibitors are an effective treatment option for patients with BRCA-mutated high-grade ovarian cancer who have received multiple prior rounds of chemotherapy. ARIEL4 (NCT02855944) is a randomised, Phase 3 study of rucaparib vs. standard-of-care platinum- and non-platinum-based chemotherapy in patients with relapsed, high-grade ovarian cancer with a germline or somatic BRCA mutation who had received ≥2 prior platinum regimens. Approximately half of patients in ARIEL4 had platinum-resistant disease vs. 14.8% in Study 10 Part 2 [17]. However, patients in ARIEL4 were less heavily pretreated, with only 28.0% of patients in the efficacy population having received ≥3 prior platinum-based chemotherapies [24], compared with 42.6% in Study 10 Part 2. Among patients in the ARIEL4 efficacy population, the ORR was 40% (95% CI 34–47%) in the rucaparib group vs. 32% (95% CI 23–43%) in the chemotherapy group ($P = 0.1287$) [17]. In the Phase 3 SOLO3 study (NCT02282020), the ORR was significantly higher with olaparib than with nonplatinum chemotherapy in a population of patients with germline BRCA-mutated, platinum-sensitive disease (72.2% vs. 51.4%, respectively; odds ratio 2.53, 95% CI 1.40–4.58, $P = 0.002$) [25]. The level of pretreatment in SOLO3 was similar to that of patients in Study 10 Part 2 (47.7% and 50.0% with ≥3 prior chemotherapies, respectively). In the Phase 2 QUADRA study (NCT02354586) evaluating niraparib in patients with relapsed high-grade ovarian cancer, treatment with niraparib resulted in an ORR of 39% in patients with platinum-sensitive germline or somatic BRCA-mutated ovarian cancer and 27% in patients with platinum-resistant/refractory BRCA-mutated ovarian cancer [26]. Almost all patients (98.9%) in QUADRA had received ≥3 prior chemotherapies.

Our results also demonstrated that patients derived clinical benefit with rucaparib as assessed by PFS (median, 8.5 months). These data are similar to those reported in integrated efficacy analyses of data from Study 10 Part 2A and ARIEL2 Parts 1 and 2 in patients with relapsed high-grade ovarian cancer. In 2017, Oza et al. reported a median PFS of 10.0 months (95% CI 7.3–12.5) with rucaparib in an integrated efficacy analysis population of 106 patients with platinum-sensitive, platinum-resistant, and platinum-refractory ovarian cancer [27]. In 2019, Kristeleit et al. reported data for an integrated efficacy population of 79 patients with platinum-sensitive ovarian cancer: median PFS was 10.6 months (95% CI 8.4–12.9) [28]. These data are also consistent with that from ARIEL4, in which the median PFS was 7.4 months (95% CI 7.3–9.1) in the rucaparib group vs. 5.7 months (95% CI 5.5–7.3) in the chemotherapy group (HR 0.64, 95% CI 0.49–0.84, $P = 0.001$) in the efficacy population [17]. Further, median OS in Study 10 Part 2B patients ($n = 12$) was 25.1 months, providing additional evidence of clinical benefit with rucaparib. OS was not a planned endpoint in Part 2A; therefore, follow-up was insufficient to report OS in this group.

Our safety analysis demonstrated that rucaparib has a manageable safety profile, which was consistent with the known adverse event profile of rucaparib in the treatment and maintenance settings [18, 27–31]. As with studies of other PARP inhibitors [25, 26], gastrointestinal disorders, haematological toxicities, and fatigue were among the more commonly reported TEAEs. Elevations in AST, ALT, or creatinine were observed during rucaparib treatment; however, no cases met Hy's law criteria for drug-induced liver injury. Per published guidance [32–34], AST, ALT or creatinine levels should be monitored on a monthly or bimonthly basis when initiating rucaparib treatment. In our study, AST and ALT elevations were transient and self-limiting, with no evidence of other signs of drug-induced liver toxicity. Our patient examples showed that grade 3 elevated ALT resolved either with or without a dose reduction, indicating that a dose reduction for grade 3 ALT elevation is not necessary, consistent with rucaparib prescribing recommendations and prior studies [12, 29, 31]. Elevation of serum creatinine was also observed; our patient examples show grade 2 elevations that were reversible with rucaparib dose interruption or treatment discontinuation. Similar patterns of creatinine elevation have been observed in other studies of rucaparib and with other PARP inhibitors [27, 28, 30, 35] and have been linked to inhibition of renal transporters MATE1 and MATE2-K [11, 36, 37]. Although creatinine elevations in serum are associated with decreased calculated creatinine clearance using the Cockcroft–Gault formula, in a study that directly measured glomerular filtration rates in patients receiving PARP inhibitors, elevated serum creatinine was not correlated with decreased renal function [38].

Importantly, median time to onset and duration of first TEAE data showed that nonhaematological events generally occurred early in treatment (mostly within 56 days, including grade ≥3 events) and resolved quickly, particularly if the events were grade ≥3 (median duration of ≤13 days). Haematological TEAEs of any grade tended to occur later in treatment (median time to onset of first event was 53 days). Neutropenia/decreased neutrophil count occurred in approximately 25% of patients treated with rucaparib, but the rate of febrile neutropenia was low (1/54 [1.9%]), and there were no cases of neutropenic sepsis observed. Grade ≥3 haematological events were transient in nature, with a median duration of 8 and 11 days reported for anaemia/decreased haemoglobin and neutropenia/decreased neutrophil count, respectively. This is consistent with similar observations from rucaparib maintenance treatment following a response to platinum-based chemotherapy. In the randomised Phase 3 ARIEL3 (NCT01968213) study of rucaparib maintenance treatment vs. placebo for recurrent ovarian cancer, the first onset of any-grade nonhaematological TEAEs generally occurred early in treatment (≤45 days), with haematological TEAEs occurring later (45–68 days), and the median duration of the first event of these TEAEs was generally <60 days [39]. The most common grade ≥3 haematological event, anaemia/decreased haemoglobin, was typically first observed after 85 days and was transient (median duration, 8 days) [39]. In comparison, data from the QUADRA study indicated that haematological TEAEs following niraparib treatment were frequent early in treatment (in the first month), and then decreased in frequency and severity during months 2–3 [40], although longer-term data are not available. Further, our analysis of the prevalence of the most common nonhaematological and haematological TEAEs with rucaparib treatment over time showed that the proportion of patients who experienced nausea decreased after month 1, the rate of asthenia/fatigue remained relatively stable, and the prevalence of anaemia/decreased haemoglobin and thrombocytopenia/decreased platelet count decreased after an initial peak. Similar trends in prevalence were observed for nausea and

anaemia/decreased haemoglobin with rucaparib maintenance treatment [39].

To date, ARIEL4 and SOLO3 are the only studies to report data directly comparing a PARP inhibitor with chemotherapy in patients with relapsed BRCA-mutated advanced ovarian cancer. In both of these studies, the rate of AEs leading to discontinuation were lower with the PARP inhibitor compared with chemotherapy (8% vs. 12% and 7% vs. 20%, respectively) [17, 25]. These findings suggest that PARP inhibitors may offer an alternative, more tolerable option than chemotherapy for some patients.

A limitation of the current study is that this was an open-label, single-arm study in a small patient population. Although Study 10 only included 8 patients with platinum-resistant disease, a lower objective response rate was observed in this population relative to patients with platinum-sensitive disease. These results were consistent with what was observed in the randomised Phase 3 study ARIEL4 [17, 24]. BRCA reversion mutations have been associated with the development of resistance to platinum and PARP inhibitors. Although none were detected in the predominately archival tissue samples available for central assessment in Study 10, it is possible that BRCA reversion mutations acquired after archival tissue collection may have contributed to a lack of response to rucaparib. In ARIEL4, BRCA reversion mutations were detected in tumours of some patients immediately prior to treatment, and patients in ARIEL4 with tumours harbouring BRCA reversion mutations were less likely to benefit from rucaparib [17]. Long-term follow-up for incidence of myelodysplastic syndrome or acute myeloid leukaemia was limited in Study 10 because these were not known AEs of special interest at the time the study was designed.

Rucaparib monotherapy demonstrated robust antitumour activity in patients with relapsed, platinum-sensitive or platinum-resistant germline BRCA-mutant high-grade ovarian cancer who received ≥2 prior chemotherapies. Rucaparib has a manageable safety profile, with no new safety concerns compared with previous safety reports in the treatment or maintenance settings. Our data also demonstrate the transient nature of transaminase elevation and the reversibility of creatinine elevations following treatment, highlighting that these AEs are manageable and do not represent liver or renal toxicity. As the use of PARP inhibitors becomes more common in earlier settings, future studies may be useful to investigate factors associated with clinical benefit of later-line treatment with a PARP inhibitor in patients with prior PARP inhibitor exposure.

DATA AVAILABILITY

Consent was not obtained from patients to allow the posting of the data to public repositories. Requests for de-identified datasets for the results reported in this publication will be made available to qualified researchers following the submission of a methodologically sound proposal to medinfo@clovisoncology.com. Data will be made available for such requests following the online publication of this article and for 1 year thereafter in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Data will be provided by Clovis Oncology. The redacted protocol for the Study 10 clinical study is available on https://clinicaltrials.gov/ProvidedDocs/15/NCT01482715/Prot_000.pdf. Clovis Oncology does not share identified participant data or a data dictionary.

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AUTHOR CONTRIBUTIONS

RSK, YD, TS, SG and LM designed the study. RSK, YD, AMO, SMD, SB, RMG, Judith Balmaña, LC, MRP, HAB, TS and RSF treated patients. RSK, YD, AMO, SMD, SB, RMG, Judith Balmaña, LC, MRP, HAB, TS, KKL and RSF acquired the data. RSK, KKL, SG and LM interpreted data. All authors wrote the manuscript and reviewed draft and final versions of it.

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COMPETING INTERESTS

RSK has received institutional funding from Clovis Oncology for this clinical trial; reports clinical trial grants from Merck Sharp & Dohme; has served as a consultant from Basilea Pharmaceutica and Shattuck Pharma; has received honoraria from Clovis Oncology, AstraZeneca, GlaxoSmithKline, and Incyte; received travelling support from AstraZeneca, GlaxoSmithKline, and Sierra Oncology; has served on data safety monitoring boards or advisory boards for Clovis Oncology, AstraZeneca, BeiGene, Eisai, GlaxoSmithKline, Incyte, iTeos Therapeutics, PharmaMar and Roche. YD has contributed to the development of rucaparib and has received royalty payments from Newcastle University for this work; has received research funding from Clovis Oncology, AstraZeneca, Merck KGaA, and Verastem; and has received honoraria for advisory boards/speakers fees from Clovis Oncology, AstraZeneca, Genmab, GlaxoSmithKline, Merck and Tesaro. AMO reports institutional research grants from AstraZeneca; served on an advisory board (uncompensated) for GlaxoSmithKline; served on advisory boards and steering committees (uncompensated) for Clovis Oncology and AstraZeneca; served as a principal investigator on investigator-initiated trials for Clovis Oncology, AstraZeneca, and GlaxoSmithKline. SMD has received research funding from Clovis Oncology and AstraZeneca; and has received honoraria from Clovis Oncology, AstraZeneca, and Bristol Myers Squibb. SB has served on advisory boards and received honoraria from Clovis Oncology, AstraZeneca, Genmab, GlaxoSmithKline, Immunogen, Merck Serono, Merck Sharp & Dohme, Mersana, Pfizer, Roche, Seattle Genetics, and Tesaro; received honoraria for lectures from AstraZeneca/Merck Sharp & Dohme, GlaxoSmithKline, Pfizer, Roche, and Tesaro; received support for travel or accommodation from NuCana and Tesaro; and reports institutional funding from AstraZeneca, GlaxoSmithKline and Tesaro. 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MRP reports a leadership position with ION Pharma; has received honoraria from Adaptive Biotechnologies, Bayer, Genentech, Janssen Oncology, Pfizer, and Pharmacyclics; has served in a consulting or advisory role for Pharmacyclics/Janssen and Pfizer/EMD Serono; has served on speakers' bureaus for Celgene, Exelixis, Genentech/Roche, and Taiho Pharmaceutical; his institution has received research funding from Clovis Oncology, Acerta Pharma, ADC Therapeutics, Agenus, Aileron Therapeutics, Artios, AstraZeneca, Bayer, Bicycle Therapeutics, BioNTech AG, BioTheryX, Black Diamond Therapeutics, Boehringer Ingelheim, Calithera Biosciences, Celgene, Checkpoint Therapeutics, CicloMed, Curis, Cyteir Therapeutics, Daiichi Sankyo, eFFECTOR Therapeutics, EMD Serono, Erasca, Evelo Biosciences, Forma Therapeutics, Genetec/Roche, Gilead Sciences, GlaxoSmithKline, H3 Biomedicine, Hengrui Therapeutics, Hutchison MediPharma, IgM Biosciences, Ignyta, Incyte, Jacobio Pharmaceuticals, Janssen, Jounce Therapeutics, Klus Pharma, Kymab, Lilly, Loxo Oncology, LSK BioPartners, Lycera, Mabspace, MacroGenics, Merck, Millennium, Mirati Therapeutics, Moderna Therapeutics, NGM Biopharmaceuticals, Novartis, Nurix, ORIC, Pfizer, Phoenix Molecular Designs, Placon, Portola Pharmaceuticals, Prelude Therapeutics, Puget Sound Biotherapeutics, PureTech, QiLu Pharmaceutical, Relay Therapeutics, Revolution Medicines, Ribon Therapeutics, Samumed, Seven and Eight Biopharmaceuticals, Silicon Therapeutics, Stemline Therapeutics, Syndax, Synthorx, Taiho Pharmaceutical, Takeda, TeneoBio, Tesaro, TopAlliance BioSciences, Treadwell Therapeutics, Vedanta Biosciences, Verastem Oncology, Vigeo, Xencor, and Zymeworks. 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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by an institutional review board at each study site and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation.

CONSENT TO PUBLISH

Not applicable.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Rebecca S. Kristeleit.