A Phase I–II Study of the Oral Poly(ADP-ribose) Polymerase Inhibitor Rucaparib in Patients with Germline *BRCA1/2*-mutated Ovarian Carcinoma or Other Solid Tumors

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Translational Relevance

Poly(ADP-ribose) polymerase-1 (PARP-1), PARP-2, and PARP-3 enzymes are key mediators of DNA repair in response to single-strand breaks. Inhibition of these enzymes results in accumulation of double-strand DNA breaks that are repaired through BRCA1- and BRCA2-mediated homologous recombination (HR). Defects in HR repair (eg, *BRCA1* and *BRCA2* mutations) can sensitize tumors to PARP inhibition through synthetic lethality. This phase I–II study was the first to fully evaluate single-agent oral rucaparib, a PARP inhibitor, in heavily pretreated patients with advanced solid tumors. In Part 1, pharmacokinetics were dose proportional, safety was manageable, and rucaparib 600 mg twice daily was the recommended phase II dose. In Part 2A, rucaparib 600 mg twice-daily treatment had robust antitumor activity in patients with platinum-sensitive ovarian cancer and a germline *BRCA1/2* mutation. These results support further clinical and translational investigation of rucaparib in tumors with HR repair deficiency, potentially extending applicability beyond *BRCA*-mutated cancers.

Abstract

Purpose: Rucaparib is a potent, oral, small-molecule poly(ADP-ribose) polymerase inhibitor. This phase I–II study was the first to evaluate single-agent oral rucaparib at multiple doses.

Experimental Design: Part 1 (phase I) sought to determine the maximum tolerated dose (MTD), recommended phase II dose (RP2D), and pharmacokinetics of oral rucaparib administered in 21-day continuous cycles in patients with advanced solid tumors. Part 2A (phase II) enrolled patients with platinum-sensitive, high-grade ovarian carcinoma (HGOC) associated with a germline *BRCA1/2* mutation who received two to four prior regimens and had a progression-free interval of 6 months or more following their most recent platinum therapy. The primary endpoint was investigator-assessed objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors version 1.1.

Results: In Part 1, 56 patients received oral rucaparib (40 to 500 mg once daily and 240 to 840 mg twice daily [BID]). No MTD was identified per protocol-defined criteria; 600 mg BID was selected as the RP2D based on manageable toxicity and clinical activity. Pharmacokinetics were approximately dose-proportional across all dose levels. In Part 2A, 42 patients with germline *BRCA1/2*-mutated HGOC received rucaparib 600 mg BID. Investigator-assessed ORR was 59.5%. The most common treatment-emergent adverse events (all grades) were asthenia/fatigue (85.7%; 36/42), nausea (83.3%; 35/42), anemia (71.4%; 30/42), alanine transaminase and/or aspartate transaminase elevations (57.1%; 24/42), and vomiting (54.8%; 23/42). Among 98 patients, five (5.1%) discontinued because of an adverse event (excluding disease progression).

Conclusions: Rucaparib was tolerable and had activity in patients with platinum-sensitive germline *BRCA1/2*-mutated HGOC.

Trial registration ID: NCT01482715

Introduction

Poly(ADP-ribose) polymerase (PARP) enzymes make up a 17-member superfamily of nuclear enzymes; PARP-1, -2, and -3 are activated by and promote the repair of DNA damage (1). PARP-1 and -2 are the most abundant enzymes and have a major role in the repair of DNA single-strand breaks through the base excision repair/single-strand break repair pathway (1). PARP inhibition results in accumulation of unrepaired single-strand breaks, which result in collapsed replication forks and an accumulation of DNA double-strand breaks (2, 3). These double-strand breaks are repaired by the homologous recombination (HR) repair pathway, in which BRCA1 and BRCA2 are key proteins (4-6). It is widely accepted that tumors with a *BRCA1/2* mutation or other HR deficiency (HRD) are selectively sensitive to PARP inhibition by a mechanism of synthetic lethality (7-9). Several recent reports have proposed additional models by which PARP inhibition may result in

synthetic lethality (10, 11). For example, PARP inhibition may affect the role these enzymes play in the alternative nonhomologous end-joining DNA repair pathway, which is upregulated in HR-deficient cells (12, 13). Additionally, PARP inhibitors have been shown to trap PARP-1 and -2 at the site of the DNA break (14). These trapped PARP-DNA complexes may directly damage the cell by obstructing replication forks, requiring HR repair for resolution (10, 14).

Several PARP inhibitors are currently in development for the treatment of patients with tumors harboring HRD, including those with a *BRCA1/2* mutation (15-26). Single-agent olaparib is approved in the United States for the treatment of patients with advanced germline *BRCA1/2*-mutated ovarian cancer who have received three or more lines of chemotherapy (27, 28). Rucaparib (CO-338; formerly known as AG-014447 and PF-01367338) is a potent small molecule inhibitor of PARP-1, -2, and -3 (29, 30), and was approved in the United States in December 2016 for the treatment of patients with advanced ovarian cancer associated with deleterious germline or somatic *BRCA* mutations who have received two or more chemotherapies (31). Consistent with the concept of synthetic lethality, rucaparib is preferentially cytotoxic to cells with a *BRCA1* or *BRCA2* mutation or epigenetically silenced *BRCA1* (7, 32).

An open-label, phase II study investigated intermittent dosing of intravenous rucaparib (5 days of a 21-day cycle), as well as intermittent and continuous dosing of oral rucaparib (7, 14, or 21 days of a 21-day cycle) in small cohorts of patients with advanced ovarian or breast cancer associated with a germline *BRCA1/2* mutation (33). This study provided evidence that continuous dosing of oral rucaparib led to a higher rate of response than intermittent intravenous dosing (response rate, 18% vs. 2%). The intravenous formulation was discontinued. However, the maximum oral dose of rucaparib 600 mg BID for 21 continuous days was only evaluated in one patient, and the study did not establish a recommended phase II dose (RP2D) for the oral formulation, which was a secondary endpoint.

The phase I–II study reported here was the first to fully evaluate single-agent oral rucaparib administered for multiple cycles in patients with an advanced solid tumor, including a cohort of patients with *BRCA1/2*-mutated ovarian cancer who had received multiple prior treatments. The objectives of this study included characterization of the safety and pharmacokinetic (PK) profiles, assessment of preliminary clinical activity, and establishment of the RP2D of rucaparib. Here we present results from Study 10 Part 1 (phase I dose escalation), as well as Part 2A (phase II expansion) that evaluated the RP2D of rucaparib as single-agent treatment in patients with platinum-sensitive, high-grade ovarian cancer (HGOC) associated with a germline *BRCA1/2* mutation.

Materials and Methods

Study design and patients

This is an ongoing, three-part, open-label, phase I–II study of single-agent oral rucaparib (ClinicalTrials.gov identifier, NCT01482715). It was approved by the institutional review board at each study site and is being conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. Patients provided written consent before participating in the study. Part 1 (phase I dose escalation) enrolled patients who were at least 18 years of age with an advanced solid tumor that had progressed on standard treatment. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1 and adequate hematologic, hepatic, and renal function. Measurable disease and a known *BRCA1/2* mutation were not required. The primary objectives of Part 1 were to characterize the safety and PK profile of oral rucaparib administered as a continuous daily dose and establish the maximum tolerated dose (MTD) and RP2D in patients with an advanced solid tumor. Antitumor activity was evaluated as a secondary objective.

Part 2A (phase II expansion) evaluated the RP2D of oral rucaparib in patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a germline *BRCA1/2* mutation. Eligible patients received between two and four prior treatment regimens, had an ECOG PS of 0 to 1, had a progression-free interval (PFI) of 6 months or longer after their most recent platinum-based regimen, and had measurable disease (of any size; with or without visceral metastasis) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST). Part 2A utilized a Simon two-stage design requiring two or more responses in the first 21 patients to continue to stage 2; total planned enrollment was 41 patients. The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST. Secondary objectives included evaluation of duration of response and safety. An independent radiology review of ORR for patients in Part 2A was performed retrospectively.

Study treatment

Using a standard 3 + 3 design for dose escalation (Part 1), patients received oral rucaparib once daily (QD) or twice daily (BID) in 21-day continuous treatment cycles, starting at 40 mg QD with escalations to 80, 160, 300, and 500 mg QD, then further escalation to 240, 360, 480, 600, and 840 mg BID. The protocol was amended approximately 10 months after enrollment began to allow intrapatient dose escalation. Patients in Part 2A received the RP2D of oral rucaparib established in Part 1. Treatment continued until disease progression or unacceptable toxicity. A new cycle of treatment could begin if a patient's absolute neutrophil count was 1.0×10^9/L or greater, platelet count was 75.0×10^9/L or greater, and nonhematologic toxicities had returned to baseline or were grade 1 or less.

Definition of dose-limiting toxicity and maximum tolerated dose

In Part 1, dose-limiting toxicities (DLTs) were defined as any of the following events that occurred during cycle 1 and were assessed by the investigator as related to rucaparib: absolute neutrophil count less than 0.5×10^9/L lasting for more than 5 days or febrile neutropenia; platelets less than 25×10^9/L or platelets less than 50×10^9/L with bleeding

requiring a platelet transfusion; grade 4 anemia; or any nonhematologic adverse event (AE) grade 3 or greater (except nausea, vomiting, and diarrhea, if well controlled by systemic medication, and alopecia). Dose escalation continued until 33% or more of patients treated at a dose level experienced a DLT. The next lower dose was then considered the MTD.

Pharmacokinetics, safety, and efficacy assessments

Pharmacokinetic assessments in Part 1 included single-dose and steady-state (day 15) profiles in cycle 1 and trough levels in selected cycles. Blood was collected prior to rucaparib dosing and from 15 minutes to 24 hours after dosing on days 1 and 15. Samples for PK analysis were collected before and/or after the morning dose for all patients on a BID dosing schedule. Safety assessments included evaluation of AEs, hematology, clinical chemistry, vital signs, body weight, concomitant medications and/or procedures, ECOG PS, electrocardiograms, and rucaparib dose modifications. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (34).

Tumor assessments consisted of clinical examination and computed tomography scans of the chest, abdomen, and pelvis (with appropriate slice thickness per RECIST) (35). Other assessments (eg, magnetic resonance imaging) were performed only if clinically required. Tumor assessments were performed at screening, prior to cycles 3, 5, and 7, and every three cycles of treatment thereafter from cycle 10. Tumor responses (per RECIST) were assessed in all patients; however, for those without measurable disease at baseline (permitted in Part 1), only a best response of stable or progressive disease could be achieved. Response in patients with ovarian cancer was also assessed using Gynecologic Cancer Intergroup (GCIG) cancer antigen 125 (CA-125) criteria (36). Confirmatory scans were required 4 to 6 weeks after an initial complete response (CR) or partial response (PR) was noted.

Dose reductions

Up to three dose reduction steps were permitted to manage treatment-related toxicity. In the event of grade 3 or 4 toxicity, treatment was held until resolution to grade 2 or less before re-administration of rucaparib. If dosing was interrupted for more than 14 consecutive days because of toxicity, treatment was discontinued unless the patient was deriving clinical benefit and the sponsor approved continuation of treatment. In Part 1, rucaparib was reduced to the next lower dose level. In Part 2A, rucaparib dose was reduced by increments of 120 mg.

Statistical analysis

For Part 1, it was estimated that six to 12 dose-escalation cohorts, with a minimum of three patients each, would be needed to evaluate the RP2D of oral rucaparib. In Part 2A, it was estimated that at least 41 patients evaluable for response would be needed to evaluate the efficacy of rucaparib.

The single-dose and steady-state rucaparib PK data following oral administration were analyzed using noncompartmental methods. The PK parameters included area under the concentration time curve (AUC) from time 0 to last measurable concentration, maximum concentration (C_{max}), time to C_{max} (T_{max}), half-life ($T_{1/2}$), apparent steady-state clearance (CL_{ss}/F), and accumulation ratio. Time to reach steady state was estimated based on the plasma trough concentration-time profile. Dose proportionality was assessed for QD and BID dosing using log-transformed PK parameters and dose by linear regression. The effect of food on single-dose rucaparib exposure, as measured by C_{max} and AUC time zero to 24 hours (AUC_{0-24}), was assessed at the 40 and 300 mg QD dose levels.

Safety analyses were performed by study part and by dose level in all patients who received at least one dose of rucaparib. The ORR was summarized for all patients enrolled in Part 2A who received at least one dose of rucaparib, and presented as percentages with 95% confidence intervals (CIs) using Clopper-Pearson methodology. Duration of confirmed response (CR or PR) was measured from the date of first response until the date that progressive disease was objectively documented, or censored at the last tumor evaluation.

Kaplan-Meier methodology was used to analyze duration of response and presented with the median and 95% CI.

RESULTS

Part 1 (phase I dose escalation)

Patients and treatments. Between December 2011 and October 2013, 56 patients were enrolled into Part 1 of the study. Results from Part 1 are based on a visit cutoff date of November 30, 2015.

Baseline characteristics are presented in Table 1. Most patients had either breast (48.2%; 27/56) or ovarian (35.7%; 20/56) cancer. The majority of patients (64.3%; 36/56) had a germline *BRCA1* or *BRCA2* mutation identified by local testing; for seven of 56 patients (12.5%), germline status was not confirmed as local *BRCA* testing was conducted using DNA extracted from tissues other than blood or buccal samples (eg, tumor tissue only). For 20 of 56 patients (35.7%), a *BRCA* mutation was not detected or no test was performed.

Twenty-six patients received rucaparib QD, at dose levels of 40 mg (*n* = 6), 80 mg (*n* = 3), 160 mg (*n* = 4), 300 mg (*n* = 9), and 500 mg QD (*n* = 4); 30 patients received rucaparib BID, at dose levels of 240 mg (*n* = 3), 360 mg (*n* = 8), 480 mg (*n* = 9), 600 mg (*n* = 7), and 840 mg BID (*n* = 3). Median treatment exposure across all dose levels was 3.2 months (range, 0.0–37.9); 20 of 56 patients (35.7%) received treatment for 6 months or more. One of eight patients treated with rucaparib 360 mg BID experienced a DLT of grade 3 nausea not well controlled by systemic medication; no DLTs were observed at any other dose level. No MTD was identified per the protocol-specified criteria.

Safety. Across dose levels, treatment-emergent AEs were mostly grade 1 or 2 in severity. No grade 4 events were reported (Table 2). The most common (≥20% of patients) treatment-emergent AEs were asthenia/fatigue, gastrointestinal disorders (nausea, vomiting, and diarrhea), myelosuppression (anemia, thrombocytopenia, and neutropenia), decreased

appetite, and elevated alanine transaminase (ALT) and/or aspartate transaminase (AST) levels. Treatment-emergent AEs of elevations in blood creatinine and ALT/AST levels were reported in 8.9% (5/56) and 25.0% (14/56) of patients and were mostly grade 1 or 2. Anemia was the most common grade 3 treatment-emergent AE, reported in five of 56 patients (8.9%) across all doses, with the highest incidence reported with the rucaparib 600 mg BID dose (28.6%; 2/7). Across all cohorts, 11 of 56 patients (19.6%) had a dose reduction because of a treatment-emergent AE. At the visit cutoff date (November 30, 2015), two of 56 patients (3.6%) continued to receive treatment, 50 of 56 patients (89.3%) had discontinued because of disease progression (71.4%) or clinical deterioration (17.9%), and one patient each (1.8%) discontinued for the following reasons: vaginal fistula (considered related to disease progression), CA-125 increase, physician's decision, or eligibility violation (QTc higher than the allowed maximum of 450 ms). No treatment-related deaths were reported; three deaths resulting from disease progression were reported during the study.

Efficacy. In this portion of the study, objective responses or prolonged stable disease (SD) occurred in patients with a germline *BRCA* mutation. There were two patients who achieved a confirmed CR in Part 1 (Table 3). One patient with platinum-sensitive ovarian cancer and a germline *BRCA1* mutation receiving rucaparib 300 mg QD had a PR at 6 weeks (first on-study assessment) and eventually achieved a CR at 54 weeks. At the visit cutoff date, the patient had been on study for 165 weeks, with a confirmed CR for 111 weeks. A patient with breast cancer and a germline *BRCA1* mutation receiving rucaparib 360 mg BID had a PR at 6 weeks (first on-study assessment) and achieved a CR at 18 weeks, which lasted for 60 weeks.

A confirmed PR was achieved in six patients (Table 3). One patient with breast cancer and a germline *BRCA1* mutation receiving rucaparib 300 mg QD had a PR for 15 weeks. One patient with pancreatic cancer and a germline *BRCA2* mutation receiving rucaparib 360 mg BID had a PR for 28 weeks. In the rucaparib 480 mg BID cohort, one patient with breast cancer and a germline *BRCA2* mutation, one patient with platinum-resistant ovarian cancer

and a germline *BRCA2* mutation, and one patient with breast cancer and a tumor *BRCA1* mutation achieved a PR of 116, 37, and 21 weeks' duration, respectively. One patient with platinum-resistant ovarian cancer and a tumor *BRCA1* mutation who received rucaparib 600 mg BID had a PR for 13 weeks. Twenty-two patients (15 with ovarian, six with breast, and one with colon cancer) had a best response of SD; 14 patients had durable SD for more than 24 weeks. Of thirteen patients with ovarian cancer associated with a *BRCA* mutation who received rucaparib BID (360 to 840 mg), two (15.4%; 95% CI, 1.9–45.4) achieved a confirmed PR, 10 (76.9%) had a best response of SD, and one (7.7%) was not evaluable. The best response in target lesions for all phase I patients with measurable disease is presented in Fig. 1A.

Pharmacokinetics. Fifty-six patients entered the dose-escalation portion of the study and received oral rucaparib with or without food at doses ranging from 40 to 500 mg QD and 240 to 840 mg BID (480 to 1680 mg/day). Pharmacokinetic parameters are summarized in Table 4. The mean plasma rucaparib concentration-time profiles by dose level on cycle 1 days 1 and 15 following QD and BID dosing are presented in Supplementary Fig. S1 and Fig. S2, and the relationship between dose level and exposure is presented in Supplementary Fig. S3. Plasma exposure of rucaparib was approximately dose proportional. The median values of T_{max} ranged from 1.5 to 6 hours across all doses, suggesting relatively fast absorption. The estimated $T_{1/2}$ for QD dosing was approximately 17 hours. Steady state appeared to be achieved by day 8 with QD or BID dosing based on the predose plasma concentration of rucaparib. The estimated mean values of CL_{SS}/F ranged from 26.7 to 47.5 L/h for QD dosing and from 26.2 to 58.6 L/h for BID dosing. The accumulation ratio of rucaparib plasma exposure at steady state ranged from 1.06 to 1.8 for C_{max} and 1.6 to 2.3 for $AUC_{0\text{-}24}$ with QD dosing, and from 2.6 to 4.9 for C_{max} and 1.47 to 5.44 for $AUC_{0\text{-}12}$ with BID dosing. The accumulation on a BID schedule was approximately twice that of the QD schedule. The time to steady state and the observed accumulation ratios are consistent with the $T_{1/2}$ values, suggesting lack of time-dependent PK. The effect of a high-fat meal on rucaparib PK was

evaluated in three patients at 40 mg QD and six patients at 300 mg QD. A high-fat meal did not cause clinically meaningful changes of rucaparib PK at these dose levels (Supplementary Table S1).

Recommended phase II dose. Based on protocol-specified criteria, no MTD was identified for dose levels of 40 mg QD up to 840 mg BID in Part 1. The 600 mg BID dose was selected as the RP2D upon consideration of the manageable safety and antitumor activity of rucaparib, as well as the PK profile observed in patients in Part 1. No patients in the 600 mg BID cohort discontinued because of an AE; however, myelosuppression requiring dose modification was observed in some patients after several cycles of treatment. Furthermore, antitumor activity was observed in patients in this cohort.

Part 2A (phase II expansion)

Patients and treatments. Part 2A of the study evaluated oral rucaparib in patients with platinum-sensitive, high-grade serous, endometrioid, mixed histology or clear cell ovarian cancer associated with a germline *BRCA1/2* mutation. The majority of patients had high-grade serous cancer (Table 1). In stage 1, three of the first five patients enrolled achieved a RECIST response, satisfying the criteria to continue to stage 2. A total of 42 patients were enrolled into Part 2A; the majority of patients (71.4%; 30/42) had a *BRCA1* mutation, and 28.6% (12/42) had a *BRCA2* mutation (Table 1). The median number of prior chemotherapy regimens was two (range, 2–4); 15 of 42 patients (35.7%) had received three or more prior chemotherapies.

At the visit cutoff date (November 30, 2015), nine of 42 patients (21.4%) remained on treatment. Twenty-six of 42 patients (61.9%) discontinued because of disease progression (52.4%) or clinical decline (9.5%), four (9.5%) discontinued because of an AE, two (4.8%) discontinued because of CA-125 increase, and one (2.4%) discontinued upon investigator decision. Median treatment exposure was 7.4 months (range, 0.1–20.2).

Efficacy. Of 42 patients, 25 (59.5%) achieved an investigator-assessed, confirmed RECIST response and 35 (83.3%) achieved an investigator-assessed, RECIST/GCIG CA-125 response (Table 3). Activity was observed in patients with either a *BRCA1* or *BRCA2* mutation, those with a PFI of 6 to 12 months or more than 12 months, as well as those who had received at least three prior chemotherapy regimens. Most patients (60.0%; 15/25) with a RECIST response achieved a response by the first disease assessment (approximately 6 weeks), and all but two of the responders achieved a response by the second disease assessment (approximately 12 weeks). The majority of patients (88.1%; 37/42) had a reduction in target lesion size (Fig. 1B). An example of a patient with visceral disease who had received two prior platinum-based regimens and achieved a PR to rucaparib at cycle 2 (51% decrease in sum of target lesions) is shown in Supplementary Fig. S4. Notably, the patient with clear cell ovarian cancer and the patient with endometrioid ovarian cancer each achieved a PR, as did many patients with serous ovarian cancer; thus the presence of a *BRCA* mutation appears to play a larger role than histology in determining response to rucaparib. The median duration of investigator-assessed confirmed response for patients in Part 2A was 7.8 months (95% CI, 5.6–10.5). Nine of the 25 responders were censored at the visit cutoff date. Of these nine patients, five were ongoing and four discontinued treatment for reasons other than disease progression (Fig. 1C). In a retrospective analysis, the confirmed ORR by independent radiology review was 52.4% (95% CI, 36.4–68.0).

Safety. Treatment-emergent AEs (all grades) were reported in all 42 patients (100.0%) (Table 2), the most common of which were asthenia/fatigue, nausea, anemia, ALT/AST elevations, vomiting, constipation, and headache. Treatment-emergent AEs of elevations in blood creatinine were reported in 33.3% of patients (14/42) and were grade 1 or 2. Grade 3 or 4 treatment-emergent AEs were reported in 32 of 42 patients (76.2%); those reported in 10% or more of patients included asthenia/fatigue (grade 3, 26.2% [11/42]; grade 4, none), anemia (grade 3, 31.0% [13/42]; grade 4, 7.1% [3/42]), and elevated ALT/AST (grade 3, 14.3% [6/42]; grade 4, none) (Table 2). Four of 42 patients (9.5%) discontinued treatment

because of an AE, including abdominal cramp, constipation, dizziness, fatigue, hypercholesterolemia, nausea, shaking, urinary tract infection, and vomiting; 26 of 42 patients (61.9%) discontinued because of disease progression or clinical deterioration. There were three deaths that resulted from disease progression; no treatment-related deaths were reported during the study.

Among 42 patients, treatment-emergent AEs led to a dose reduction in 29 patients (69.0%) and treatment interruption in 27 patients (64.3%). Thirty-eight patients (90.5%) had at least one dose reduction or treatment delay because of a treatment-emergent AE. Grade 3 or 4 AEs were managed with treatment modification and/or supportive care. In most patients, myelosuppression was a cumulative effect that manifested after cycle 1 and was successfully treated with supportive care and/or dose interruption or modification. Transient elevations in ALT and/or AST, with no other evidence of liver dysfunction, occurred relatively early after initiation of treatment (middle of cycle 1 or start of cycle 2) and resolved or stabilized over time, including during continued rucaparib exposure (Fig. 2).

Discussion

In this phase I–II study, oral rucaparib had a manageable safety profile and favorable PK properties. During dose escalation, rucaparib was active in patients who had a germline *BRCA1/2* mutation, with responses observed in patients with ovarian (platinum-sensitive and platinum-resistant), breast, and pancreatic tumors. Part 2A data indicated that administration of rucaparib 600 mg BID led to robust responses in patients with platinum-sensitive, relapsed, high-grade, serous, endometrioid, and/or clear cell ovarian cancer associated with a germline or tumor *BRCA1/2* mutation.

This study was the first to fully evaluate daily, single-agent oral rucaparib in patients with an advanced solid tumor and to provide a comprehensive characterization of its safety and PK profile. Continuous dosing of oral rucaparib was associated with approximately dose-

proportional rucaparib exposure in the tested dose ranges following QD and BID administration, with moderate interpatient variability and a $T_{1/2}$ of approximately 17 hours independent of dose. In a small cohort of patients, a high-fat meal did not cause clinically meaningful changes in rucaparib PK, indicating that patients may take rucaparib with or without food. During the dose escalation phase of the study (Part 1), no MTD was identified in patients treated with rucaparib doses up to 840 mg BID; however, delayed myelosuppression requiring dose modification was observed in some patients treated with rucaparib 600 mg BID. The 600 mg BID dose was selected as the RP2D based on manageable safety and clinical activity, and was further characterized in the phase II portion.

Oral rucaparib 600 mg BID was tolerable, with a manageable safety profile that was consistent with its mechanism of action. Toxicities observed with rucaparib, such as myelosuppression, fatigue, and gastrointestinal disorders, are commonly observed with other PARP inhibitors (19, 23, 24, 37, 38). Myelosuppression, which generally occurs at a lower frequency with PARP inhibitors in relation to platinum-based chemotherapy, was generally observed after several cycles of rucaparib treatment and was successfully managed with supportive care and treatment modification (dose reduction and/or interruption). Other common low-grade AEs included fatigue and gastrointestinal side effects, such as nausea and vomiting. These AEs were successfully managed with supportive care and/or dose modification, as needed. Elevated serum creatinine was observed during rucaparib treatment. Elevations in creatinine have also been observed following the use of the PARP inhibitor olaparib (27). Elevations in creatinine may be attributed to the inhibition of the active tubular secretion of creatinine into the proximal tubule and subsequent apical efflux into the urine, as rucaparib has demonstrated potent inhibition of MATE1 and MATE2-K and moderate inhibition of OCT-2 in vitro. Inhibition of these transporters has also been demonstrated in vitro with the PARP inhibitor veliparib and other drugs (39, 40). Some AEs observed with rucaparib treatment, such as elevations in ALT and AST, have not been previously associated with PARP inhibitors. The mechanism

responsible for the transaminase elevations has not been identified; however, such elevations were transient and resolved or stabilized during treatment. Of the 98 patients treated in Study 10 (Parts 1 and 2 combined), 87 patients discontinued treatment because of disease progression (62/98; 63.3%), clinical progression (14/98; 14.3%), treatment-emergent AE (5/98; 5.1%), or other reason (6/98; 6.1%). No treatment-related deaths were reported in either Part 1 or Part 2A.

The benefits of PARP inhibitors for treatment of germline *BRCA1/2*-mutated ovarian cancer are well established, with response rates in the range of 38% to 60% reported in patients with platinum-sensitive disease (16, 18, 19, 24, 41-43). In the 42 patients with platinum-sensitive, relapsed HGOC associated with a germline *BRCA1/2* mutation enrolled in Part 2A of this study (600 mg BID), the investigator-assessed ORR was 59.5% by RECIST and 83.3% by RECIST/CA-125 criteria.

Part 2B of this study is currently assessing the efficacy of rucaparib in patients with platinum-sensitive, relapsed HGOC associated with a germline or somatic *BRCA1/2* mutation who had received at least three prior chemotherapy regimens. Part 3 is ongoing and currently assessing the PK (including the effect of food) and safety profile of a higher dose tablet of rucaparib in patients with a relapsed solid tumor associated with a germline or somatic *BRCA1/2* mutation.

This study provides evidence of the antitumor activity of rucaparib in patients with germline *BRCA1/2*-mutated ovarian cancer. Results from this study and the ongoing phase II ARIEL2 study (NCT01891344) supported the accelerated approval of rucaparib (600 mg BID) by the United States Food and Drug Administration for the treatment of patients with advanced ovarian cancer associated with deleterious germline or somatic *BRCA* mutations who have received two or more chemotherapies. Additional preclinical data indicate that the antitumor activity of rucaparib extends beyond tumors with a *BRCA1/2* mutation to a broader group of tumors with HRD (32, 44, 45). For this reason, rucaparib is being developed for the treatment of tumors with HRD, including those with a *BRCA1* or *BRCA2* mutation

(ClinicalTrials.gov identifiers: NCT00664781, NCT01074970, NCT01482715, NCT01891344, NCT01968213, NCT02042378, and NCT02505048). In addition to the ARIEL2 study, which is investigating rucaparib in the treatment setting, rucaparib is being evaluated in the maintenance setting in patients with relapsed HGOC in the phase III ARIEL3 study (NCT01968213). The ARIEL2 and ARIEL3 studies are enrolling patients with or without a germline or somatic *BRCA1/2* mutation in order to investigate the activity of rucaparib in a wider group of patients with HRD-associated ovarian cancer. The ARIEL clinical development program is prospectively testing a novel next-generation sequencing HRD assay and algorithm to predict which patients with ovarian cancer, including those whose tumors lack a *BRCA1* or *BRCA2* mutation, who may benefit from rucaparib. Results from ARIEL2 Part 1 indicate that some patients who have *BRCA1/2* wild-type tumors and have a high percentage of tumor genomic loss of heterozygosity respond to rucaparib treatment (43). In ARIEL3, this novel HRD assay will be prospectively applied to the primary analysis of investigator-assessed progression-free survival by RECIST with the aim of validating the test to identify patients with HRD tumors who will be most likely to benefit from rucaparib.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Supplementary data include the following:

Figure S1. Rucaparib plasma concentration-time profiles following once daily oral administration

Figure S2. Rucaparib plasma concentration-time profiles following twice daily oral administration

Figure S3. Observed and predicted relationship between rucaparib dose and exposure at steady state on once-daily (QD) and twice-daily (BID) dosing schedules

Figure S4. Radiological response to rucaparib 600 mg BID in a patient with ovarian cancer who had a germline *BRCA2* mutation and visceral disease at baseline.

Table S1. Summary of pharmacokinetics parameters of rucaparib administered under fasting and fed conditions

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634

635 **Table 1.** Baseline patient and disease characteristics

Parameter	Part 1 Phase I (*n* = 56)	Part 2A Phase II (*n* = 42)
Age, median (range), y	51 (21–71)	57 (42–84)
Gender, *n* (%)		
Female	51 (91.1)	42 (100.0)
Male	5 (8.9)	0 (0)
ECOG PS, *n* (%)		
0	29 (51.8)	26 (61.9)
1	27 (48.2)	16 (38.1)
Germline *BRCA1/2* mutation, *n* (%)		
Yes	36 (64.3)	42 (100.0)
No mutation detected	9 (16.1)	0 (0)
No test performed[a]	11 (19.6)	0 (0)
BRCA gene mutation, *n* (%)		
BRCA1	22 (39.3)	30 (71.4)
BRCA2	14 (25.0)	12 (28.6)
Type of cancer, *n* (%)		
Breast	27 (48.2)	0 (0)
Ovarian	20 (35.7)	42 (100.0)
Pancreatic (exocrine)	2 (3.6)	0 (0)
Other[b]	7 (12.5)	0 (0)
Histological classification, *n* (%)		
Serous	NA	37 (88.1)
Mixed	NA	3 (7.1)
Endometrioid	NA	1 (2.4)
Clear cell	NA	1 (2.4)
Platinum status of patients with ovarian		

cancer, *n* (%)[c]		
Refractory	1 (1.8)	0 (0)
Resistant	11 (19.6)	0 (0)
Sensitive	8 (14.3)	42 (100.0)
Progression-free interval from last platinum therapy, *n* (%)		
≥6–12 mo	NA	32 (76.2)
>12 mo	NA	10 (23.8)
Previous anticancer therapies, median (range)	4 (1–15)	2 (2–4)
≥3 previous anticancer therapies, *n* (%)	41 (73.2)	15 (35.7)
Previous chemotherapies, median (range)	3 (1–13)	2 (2–4)
≥3 previous chemotherapies, *n* (%)	37 (66.1)	15 (35.7)
Previous platinum-based chemotherapies, median (range)	1 (0–5)	2 (2–4)
≥3 previous platinum-based chemotherapies, *n* (%)	9 (16.1)	13 (31.0)

[a]Patients did not have local or central BRCA testing performed.

[b]One each of the following: small-cell lung cancer, gastric cancer, colon cancer, desmoplastic round cell tumor, mesenchymal chondrosarcoma of the skull, astrocytoma, and angiosarcoma.

[c]Platinum status was not applicable for 36 patients (64.3%) in Part 1.

NA, not applicable.

636

637 **Table 2.** Treatment-emergent adverse events (occurring in ≥20% of patients in Part 1 or Part 2a) by rucaparib dose

	Part 1 (Phase I Dose Escalation), *n* (%)							Part 2A (Phase II Expansion), *n* (%)				
	40–500 mg QD (*n* = 26)[a]	240 mg BID (*n* = 3)	360 mg BID (*n* = 8)	480 mg BID (*n* = 9)	600 mg BID (*n* = 7)	840 mg BID (*n* = 3)	All doses (*n* = 56)	600 mg BID (*n* = 42)				
Adverse Event	All Grade	All Grade	All Grade	All Grade	All Grade	All Grade	All Grade	Grade 1	Grade 2	Grade 3	Grade 4	All Grade
Any adverse event	26 (100.0)	3 (100.0)	8 (100.0)	8 (88.9)	7 (100.0)	3 (100.0)	55 (98.2)	0 (0)	7 (16.7)	26 (61.9)	6 (14.3)	42 (100.0)
Asthenia/fatigue	10 (38.5)	2 (66.7)	5 (62.5)	5 (55.6)	5 (71.4)	1 (33.3)	28 (50.0)	8 (19.0)	17 (40.5)	11 (26.2)	0 (0)	36 (85.7)
Nausea	12 (46.2)	0 (0)	6 (75.0)	4 (44.4)	4 (57.1)	3 (100.0)	29 (51.8)	17 (40.5)	15 (35.7)	3 (7.1)	0 (0)	35 (83.3)
Anemia[b]	5 (19.2)	0 (0)	4 (50.0)	3 (33.3)	4 (57.1)	1 (33.3)	17 (30.4)	7 (16.7)	7 (16.7)	13 (31.0)	3 (7.1)	30 (71.4)
AST/ALT increased	2 (7.7)	0 (0)	2 (25.0)	3 (33.3)	6 (85.7)	1 (33.3)	14 (25.0)	11 (26.2)	7 (16.7)	6 (14.3)	0 (0)	24 (57.1)
Vomiting	10 (38.5)	0 (0)	3 (37.5)	5 (55.6)	4 (57.1)	2 (66.7)	24 (42.9)	12 (28.6)	8 (19.0)	3 (7.1)	0 (0)	23 (54.8)
Constipation	8 (30.8)	0 (0)	2 (25.0)	2 (22.2)	1 (14.3)	0 (0)	13 (23.2)	15 (35.7)	7 (16.7)	0 (0)	0 (0)	22 (52.4)
Headache	5 (19.2)	0 (0)	2 (25.0)	1 (11.1)	2 (28.6)	1 (33.3)	11 (19.6)	13 (31.0)	5 (11.9)	1 (2.4)	0 (0)	19 (45.2)
Abdominal pain	7 (26.9)	0 (0)	2 (25.0)	3 (33.3)	1 (14.3)	1 (33.3)	14 (25.0)	8 (19.0)	7 (16.7)	3 (7.1)	0 (0)	18 (42.9)
Dysgeusia	1 (3.8)	1 (33.3)	2 (25.0)	1 (11.1)	1 (14.3)	2 (66.7)	8 (14.3)	11 (26.2)	6 (14.3)	0 (0)	0 (0)	17 (40.5)
Diarrhea	4 (15.4)	1 (33.3)	1 (12.5)	2 (22.2)	2 (28.6)	3 (100.0)	13 (23.2)	8 (19.0)	8 (19.0)	0 (0)	0 (0)	16 (38.1)
Thrombocytopenia[c]	0 (0)	0 (0)	1 (12.5)	2 (22.2)	5 (71.4)	0 (0)	8 (14.3)	8 (19.0)	6 (14.3)	1 (2.4)	0 (0)	15 (35.7)
Blood creatinine increased	2 (7.7)	1 (33.3)	0 (0)	1 (11.1)	1 (14.3)	0 (0)	5 (8.9)	9 (21.4)	5 (11.9)	0 (0)	0 (0)	14 (33.3)
Neutropenia[d]	3 (11.5)	0 (0)	1 (12.5)	3 (33.3)	3 (42.9)	0 (0)	10 (17.9)	4 (9.5)	2 (4.8)	4 (9.5)	3 (7.1)	13 (31.0)
Decreased appetite	9 (34.6)	2 (66.7)	3 (37.5)	1 (11.1)	0 (0)	1 (33.3)	16 (28.6)	6 (14.3)	5 (11.9)	1 (2.4)	0 (0)	12 (28.6)
Abdominal distension	3 (11.5)	0 (0)	2 (25.0)	2 (22.2)	1 (14.3)	0 (0)	8 (14.3)	6 (14.3)	4 (9.5)	0 (0)	0 (0)	10 (23.8)

Blood alkaline phosphatase increased	2 (7.7)	0 (0)	0 (0)	2 (22.2)	4 (57.1)	0 (0)	8 (14.3)	10 (23.8)	0 (0)	0 (0)	0 (0)	10 (23.8)
Dyspnea	2 (7.7)	0 (0)	3 (37.5)	3 (33.3)	1 (14.3)	1 (33.3)	10 (17.9)	8 (19.0)	1 (2.4)	1 (2.4)	0 (0)	10 (23.8)
Upper respiratory tract infection	1 (3.8)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)	2 (3.6)	6 (14.3)	4 (9.5)	0 (0)	0 (0)	10 (23.8)
Cough	3 (11.5)	1 (33.3)	0 (0)	3 (33.3)	2 (28.6)	2 (66.7)	11 (19.6)	7 (16.7)	1 (2.4)	1 (2.4)	0 (0)	9 (21.4)
Dizziness	2 (7.7)	1 (33.3)	2 (25.0)	2 (22.2)	2 (28.6)	0 (0)	9 (16.1)	7 (16.7)	1 (2.4)	1 (2.4)	0 (0)	9 (21.4)

Table is sorted by decreasing incidence in Part 2A patients.

[a]40 mg QD (*n* = 6), 80 mg QD (*n* =3), 160 mg QD (*n* = 4), 300 mg QD (*n* = 9), and 500 mg QD (*n* = 4).

[b]Anemia and/or low/decreased hemoglobin.

[c]Thrombocytopenia and/or low or decreased platelets.

[d]Neutropenia and/or low or decreased absolute neutrophil count.

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Table 3. Antitumor activity in patients with advanced tumors who received rucaparib in Part 1 and investigator-assessed response in patients with germline *BRCA1/2*-mutated ovarian cancer from Part 2A

Part 1 (Phase I Dose Escalation) **Patients with Advanced Solid Tumors (*n* = 56)**					
Dose Received	**Confirmed CR or PR (RECIST)**	**Duration of Response (wk)**	**Type of Cancer**	***BRCA* Mutation**	**Platinum Status**
300 mg QD	CR	111	Ovarian	Germline *BRCA1*	Sensitive
300 mg QD	PR	15	Breast	Germline *BRCA1*	NA
360 mg BID	CR	60	Breast	Germline *BRCA1*	NA
360 mg BID	PR	28	Pancreatic	Germline *BRCA2*	NA
480 mg BID	PR	116	Breast	Germline *BRCA2*	NA
480 mg BID	PR	37	Ovarian	Germline *BRCA2*	Resistant
480 mg BID	PR	21	Breast	Tumor *BRCA1*	NA
600 mg BID	PR	13	Ovarian	Tumor *BRCA1*	Resistant

Part 2A (Phase II Expansion) **Patients with Germline *BRCA1/2*-Mutated Ovarian Cancer (*n* = 42)**	
RECIST best confirmed response	***n* (% [95% CI])**
CR	4 (9.5)
PR	21 (50.0)
SD	12 (28.6)
PD	2 (4.8)
NE	3 (7.1)
RECIST ORR	25 (59.5 [43.3–74.4])
RECIST/CA-125 ORR	35 (83.3 [68.6–93.0])
RECIST ORR by Part 2A patient subsets	***n*/*N* (% [95% CI])**
BRCA gene mutation	
BRCA1	19/30 (63.3 [43.9–80.1])
BRCA2	6/12 (50.0 [21.1–78.9])
PFI	
6–12 mo	17/32 (53.1 [34.7–70.9])
>12 mo	8/10 (80.0 [44.4–97.5])
≥3 prior chemotherapy regimens	9/15 (60.0 [32.3–83.7])
Duration of response, median (95% CI), mo	7.8 (5.6–10.5)

NA, not available; NE, not evaluable; PD, progressive disease.

644 **Table 4.** Single-dose and steady-state plasma pharmacokinetic parameters of rucaparib following once or twice daily continuous oral

645 administration (Part 1, phase I dose escalation)

Dosage	*N*	Day	Arithmetic Mean C_{max} (CV%), ng/mL	Median T_{max} (range), h	Arithmetic Mean $AUC_{0-\tau}$ (CV%), ng×h/mL	Arithmetic Mean CL_{ss}/F (CV%), L/h	AR (CV%)	Arithmetic Mean $T_{1/2}$ (CV%), h
40 mg QD	3	1	129 (28)	2.5 (1–4)	915[a]	NR	NA	13.9 (57)
		15	138 (36)	4 (1–4.05)	1810 (44)	26.7 (59)	1.68[a]	25.7 (23)
80 mg QD	3	1	114 (41)	1.5 (1–2.5)	800 (27)	NR	NA	11.0[a]
		15	175 (37)	2.5 (2.5–2.57)	1740 (20)	47.5 (23)	2.33 (42)	19.5[a]
160 mg QD	4	1	261 (51)	4.0 (4–6.05)	3050 (51)	NR	NA	19.9 (21)
		15	288 (29)[b]	3.75 (2.5–4)[b]	4110 (33)[b]	41.6 (29)[b]	1.84 (31)[b]	33.6 (12)[b]
300 mg QD	3	1	629 (37)	2.5 (1–4.08)	5740 (38)	NR	NA	15.2 (72)
		15	693 (76)	2.53 (2.5–8)	9610 (83)	46.7 (63)	1.60 (53)	29.8[a]
500 mg QD	3	1	949 (52)	4 (4–4)	11,000 (61)	NR	NA	15.0 (32)
		15	1390 (23)	4 (4–4.17)	19,900 (41)	27.8 (35)	1.94 (17)	20.8 (38)
240 mg BID	3	1	219 (72)	6 (4.05–6)	2800[c]	NR	NA	NR[h]
		15	971 (49)	1.5 (1–4)	10,700[a]	27.3[a]	5.44[c]	
360 mg BID	8	1	666 (58)	3.23 (1.5–6)	4860 (58)[d]	NR	NA	
		15	1300 (43)[d]	3.3 (0–6.33)[d]	9430[a]	40.4[a]	4.08[a]	
480 mg BID	9	1	1150 (57)	2.5 (1.5–4)	8810 (63)[e]	NR	NA	
		15	3170 (69)[e]	1.51 (0–6)[e]	26,300 (73)[d]	26.2 (63)[d]	3.97 (38)[f]	

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Dosage	*N*	Day	Arithmetic Mean C_{max} (CV%), ng/mL	Median T_{max} (range), h	Arithmetic Mean $AUC_{0-\tau}$ (CV%), ng×h/mL	Arithmetic Mean CL_{ss}/F (CV%), L/h	AR (CV%)	Arithmetic Mean $T_{1/2}$ (CV%), h
600 mg BID	7	1	1030 (61)	4 (2.42–10)	7200 (66)[g]	NR	NA	
		15	2420 (45)	4 (2.53–10)	21,400 (61)[g]	58.6 (123)[g]	3.23 (66)[g]	
840 mg BID	3	1	1380 (69)	4 (2.5–8)	13,200[a]	NR	NA	
		15	3030 (NR)[a]	4.04 (4–4.07)[a]	29,000[c]	29[c]	1.47[c]	

[a]*n* = 2; [b]*n* = 3; [c]*n* = 1; [d]*n* = 6; [e]*n* = 8; [f]*n* = 5; [g]*n* = 4; [h]$T_{1/2}$ is too long to allow for accurate estimate in BID dosing.

AR, accumulation ratio based on AUC; $AUC_{0-\tau}$, area under the plasma concentration-time curve from 0 to the end of dosing interval (τ = 24 h for QD; τ = 12 h for BID; for BID dosing, concentration at 12 h was calculated by extrapolation from last observed concentration in the same dosing interval); NA, not available; NR, not reportable; CV, coefficient of variation.

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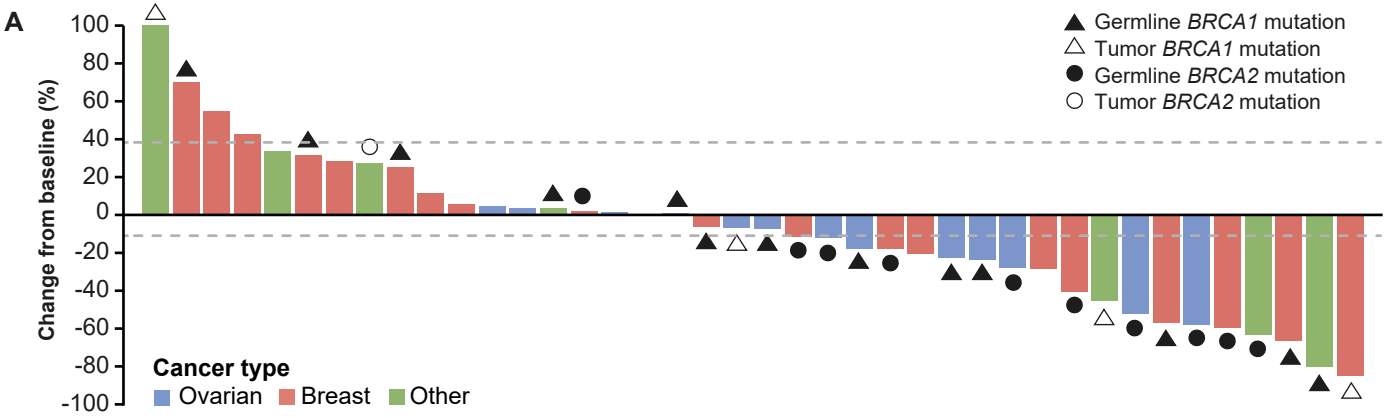
FIGURE LEGENDS

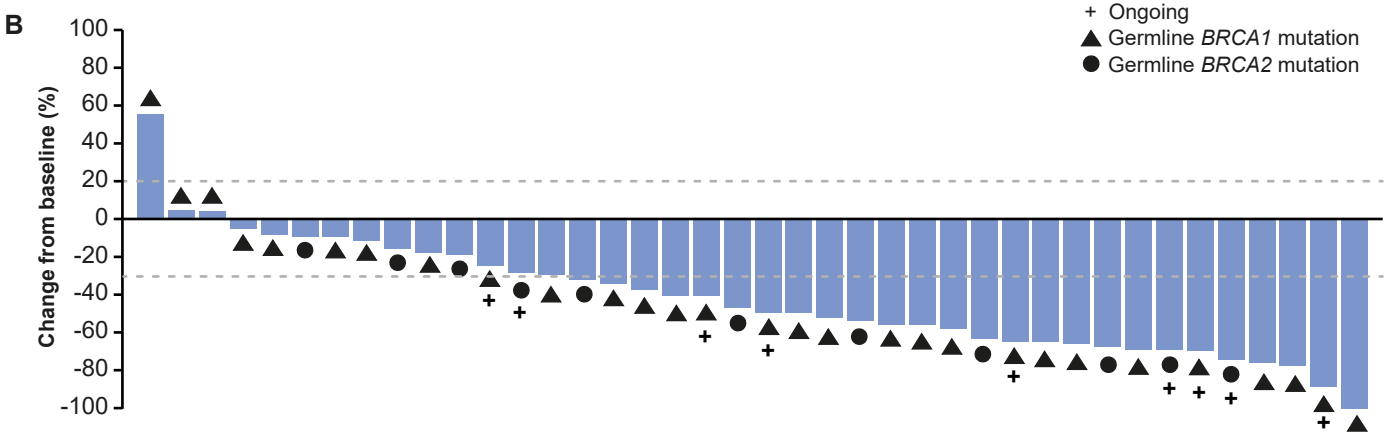
Figure 1.

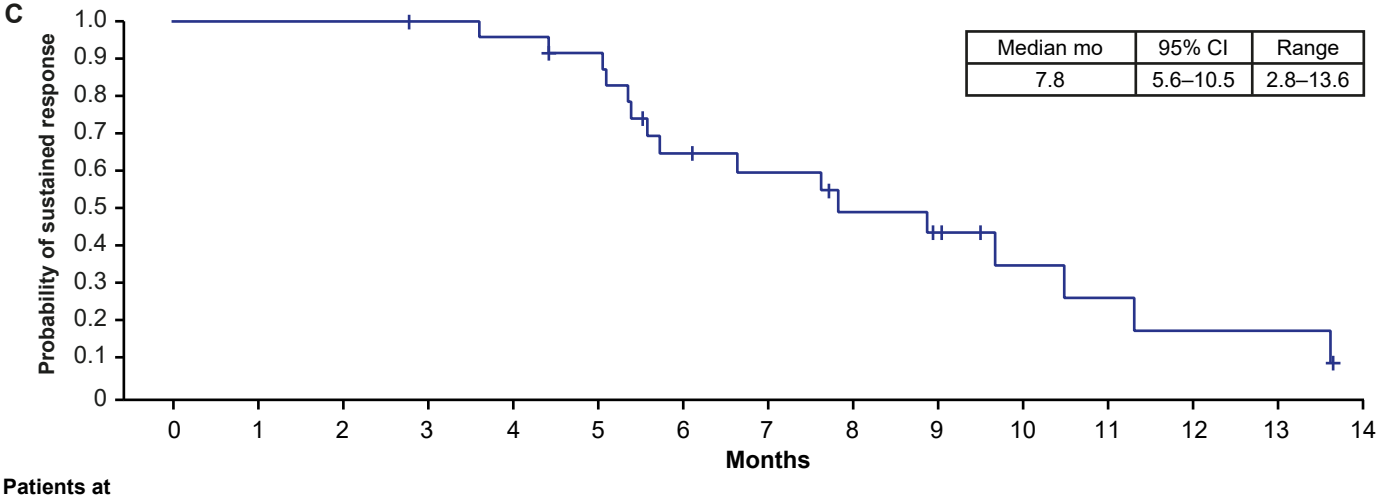
Waterfall plots for best overall change from baseline in target lesions in (A) patients with advanced solid tumors (Part 1, phase I dose escalation; *n* = 40) and (B) patients with germline *BRCA1/2*-mutated high grade ovarian cancer (Part 2A, phase II expansion; *n* = 40) who had both baseline and postbaseline measurements. (C) Duration of response for patients in Part 2A. In panel A, patients with a *BRCA1* or *BRCA2* mutation detected by local testing are indicated with triangles or circles; for mutations detected in tumor tissue only (open triangles and circles), germline status was not determined.

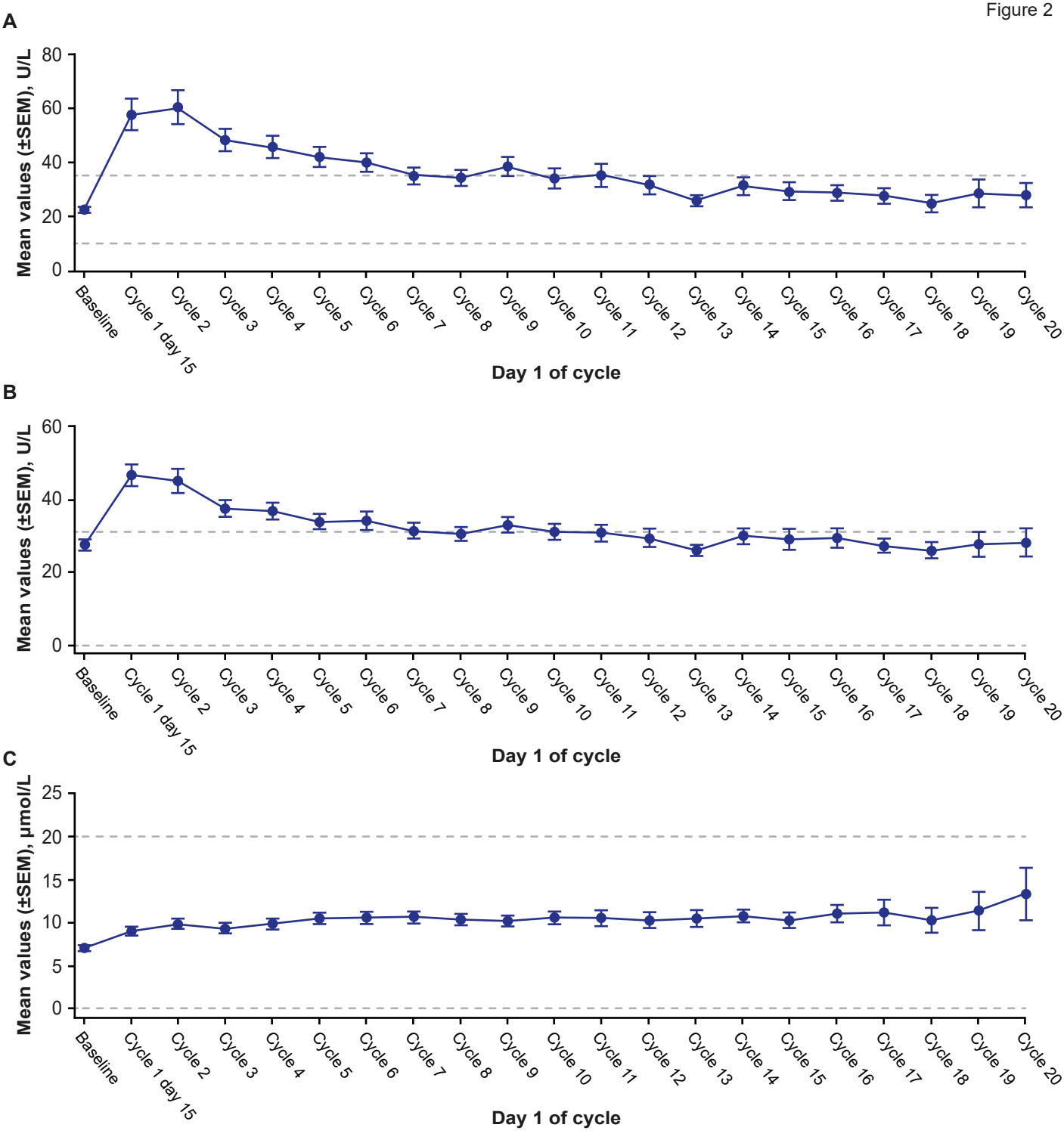
Figure 2.

Baseline and on-treatment values for (A) alanine aminotransferase, (B) aspartate aminotransferase, and (C) bilirubin for patients in Part 2A (*n* = 42). Dashed grey lines indicate the upper and lower limits of the normal range. SEM, standard error of the mean.


A
Change from baseline (%)
100
80
60
40
20
0
-20
-40
-60
-80
-100
Germline BRCA1 mutation
Tumor BRCA1 mutation
Germline BRCA2 mutation
Tumor BRCA2 mutation
Cancer type
Ovarian
Breast
Other


B
Change from baseline (%)
100
80
60
40
20
0
-20
-40
-60
-80
-100
+ Ongoing
Germline BRCA1 mutation
Germline BRCA2 mutation


C
Probability of sustained response
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Months
Median mo | 95% CI | Range
7.8 | 5.6–10.5 | 2.8–13.6
Patients at risk (events)
25 (0) 25 (0) 25 (0) 24 (0) 23 (1) 21 (2) 14 (8) 12 (9) 9 (11) 9 (12) 4 (13) 3 (14) 2 (15) 2 (15) 0 (16)


A
Mean values (±SEM), U/L
80
60
40
20
0
Baseline
Cycle 1 day 15
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9
Cycle 10
Cycle 11
Cycle 12
Cycle 13
Cycle 14
Cycle 15
Cycle 16
Cycle 17
Cycle 18
Cycle 19
Cycle 20
Day 1 of cycle
B
Mean values (±SEM), U/L
60
40
20
0
Baseline
Cycle 1 day 15
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9
Cycle 10
Cycle 11
Cycle 12
Cycle 13
Cycle 14
Cycle 15
Cycle 16
Cycle 17
Cycle 18
Cycle 19
Cycle 20
Day 1 of cycle
C
Mean values (±SEM), µmol/L
25
20
15
10
5
0
Baseline
Cycle 1 day 15
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9
Cycle 10
Cycle 11
Cycle 12
Cycle 13
Cycle 14
Cycle 15
Cycle 16
Cycle 17
Cycle 18
Cycle 19
Cycle 20
Day 1 of cycle