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PHASE I STUDIES

Phase I study of intermittent olaparib capsule or tablet dosing in combination with carboplatin and paclitaxel (part 2)

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Summary

Background In the first part of this extensive phase I study (NCT00516724), continuous olaparib twice daily (bid) with carboplatin and/or paclitaxel resulted in myelosuppression and dose modifications. Here, we report the safety, tolerability, and efficacy of intermittent olaparib dosing combined with carboplatin and paclitaxel. *Methods* Patients with advanced solid tumors (part D) and enriched for ovarian and breast cancer (part E) received olaparib (capsule and tablet formulations) using intermittent schedules (2 to 10 days of a 21-day cycle) combined with carboplatin/paclitaxel. Safety assessments included evaluation of dose-limiting toxicities (DLTs; cycle 1 only), adverse events (AEs), and physical examinations. Pharmacokinetic assessments of olaparib capsule and tablet combined with carboplatin/paclitaxel were performed. Tumor responses (RECIST) were assessed every 2 cycles. *Results* In total, 132 heavily pre-treated patients were included. One DLT of grade 3 elevated alanine aminotransferase lasting for 8 days was reported (olaparib tablet 100 mg bid days 3–12, carboplatin area under the curve 4 and paclitaxel 175 mg/m^2). The most common hematological AEs were neutropenia (47%) and thrombocytopenia (39%), which frequently led to dose modifications. Non-hematological AEs were predominantly grade 1–2, including alopecia (89%) and fatigue (84%). Overall objective response rate was 46%. *Conclusions* Discontinuous dosing of olaparib resulted in significant myelosuppression leading to dose interruptions and/or delays. Anti-tumor activity was encouraging in patients enriched with BRCA-mutated breast and ovarian cancer. The most appropriate olaparib tablet dose for use in further studies evaluating olaparib in combination with carboplatin and paclitaxel is 50 mg bid (days 1–5).

Keywords Olaparib · Carboplatin · Paclitaxel · PARP inhibitor · Pharmacokinetics · Phase I

Introduction

This is the second part (part 2) of an extensive phase I study (NCT00516724; AstraZeneca study code D0810C0004), which aimed to combine the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib (Lynparza™, AstraZeneca UK Ltd., Macclesfield, UK; capsule and tablet formulations) with the cytotoxic anti-cancer agents carboplatin and paclitaxel. Part 1 of the study evaluated olaparib capsule dosing, continuously twice daily (bid), in combination with carboplatin and/or paclitaxel and is published as a companion article. [Note to *Invest New Drugs* Editor: please can we include a link to the

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companion article here] These studies were performed following the observation in preclinical experiments which demonstrated that PARP inhibitors, such as olaparib, could increase the sensitivity of tumor cells to DNA-damaging agents [1–8].

Phase II and III monotherapy studies of olaparib (capsule and tablet formulations) have demonstrated significant efficacy in patients with ovarian and breast cancers, with the greatest effects in patients with mutations in the breast cancer genes *BRCA1* or *BRCA2* [9, 10]. Following the completion of these studies, olaparib obtained approval in the USA, Europe, and other countries for the treatment of patients with ovarian and breast cancer (USA only for patients with breast cancer). Olaparib monotherapy (capsule and tablet formulations) has been shown to be generally well tolerated with the most frequent adverse events (AEs) being nausea, fatigue, and vomiting [3–8], with some patients experiencing long-term benefit from treatment with no significant toxicity for up to 6 years [3–8].

In part 1 of this study [Note to *Invest New Drugs* Editor: please can we include a link to the companion article here], the combination of olaparib with carboplatin resulted in an increased frequency and severity of myelosuppression, particularly thrombocytopenia. The addition of paclitaxel, which is thought to reduce the rate of thrombocytopenia, to olaparib alone or olaparib in combination with carboplatin, still resulted in increased myelosuppression, most commonly neutropenia. While this myelosuppression rarely led to study drug discontinuation, it did lead to extensive dose modifications, including dose interruptions, dose reductions, and cycle delays [11]. In part 1 of the study, olaparib was administered continuously bid; we therefore wanted to investigate whether an intermittent dosing schedule of olaparib could reduce the frequency and severity of myelosuppression. In part 2 of the study presented here, intermittent dosing of olaparib for 2 to 10 days of a 21-day cycle was evaluated in combination with carboplatin and paclitaxel. We also investigated whether the day of olaparib initiation (i.e., day 3 of each cycle rather than day 1) reduced the frequency and severity of myelosuppression. In addition, following the initiation of this study, the olaparib formulation was switched from a capsule (16 capsules/day) to a tablet (4 tablets/day) to reduce the pill burden for patients [12, 13]. Thus, it was decided to also switch the formulation during part 2 of the study.

This phase I study therefore aimed to determine a tolerable dose of intermittent olaparib capsule or tablet dosing, in combination with carboplatin and paclitaxel.

Methods

Study design

The initial cohorts of part 1 of the study evaluated olaparib (capsule) bid dosing in combination with carboplatin (part A), in combination with carboplatin and paclitaxel (part B) and in combination with paclitaxel (part C); no suitable combination dose could be determined because of hematological toxicities. Here, we present parts D and E of the study, which evaluated the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), and preliminary efficacy of intermittent dosing of olaparib (capsule or tablet) in combination with carboplatin and paclitaxel.

Part D of the study initially evaluated intermittent dosing of olaparib (Gelucire® capsules; given for 5 to 10 days of a 21-day cycle) in combination with carboplatin and paclitaxel (Table 1). Toward the end of Part D, the olaparib melt-extrusion tablet formulation became available; once a tolerable olaparib capsule dose schedule was identified in part D, this dose level (olaparib 200 mg bid days 1–10, carboplatin area under the concentration–time curve [AUC] 4, and paclitaxel 175 mg/m^2) was evaluated using the olaparib tablet formulation (part E). However, this tablet dose schedule showed less favorable toxicity and was judged not to be appropriate for further studies. Therefore, additional cohorts were initiated using the tablet formulation (part E) of olaparib to evaluate other intermittent dosing schedules of olaparib (given for 2–10 days), including off-setting of the starting day of olaparib treatment (from day 1 to day 3 of each cycle) in combination with carboplatin and paclitaxel (21-day cycles; Table 1).

For each new cohort, the duration and timing of dosing was determined by the investigators and sponsor upon review of the safety and tolerability of prior regimens. For all treatment combinations, the MTD was defined as the dose schedule below that which caused a dose-limiting toxicity (DLT) in two patients in a cohort consisting of at least three patients.

All patients provided written informed consent. The institutional review boards or independent ethics committees of all investigational sites approved the protocol. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on Bioethics [14]. The study is registered at ClinicalTrials.gov, number NCT00516724.

Patient selection

Eligible patients were aged ≥ 18 years and had a confirmed (histologically or, where appropriate, cytologically) malignant solid tumor refractory or resistant to standard therapy and for which no suitable standard therapy exists. In the dose-expansion phase of the study (part E, cohorts 17 and 21; Table 1), only female patients with histologically or cytologically diagnosed metastatic triple-negative breast cancer (TNBC; platinum-naïve) or advanced ovarian cancer (where further treatment with platinum-based chemotherapy was indicated) were eligible. Patients also needed to have an Eastern Cooperative Oncology Group performance status ≤ 2 and have adequate bone marrow, hepatic, and renal function

Table 1 Dosing regimens used in each part of the study

	Cohort	Olaparib dose, mg, and schedule	Carboplatin dose, AUC	Paclitaxel dose, mg/m^2	Cycle length, days
Part D	11	200 bid day 1–10[a]	4	175	21
	12	200 bid day 1–10[a]	5	175	21
	13	400 bid day 1–10[a]	4	175	21
	14	200 bid day 1–5[a]	5	175	21
	15	400 bid day 1–5[a]	4	175	21
Part E	16[b]	200 bid day 1–10[d]	4	175	21
	17[c]	100 bid day 1–10[d]	4	175	21
	18	100 bid day 1–9.5[d]	4	175	21
	19	100 bid day 1–5[d]	4	175	21
	20	100 bid day 3–12[d]	4	175	21
	21	50 bid day 1–5[d]	5	175	21
	22	200 bid day 1–2[d]	5	175	21
	23	100 bid day 1–2[d]	6	175	21
	24	100 bid day 1–5[d]	5	175	21
	25	100 bid day 1–2[d]	5	175	21
	26	50 bid day 1–2[d]	6	175	21
	27	50 bid day 1–2[d]	5	175	21
	28	50 qd day 1–5[d]	5	175	21

AUC area under the concentration–time curve, *bid* twice daily, *qd* once daily

[a] Olaparib capsule formulation

[b] Most tolerable dose of olaparib capsules in combination with carboplatin and paclitaxel determined to initially evaluate the tablet formulation

[c] Dose-escalation and expansion cohort

[d] Olaparib tablet formulation

(defined as hemoglobin ≥ 10.0 g/dL, absolute neutrophil count ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, total bilirubin ≤ 1.25 × upper normal limit [ULN], serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤ 2.5 × ULN, and creatinine ≤ 1.5 × ULN), and had at least 28 days since their last anti-cancer therapy. Patients in the dose-escalation phase and patients with ovarian cancer in the dose-expansion phase should not have received > 2 previous courses of platinum-containing chemotherapy, and patients with TNBC in the dose-expansion phase were not allowed to have received any previous platinum-containing chemotherapy.

Study objectives

The primary objective of the study was to investigate the safety and tolerability and establish the MTD of olaparib in combination with carboplatin and paclitaxel. Secondary objectives included assessment of the PK of olaparib monotherapy and in combination with carboplatin and paclitaxel, and to assess the preliminary efficacy of olaparib in combination with carboplatin and paclitaxel.

Safety assessments

All AEs were monitored and graded according to the National Cancer Institute Common Terminology Toxicity Criteria for Adverse Events (NCI CTCAE) version 3.0 [15].

A DLT was defined as any of the following study drug-related events experienced during the first treatment cycle: thrombocytopenia with platelets < 25×10^9/L or grade 4 neutropenia lasting ≥ 7 days; grade 3 or 4 febrile neutropenia; grade ≥ 3 non-hematological toxicities (excluding grade 3 diarrhea, nausea, or vomiting despite adequate treatment, and grade 3 fatigue, lethargy, and gamma-glutamyltransferase elevation); a delay of > 2 weeks for the next scheduled carboplatin or paclitaxel dose because of toxicity.

Pharmacokinetic assessments

Extensive PK assessments for the combination and olaparib capsule monotherapy were completed in part 1 (parts A–C) of the study. Therefore, only single-dose PK of olaparib capsules (all part D cohorts) and tablets (cohorts 16 and 17 from part E) in combination with carboplatin and paclitaxel were evaluated in this part of the study.

Blood samples were taken for olaparib PK analysis pre-dose and at 0.5, 1, 2, 3, 4, 6, and 8 h post-dose on days 1, 2, and 8 of cycle 1. Concentrations of olaparib were determined by solid phase extraction and analyzed using reversed-phase high performance liquid chromatography with turbo ion spray tandem mass spectrometric (MS)/MS detection (positive ion mode) [16].

All plasma concentration–time data were analyzed with non-compartmental methods using Phoenix® WinNonlin® (Certara, Princeton, NJ, USA).

Efficacy evaluations

Tumor assessments were performed by computed tomography/magnetic resonance imaging scans at baseline and at the end of every 2 cycles. Patients with measurable disease had objective response assessments determined by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.0 [17]. The clinical endpoint for response was the overall objective response rate (ORR), defined as the number of patients with a complete response (CR) and a partial response (PR).

Statistical analyses

Safety and tolerability were assessed for all patients who received ≥ 1 dose of study medication. No formal statistical analyses were performed on safety, PK, and efficacy data.

Results

Patient population

A total of 132 patients were included in parts D and E of the study (18 cohorts in total; Table 1). Patient demographics and baseline characteristics are summarized in Table 2. The majority of patients were female (88%) and the most common tumor types were breast (49%) and ovarian (29%) cancer. Most patients were heavily pre-treated with surgery, radiotherapy, and several lines of chemotherapy. Although part D of the study was in an unselected patient population, part E was enriched with TNBC and ovarian cancer patients likely to have a BRCA mutation, as emerging evidence at this time suggested that these patients were expected to benefit most from olaparib treatment.

Safety

One DLT was observed; this was grade 3 elevated ALT lasting for 8 days, which led to an olaparib dose interruption (cohort 20; olaparib 100 mg bid days 3–12, carboplatin AUC 4, and paclitaxel 175 mg/m^2).

The two most tolerable cohorts were selected for further evaluation. Cohort 17 (olaparib tablet 100 mg bid given on days 1–10, carboplatin AUC 4, and paclitaxel 175 mg/m^2) initially appeared to be the best tolerated regimen, although there were four patients (67%) with treatment-emergent AEs (TEAEs) of grade ≥ 3; these were all due to bone marrow suppression and no non-hematological grade ≥ 3 TEAEs were observed. In addition, no patients in this cohort discontinued because of a TEAE and thus cohort 17 was selected for an expansion phase with 15 additional patients (21 patients in total). However, of the patients included in the expansion of cohort 17, 14 (93%) experienced grade ≥ 3 TEAEs—most notably neutropenia, fatigue, peripheral sensory neuropathy, and adverse reactions to the chemotherapy—and four patients (27%) discontinued because of TEAEs. The second cohort that was selected for expansion was cohort 21. No thrombocytopenia was reported for the first 6 patients enrolled into cohort 21 (olaparib tablet 50 mg bid given on days 1–5, carboplatin AUC 5, and paclitaxel 175 mg/m^2); therefore, this dose level was selected for a small exploratory expansion phase with seven additional patients recruited (13 patients in total). Overall, in cohort 21, 5 patients (39%) experienced olaparib-related AEs of grade ≥ 3; this was a slightly lower incidence than that seen in both cohorts 24 and 27 (67% and 50%, respectively). However, in cohort 21, more neutropenia was observed in earlier treatment cycles and more than half of patients within this cohort had treatment delays of > 7 days. Despite two dose levels being expanded (cohorts 17 and 21; Table 1), an MTD of olaparib in combination with carboplatin and paclitaxel was not established in this study as extensive dose modifications were required because of increased bone marrow toxicity.

All patients were evaluable for safety and all experienced at least one TEAE. The most frequently reported TEAEs were alopecia (89%), fatigue (84%), and gastrointestinal disorders, including nausea (71%), constipation (50%), and diarrhea (45%) (Table 3). Most non-hematological toxicities were mild (grade 1–2) in severity.

In total, 99 (75%) patients experienced a TEAE of grade ≥ 3 in severity. As previously observed in the first two parts (part A and part B/C) of this study, these were primarily hematological, mainly neutropenia (39% overall; Table 3). Fatigue was the most common grade ≥ 3 non-hematological AE, which occurred in 9% of patients overall (occurring in seven [14%] patients in part D and five [5%] patients in part E).

Despite the intermittent dosing of olaparib, bone marrow suppression incidence of all grades remained high, most prominently neutropenia (47% overall) and thrombocytopenia (39%). These AEs were common throughout all dosing cohorts; however, the frequency and severity decreased after the formulation switch from capsules (part D) to tablets (part E; Table 3). Prolonged bone marrow suppression often

Table 2 Patient demographics and baseline characteristics

	Part D	Part E	Overall
Patients, *n*	30	102	132
Sex			
Male	11 (37)	5 (5)	16 (12)
Female	19 (63)	97 (95)	116 (88)
Age, years, mean (range)	53 (35–70)	52 (25–74)	52 (25–74)
Ethnic origin			
Caucasian	28 (93)	101 (99)	129 (98)
Black	1 (3)	1 (1)	2 (2)
Other	1 (3)	0	1 (1)
ECOG performance status			
0	13 (43)	55 (54)	68 (52)
1	17 (57)	43 (42)	60 (45)
2	0	2 (2)	2 (2)
Unknown	0	2 (2)	2 (2)
Primary site of disease			
Breast	11 (37)	54 (53)	65 (49)
Ovary	4 (13)	34 (33)	38 (29)
Melanoma	4 (13)	0	4 (3)
Large intestine	2 (7)	0	2 (2)
Other	9 (30)	9 (9)	18 (14)
Unknown	0	5 (5)	5 (4)
Mutation status			
Wild type	2 (7)	16 (16)	18 (14)
BRCA1	4 (13)	29 (28)	33 (25)
BRCA2	0	11 (11)	11 (8)
Unknown	24 (80)	46 (45)	70 (53)
Duration of disease, months, mean (range)	50 (2–156)	38 (1–211)	44 (1–211)
Prior therapies			
Surgery[a]	30 (100)	102 (100)	132 (100)
Chemotherapy	28 (93)	90 (88)	118 (89)
Radiotherapy	21 (70)	45 (44)	66 (50)

Data are *n* (%) unless stated otherwise

ECOG Eastern Cooperative Oncology Group

[a] Including biopsies for diagnosis

led to dose modifications (dose interruptions, delays, and/or reductions; Table 3) for patients to recover to grade ≤ 1 and some patients required frequent granulocyte colony-stimulating factor treatment. Overall, the number of carboplatin (64%) and paclitaxel (67%) dose delays was relatively high throughout the study with no obvious differences between parts D and E of the study (Table 3). Olaparib dose reductions were required in approximately one-quarter of patients overall and olaparib dose interruptions were required in 14% of patients (Table 3). TEAEs resulting in treatment discontinuation occurred in 19% of patients.

TEAEs that occurred in each cohort included in the study are presented in Table 4. There were no obvious differences in the number or type of TEAEs occurring between the different cohorts evaluated. An overview of olaparib dose modifications in all dose levels of this study is provided in Table 5. Due to the relatively high number of dose modifications required, most cohorts were declared intolerable for multiple cycles. When combined with carboplatin and paclitaxel, intermittent dosing with olaparib 50 mg (cohorts 21, 26–28) required the fewest dose modifications and was the most tolerated dose.

Pharmacokinetics

A total of 38 patients had reportable single-dose olaparib (capsule or tablet) PK data on day 1 of dosing when co-administered with carboplatin and paclitaxel. The geometric

Table 3 Treatment-emergent adverse events of all grades occurring in ≥ 20% of patients in any study part, grade ≥ 3 events occurring in ≥ 5% of patients in any study part, and dose modifications due to treatment-emergent adverse events

TEAE, *n* (%)	Part D (*n* = 30)	Part E (*n* = 102)	Overall (*N* = 132)
Blood and lymphatic system disorders			
Neutropenia			
All grades	18 (60)	44 (43)	62 (47)
Grade ≥ 3	13 (43)	38 (37)	51 (39)
Thrombocytopenia			
All grades	9 (30)	42 (41)	51 (39)
Grade ≥ 3	5 (17)	12 (12)	17 (13)
Anemia			
All grades	13 (43)	20 (20)	33 (25)
Grade ≥ 3	7 (23)	6 (6)	13 (10)
Gastrointestinal disorders			
Nausea	20 (67)	74 (73)	94 (71)
Constipation	10 (33)	56 (55)	66 (50)
Diarrhea	11 (37)	49 (48)	60 (45)
Vomiting	9 (30)	33 (32)	42 (32)
Stomatitis	6 (20)	17 (17)	23 (17)
General disorders			
Fatigue			
All grades	27 (90)	84 (82)	111 (84)
Grade ≥ 3	7 (23)	5 (5)	12 (9)
Dyspnea	14 (47)	26 (26)	40 (30)
Pyrexia	3 (10)	22 (22)	25 (19)
Nervous system disorders			
Peripheral sensory neuropathy	10 (33)	70 (69)	80 (61)
Infections			
Nasopharyngitis	3 (10)	23 (23)	26 (20)
Skin and subcutaneous tissue disorders			
Alopecia	22 (73)	95 (93)	117 (89)
Dry skin	1 (3)	7 (7)	8 (6)
Dose modifications due to TEAEs, *n* (%)			
Olaparib dose reduction	11 (36)	23 (23)	34 (26)
Olaparib dose interruption	4 (13)	14 (14)	18 (14)
Carboplatin dose reduction	2 (7)	9 (9)	11 (8)
Carboplatin dose delay	18 (60)	66 (65)	84 (64)
Paclitaxel dose reduction	2 (7)	9 (9)	11 (34)
Paclitaxel dose delay	18 (60)	70 (69)	88 (67)
TEAEs leading to discontinuation	8 (27)	17 (17)	25 (19)

TEAE treatment-emergent adverse event

mean single-dose exposure to olaparib tablet 200 mg in combination with carboplatin and paclitaxel (cohort 16; maximum plasma concentration [C_{max}], 6.16 μg/mL [coefficient of variation (CV%) 19.3] and AUC from time 0 to 8 h [$AUC_{0–8}$], 16.7 μg h/mL [18.6]) was higher than after the same dose and combination given in capsule formulation (cohort 11; 2.08 μg/mL [40.9] and 8.60 μg h/mL [36.0], respectively). C_{max} was also higher with 200 mg tablets in combination with carboplatin and paclitaxel than after administration of the 400 mg capsule formulation in combination with carboplatin and paclitaxel (cohort 13; 4.35 μg/mL [28.5]). However, $AUC_{0–8}$ was similar between olaparib tablet 200 mg and olaparib capsule 400 mg doses (cohort 13; 17.4 μg h/mL [36.2]) in combination with carboplatin and paclitaxel. Figure 1 shows the plasma concentration–time curves of olaparib 200 mg bid dosing for both the capsule and tablet formulations when combined with carboplatin AUC 4 and paclitaxel 175 mg/m^2.

Table 4 Treatment-emergent adverse events occurring in ≥20% of patients overall in any study cohort

TEAE, *n* (%)	Part D treatment cohort (olaparib dose,[a] mg bid [schedule]/carboplatin dose, AUC/paclitaxel dose mg/m^2) [*n*]					Part E treatment cohort (olaparib dose,[b] mg bid [schedule]/carboplatin dose, AUC/paclitaxel dose mg/m^2) [*n*]												
	11 (200 [10] /4/ 175) [6]	12 (200 [10] /5/ 175) [6]	13 (400 [10] /4/ 175) [6]	14 (200 [5] /5/ 175) [6]	15 (400 [5] /5/ 175) [6]	16 (200 [10] /4/ 175) [8]	17 (100 [10] /4/ 175) [21]	18 (100 [9.5] /4/ 175) [6]	19 (100 [5] /4/ 175) [6]	20 (100 [3–12] /4/ 175) [6]	21 (50 [5] /5/ 175) [13]	22 (200 [2] /5/ 175) [6]	23 (100 [2] /6/ 175) [6]	24 (100 [5] /5/ 175) [6]	25 (100 [2] /5/ 175) [6]	26 (50 [2] /6/ 175) [6]	27 (50 [2] /5/ 175) [6]	28 (50 qd [5] /5/ 175) [6]
Any TEAE	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	8 (100)	21 (100)	6 (100)	6 (100)	6 (100)	13 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)
Blood and lymphatic system disorders																		
Anemia	2 (33)	3 (50)	3 (50)	3 (50)	2 (33)	1 (13)	0	0	1 (17)	1 (17)	3 (23)	0	5 (83)	1 (17)	2 (33)	3 (50)	2 (33)	1 (17)
Neutropenia	2 (33)	4 (67)	4 (67)	3 (50)	5 (83)	7 (88)	11 (52)	3 (50)	2 (33)	4 (67)	6 (46)	1 (17)	2 (33)	3 (50)	2 (33)	4 (67)	4 (67)	5 (83)
Thrombocytopenia	0	3 (50)	2 (33)	2 (33)	2 (33)	6 (75)	4 (19)	3 (50)	1 (17)	3 (50)	4 (31)	1 (17)	5 (83)	3 (50)	3 (50)	3 (50)	3 (50)	3 (50)
Gastrointestinal disorders																		
Constipation	2 (33)	0	3 (50)	3 (50)	2 (33)	5 (63)	9 (43)	4 (67)	3 (50)	3 (50)	10 (77)	3 (50)	3 (50)	2 (33)	3 (50)	4 (68)	4 (67)	3 (50)
Diarrhea	1 (17)	2 (33)	2 (33)	3 (50)	3 (50)	4 (50)	6 (29)	3 (50)	3 (50)	3 (50)	7 (54)	3 (50)	2 (33)	4 (67)	3 (50)	5 (83)	1 (17)	5 (83)
Nausea	5 (83)	2 (33)	5 (83)	4 (67)	4 (67)	7 (88)	17 (81)	5 (83)	6 (100)	2 (33)	11 (85)	3 (50)	2 (33)	5 (83)	4 (67)	5 (83)	3 (50)	4 (67)
Stomatitis	2 (33)	1 (17)	0	1 (17)	2 (33)	2 (25)	3 (14)	0	1 (17)	1 (17)	3 (23)	0	2 (33)	0	1 (17)	0	1 (17)	3 (50)
Vomiting	4 (67)	1 (17)	1 (17)	3 (50)	0	1 (13)	5 (24)	2 (33)	1 (17)	1 (17)	8 (62)	1 (17)	2 (33)	2 (33)	2 (33)	2 (33)	1 (17)	5 (83)
General disorders and administration site conditions																		
Adverse drug reaction	0	1 (17)	0	0	1 (17)	1 (13)	5 (24)	1 (17)	2 (33)	1 (17)	6 (46)	3 (50)	2 (33)	1 (17)	2 (33)	1 (17)	1 (17)	1 (17)
Fatigue	5 (83)	6 (100)	5 (83)	6 (100)	5 (83)	8 (100)	18 (86)	5 (83)	5 (83)	4 (67)	12 (92)	5 (83)	4 (67)	6 (100)	4 (67)	4 (67)	5 (83)	4 (67)
Pyrexia	0	1 (17)	0	1 (17)	1 (17)	1 (13)	7 (33)	2 (33)	2 (33)	1 (17)	1 (8)	0	1 (17)	1 (17)	3 (50)	1 (17)	1 (17)	1 (17)
Infections and infestations																		
Nasopharyngitis	0	0	0	2 (33)	1 (17)	3 (38)	6 (29)	1 (17)	0	1 (17)	3 (23)	1 (17)	1 (17)	1 (17)	1 (17)	1 (17)	2 (33)	2 (33)
Metabolism and nutrition disorders																		
Anorexia	0	0	1 (17)	1 (17)	3 (50)	3 (38)	9 (43)	3 (50)	2 (33)	0	2 (15)	3 (50)	2 (33)	1 (17)	2 (33)	2 (33)	2 (33)	1 (17)
Musculoskeletal and connective tissue disorders																		
Myalgia	1 (17)	0	4 (67)	2 (33)	4 (67)	4 (50)	10 (48)	2 (33)	3 (50)	4 (67)	8 (62)	2 (33)	5 (83)	1 (17)	0	4 (67)	4 (67)	4 (67)
Nervous system disorders																		
Dysgeusia	0	1 (17)	1 (17)	1 (17)	2 (33)	2 (25)	5 (24)	3 (50)	4 (67)	3 (50)	5 (39)	2 (33)	3 (50)	2 (33)	2 (33)	2 (33)	1 (17)	1 (17)
Peripheral sensory neuropathy	0	1 (17)	3 (50)	3 (50)	3 (50)	5 (63)	13 (62)	5 (83)	6 (100)	4 (67)	10 (77)	5 (83)	5 (83)	3 (50)	4 (67)	3 (50)	3 (50)	4 (67)
Respiratory, thoracic, and mediastinal disorders																		
Dyspnea	2 (33)	1 (17)	4 (67)	3 (50)	4 (67)	0	7 (33)	1 (17)	3 (50)	1 (17)	5 (39)	1 (17)	4 (68)	2 (33)	0	2 (33)	0	0
Skin and subcutaneous tissue disorders																		
Alopecia	5 (83)	4 (67)	4 (67)	4 (67)	5 (83)	8 (100)	19 (90)	6 (100)	5 (83)	5 (83)	12 (92)	6 (100)	5 (83)	6 (100)	5 (83)	6 (100)	6 (100)	6 (100)

AUC area under the concentration–time curve, *bid* twice daily, *qd* once daily, *TEAE* treatment-emergent adverse event

[a] Olaparib capsule formulation

[b] Olaparib tablet formulation

Anti-tumor activity

In total, 109 patients were evaluable for at least one response assessment (Table 6). Four patients achieved CR and 46 patients had a PR, resulting in an ORR of 46% for the total evaluable population. In addition, there were nine unconfirmed PRs.

Discussion

Due to the extensive nature of this phase I study, two companion manuscripts were developed. In part 1 of the study (parts A–C), combining continuous bid dosing of olaparib with carboplatin led to a significant increase in bone marrow suppression. Paclitaxel was added to this combination with the aim of reducing the incidence of thrombocytopenia [18]. However, the addition of paclitaxel to olaparib and carboplatin had no significant effect on reducing the rate of myelosuppression, which remained the cause of many dose modifications in part 1 of the study (https://doi.org/10.1007/s10637-019-00856-7).

In part 2 of the study presented here (parts D and E), it was decided to evaluate intermittent olaparib dosing (ranging from 2 to 10 days in a 21-day cycle) in combination with carboplatin and paclitaxel to determine if alternative dosing schedules could reduce the hematological toxicities observed following continuous bid olaparib dosing in combination with carboplatin and/or paclitaxel (part 1). However, the incidence and duration of myelosuppression remained high (neutropenia 47% and thrombocytopenia 39%), with olaparib dose interruptions required for 14% of patients and carboplatin or paclitaxel dose delays required for 64% and 67% of patients, respectively.

The two most tolerable cohorts were selected for further evaluation; cohort 17 (olaparib tablet 100 mg bid given on days 1–10, carboplatin AUC 4, and paclitaxel 175 mg/m^2) and cohort 21 (olaparib tablet 50 mg bid given on days 1–5, carboplatin AUC 5, and paclitaxel 175 mg/m^2). Cohort 17 initially appeared to be the best tolerated regimen; however, of the 15 patients included in the expansion of this cohort, 14 (93%) experienced grade ≥ 3 TEAEs, most notably neutropenia, fatigue, peripheral sensory neuropathy, and adverse reactions to the chemotherapy; and four patients (27%) discontinued because of TEAEs. It is unclear why there was a difference in TEAEs and myelosuppression between the escalation and expansion population groups even when taking into account stage of disease at study entry, prior therapies, and other demographic variables. No thrombocytopenia was reported for the first 6 patients enrolled into cohort 21; therefore, 7 additional patients were recruited (13 patients in total). Overall in cohort 21, 5 patients (39%) experienced olaparib-related AEs of grade ≥ 3, which was a slightly lower proportion than that seen in other cohorts; however, neutropenia was increased in earlier treatment cycles and more than half of patients within this cohort had treatment delays of > 7 days. Therefore, an MTD of olaparib in combination with carboplatin and paclitaxel was not established in this study.

Results of other clinical trials in which olaparib were combined with chemotherapeutic agents have also shown increased myelosuppression, hampering the development of these combinations [19, 20]. Interestingly, two phase I studies, of olaparib combined with either gemcitabine or cisplatin, both found a tolerable dosing regimen when olaparib was given intermittently, while continuous dosing of olaparib resulted in unacceptable hematological toxicities [19, 21]. As previously reported [12], the tablet formulation of olaparib resulted in higher olaparib exposure compared with the capsule formulation, which might account for the increased incidence of AEs observed with the tablet formulation in the current study. PK analyses in part D of the current study also showed that exposure to olaparib 200 mg bid was increased following dosing with the tablet formulation when compared with the capsule formulation. As noted, this was also observed in a phase I bioavailability study of olaparib capsule and tablet formulations, which showed that following multiple dosing, steady-state exposure with olaparib tablet 300 mg bid matched or exceeded that of the capsule when dosed at 400 mg bid [13].

The ORR observed for parts D and E of the study was 46% overall. Of patients included in parts C and D of the study, 78% had either breast or ovarian cancer. Therefore, the ORR of 46% observed in part 2 of the study was expected to be greater than that observed in part 1 of the study (11%), as by this time in the study there was a selection bias: sites included more patients with breast and ovarian cancer with BRCA mutations, who were expected to gain a greater benefit from PARP inhibition treatment. In addition, the observed response rates were higher for patients receiving olaparib tablets in combination with carboplatin and paclitaxel (part E, ORR 51%) than in those receiving olaparib capsules in combination with carboplatin and paclitaxel (part D, ORR 30%). At the time of the formulation switch in the study, more stringent patient selection criteria were implemented for the part E expansion cohorts, which resulted in a population further enriched with breast and ovarian cancer patients with a BRCA mutation. These patients were included in the study as they were expected to gain a greater benefit from PARP inhibition treatment, which was observed with the greater ORR in part E compared with the other parts of the study. Response rates observed in the current study are difficult to compare with published carboplatin/paclitaxel treatment data since this phase I study included a heavily pre-treated patient population with various tumor types. The duration of response was not calculated because data were not collected for more

Table 5 Olaparib dose interruptions, reductions, or delays > 7 days occurring in each treatment cycle of each cohort

Study part	Patients, *n*	Olaparib, mg bid (days of treatment)	Carboplatin, AUC	Paclitaxel, mg/m^2	Cycle					
					1	2	3	4	5	6
Part D										
11	6	200 (10)	4	175	1[a]/6	0/6	0/4	1[a], 1[b]/4	1[a]/4	1[b], 1[c]/3
12	6	200 (10)	5	175	2[b]/6	1[a]/6	0/3	0/2	0/2	1[c]/2
13	6	400 (10)	4	175	0/6	3[a]/6	1[b], 1[c]/5	1[c]/5	1[b], 2[c]/5	1[c]/5
14	6	200 (5)	5	175	0/6	0/6	1[b], 1[c]/6	0/4	0/3	0/3
15	6	400 (5)	5	175	0/6	0/6	3[b], 3[c]/6	1[b]/5	1[b]/5	1[c]/5
Part E										
16	8	200 (10)	4	175	0/8	1[a]/8	1[a], 1[b]/7	1[a], 2[b]/6	1[a]/6	1[a]/6
17	21	100 (10)	4	175	0/21	3[a], 1[b]/20	3[a], 1[b]/16	3[b]/15	2[a]/14	1[a], 1[b]/13
18	6	100 (9.5)	4	175	1[a]/6	2[a]/6	0/6	2[a], 2[b]/6	1[a]/4	1[a]/4
19	6	100 (5)	4	175	0/6	0/6	1[b]/6	0/6	1[b]/5	1[b]/5
20	6	100 (days 3–12)	4	175	1[a]/6	1[b]/6	1[a]/5	1[a], 1[b]/5	1[a]/5	0/5
21	13	50 (5)	5	175	0/13	0/12	0/11	0/11	1[b]/10	0/9
22	6	200 (2)	5	175	0/6	1[b]/6	0/5	0/5	1[b]/5	1[b]/5
23	6	100 (2)	6	175	0/6	0/6	0/6	0/5	1[b]/3	0/2
24	6	100 (5)	5	175	0/6	0/6	1[b]/5	1[b]/5	0/4	0/4
25	6	100 (2)	5	175	0/6	0/6	0/5	2[b]/5	0/5	1[b]/5
26	6	50 (2)	6	175	0/6	0/6	1[b]/6	0/5	0/3	0/3
27	6	50 (2)	5	175	0/6	0/6	0/5	0/5	0/4	0/3
28	6	50 qd (5)	5	175	0/6	0/6	0/6	0/6	0/4	0/4

AUC area under the concentration–time curve, *bid* twice daily, *qd* once daily

[a] Dose interruptions

[b] Dose reductions

[c] Dose delays >7 days

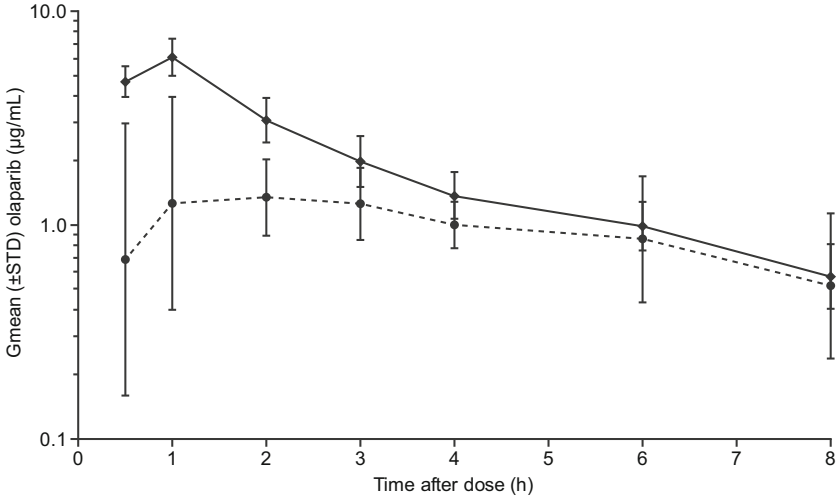

Fig. 1 Plasma concentration–time curves of olaparib capsule or tablet following day 1 dosing in combination with carboplatin and paclitaxel (part D). Dotted line (cohort 11; $n = 5$), olaparib capsule (200 mg bid) in combination with carboplatin (AUC 4) and paclitaxel (175 mg/m^2). Solid line (cohort 16; $n = 5$), olaparib tablet (200 mg bid) in combination with carboplatin (AUC 4) and paclitaxel (175 mg/m^2). *AUC* area under the concentration–time curve, *bid* twice daily, *Gmean* geometric mean, *STD* standard deviation

than 6 cycles. Patients who showed a response in this study but did not tolerate the combination of olaparib with carboplatin and/or paclitaxel switched to continuous olaparib monotherapy after 6 cycles, as it was believed they would experience further clinical benefit from continued PARP inhibition. Interestingly, this hypothesis was strengthened with results from a phase II study in which patients with platinum-sensitive ovarian cancer were initially given a lower dose of olaparib in combination with carboplatin and paclitaxel, followed by a higher dose of olaparib as monotherapy. Progression-free survival was shown to be significantly improved in patients receiving olaparib combined with carboplatin and paclitaxel followed by olaparib maintenance treatment compared with those receiving carboplatin and paclitaxel alone (12.2 vs 9.6 months, respectively), with a greater effect observed in patients carrying a BRCA mutation [22].

Due to the increased frequency, severity, and duration of myelosuppression seen when adding olaparib to carboplatin and/or paclitaxel, it was difficult to find a tolerable dosing regimen for combination therapy. None of the regimens explored could be given for multiple cycles without the need for dose modifications within 6 cycles. When evaluating the results from the whole of this phase I study (parts 1 and 2), it appears that only a low dose of olaparib (50 mg bid) could be given in combination with carboplatin and paclitaxel. Interestingly, it has been reported that when combined with radiotherapy, low doses of olaparib were sufficient to achieve effective radiosensitization [23]. Therefore, it is possible that a low daily dose of olaparib would be sufficient to inhibit PARP while enhancing the effects of chemotherapy. A trial is currently underway investigating low-dose olaparib combined with carboplatin for two treatment cycles, followed by high-dose olaparib monotherapy versus capecitabine in patients with BRCA-mutated human epidermal growth factor receptor 2-negative advanced breast cancer [24]; it will be interesting to find out whether the hypotheses from our phase I study are confirmed in this trial [24].

In conclusion, this extensive phase I study did not determine an MTD or appropriate treatment schedule of olaparib in combination with carboplatin and paclitaxel because of the

Table 6 Anti-tumor activity of intermittent olaparib dosing in combination with carboplatin and paclitaxel in patients evaluable for efficacy

	Patients with measurable disease, *n*	CR, *n* (%)	PR, *n* (%)	SD for at least 2 cycles, *n* (%)	PD, *n* (%)	NE, *n* (%)
Part D	27	1 (4)	7 (26)	15 (56)[a]	4 (15)	0
Part E	82	3 (4)	39 (48)	22 (27)[a]	17 (21)	1 (1)
Overall	109	4 (4)	46 (42)	37 (34)	21 (19)	1 (1)

CR complete response, *NE* not evaluable, *PD*, progressive disease, *PR* partial response, *SD* stable disease

[a] Unconfirmed responses: three PRs in part D; six PRs in part E

high rates of myelosuppression observed with the combination. The most appropriate olaparib dose for use in further studies evaluating this combination is 50 mg bid.

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Compliance with ethical standards

Conflict of interest Ilian Tchakov was an employee of AstraZeneca at the time of this study. The other authors have no conflicts of interest.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was performed in accordance with the Good Clinical Practice and the AstraZeneca policy on Bioethics.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and all applicable laws and regulations.

Informed consent Informed consent was obtained from all individual participants included in the study.

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