



Phase I study of continuous olaparib capsule dosing in combination with carboplatin and/or paclitaxel (Part 1)

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Summary

Background The PARP inhibitor olaparib has shown acceptable toxicity at doses of up to 400 mg twice daily (bid; capsule formulation) with encouraging signs of antitumor activity. Based on its mode of action, olaparib may sensitize tumor cells to DNA-damaging agents. This Phase I trial (NCT00516724) evaluated the safety, pharmacokinetics (PK) and preliminary efficacy of olaparib combined with carboplatin and/or paclitaxel. **Methods** Patients with advanced solid tumors received olaparib (capsule bid) plus carboplatin (Part A), carboplatin and paclitaxel (Part B), or paclitaxel (Part C). In each part of the study, different drug doses were given to define the most appropriate dose/drug combination to use in further studies. Safety assessments included evaluation of dose-limiting toxicities (DLTs; cycle 1 only), adverse events (AEs) and physical examinations. PK assessments of olaparib, carboplatin and paclitaxel were performed. Tumor responses (RECIST) were assessed every two cycles. **Results** Fifty-seven patients received treatment. DLTs were reported in two patients (both receiving olaparib 100 mg bid and carboplatin AUC 4; Part A, cohort 2): grade 1 thrombocytopenia with grade 2 neutropenia lasting for 16 days, and grade 2 neutropenia lasting for 7 days. Non-hematologic AEs were predominantly grade 1–2 and included fatigue (70%) and nausea (40%). Bone marrow suppression, mainly neutropenia (51%) and thrombocytopenia (25%), frequently led to dose modifications. **Conclusions** Olaparib in combination with carboplatin and/or paclitaxel resulted in increased hematologic toxicities, making it challenging to establish a dosing regimen that could be tolerated for multiple cycles without dose modifications.

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

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Introduction

Development of new anticancer drugs is focusing ever more on targeted therapies that, in contrast to classic chemotherapy, can discriminate between the tumor and healthy tissues by targeting specific molecular abnormalities that are only present in tumor cells. Some targeted treatments have the potential to act synergistically and result in improved efficacy when combined with chemotherapy regimens.

One of the most promising targeted therapies is the class of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors. PARP is involved in the repair of single-strand DNA breaks (SSBs), and inhibition of PARP leads to accumulation of SSBs, resulting in the formation of double-strand DNA breaks (DSBs) during replication. The homologous recombination repair (HRR) process is required for the effective repair of DSBs. In cells deficient in HRR (ie cells with a BRCA mutation), DSB repair occurs through the error-

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prone non-homologous end-joining pathway. Cells deficient in either PARP or HRR alone are viable; however, the loss of both results in a lethal phenotype and cell death. Defects in the HRR process have been observed in a variety of cancers, including ovarian, breast and prostate cancers [1]. The use of PARP inhibitors in tumors that are HRR deficient leads to an accumulation of DNA damage and tumor-cell death [2–7]. This concept of ‘synthetic lethality’ has been proven to be effective and is currently being exploited in a variety of clinical trials with PARP inhibitors.

Olaparib (Lynparza™) is a potent, selective PARP inhibitor that has demonstrated significant efficacy in patients with ovarian, breast and other cancers [8–13], with the greatest effects being in patients with BRCA1/2 mutations. The initial approval of olaparib by the US FDA was as monotherapy in patients with deleterious or suspected deleterious germline BRCA-mutated (BRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy [14], and by the EMA as monotherapy for the maintenance treatment of adult patients with BRCAm (germline and/or somatic), platinum-sensitive relapsed, high-grade serous epithelial ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy [15]. The unprecedented long-term efficacy of olaparib in both BRCAm and non-BRCAm patients [8], as well as results from SOLO2 [12] and other PARP inhibitor ovarian cancer trials, led to the expansion of the olaparib US FDA and EMA labels (tablet formulation) for the treatment of women with advanced relapsed ovarian cancer regardless of their BRCA mutation status [14, 15]. Olaparib is also approved in the US, Europe and other countries for the first-line treatment of women with advanced ovarian cancer [15, 16]. In addition, the FDA and EMA have approved olaparib (tablet formulation) for the treatment of patients with germline BRCAm, HER2-negative, hormone-receptor-positive metastatic breast cancer [14, 15]. Clinical studies have shown that olaparib monotherapy (capsule formulation) at doses of up to 400 mg twice daily (bid) is well tolerated, with the most frequent adverse events (AEs) being nausea, fatigue and vomiting [8–13].

Preclinical data have shown that olaparib sensitizes tumor cells to the DNA-damaging effects of cytotoxic anticancer treatments, including platinum-based chemotherapies [17–20]. Clinical studies have also demonstrated the efficacy and safety of olaparib when combined with paclitaxel [21] or carboplatin [22] in patients with metastatic breast and ovarian cancer. The combination of carboplatin and paclitaxel has also been shown to be an effective treatment modality in ovarian and breast cancer patients, with a more favorable toxicity profile compared with cisplatin combined with paclitaxel [23–29].

This Phase I study (NCT00516724; AstraZeneca study code D0810C0004) was performed to establish the safety, tolerability and maximum tolerated dose (MTD) of olaparib given continuously (daily) or intermittently (for 5–10 days of a 21-

day cycle) in combination with carboplatin and/or paclitaxel in patients with advanced solid tumors, to facilitate future clinical development of these combinations. Here we present Part 1 of this study with continuous olaparib dosing combined with carboplatin and/or paclitaxel; Part 2 of the study evaluates intermittent olaparib dosing in combination with carboplatin and paclitaxel and is published as a companion article (see, <https://doi.org/10.1007/s10637-019-00857-6>).

Methods

Study design

Part A of the study evaluated the MTD, safety, pharmacokinetics (PK) and preliminary efficacy of continuous dosing of olaparib in combination with carboplatin. Following the initiation of Part A, a high frequency and severity of thrombocytopenia was observed; it was therefore decided also to investigate continuous olaparib dosing in combination with carboplatin and paclitaxel (Part B) and in combination with paclitaxel (Part C). In Parts A and B, olaparib (Gelucire® capsules) was given continuously twice daily together with 3-weekly carboplatin and paclitaxel/carboplatin, respectively. In Part C, olaparib (Gelucire® capsules) was given continuously with weekly paclitaxel. Treatment cohorts and dose levels are provided in Table 1. For all cohorts, cycle 1 had a 7-day run-in of olaparib monotherapy for PK sampling followed by 21-day treatment cycles for Parts A and B and 28-day treatment cycles for Part C. In Parts B and C, patients received treatment for up to six cycles and could continue treatment at the discretion of the investigator if they had at least stable disease.

Table 1 Dosing regimens used in each part of the study

	Cohort	Olaparib dose, mg bid	Carboplatin dose, AUC	Paclitaxel dose, mg/m ²	Cycle length, days*
Part A	1	50	4	X	21
	2	100	4	X	21
	3	50	5	X	21
	7	200	4	X	21
Part B	4	50	4	90	21
	5	50	4	135	21
	8	50	4	175	21
	9	100	4	175	21
Part C	6	100	X	80	28
	10	200	X	80	28

*Cycle 1 included an additional olaparib monotherapy run-in of 7 days prior to carboplatin and/or paclitaxel dosing. AUC, area under the concentration–time curve; bid, twice daily

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 that consisted 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 [30].

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. Patients also needed to have an Eastern Cooperative Oncology Group performance status of ≤ 2 , adequate bone marrow, hepatic and renal function (defined as hemoglobin ≥ 10.0 g/dL, absolute neutrophil count $\geq 1.5 \times 10^9$ /L, platelets $\geq 100 \times 10^9$ /L, total bilirubin ≤ 1.25 x upper normal limit [ULN], serum aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN, and creatinine ≤ 1.5 x ULN), and had at least 28 days since their last anticancer therapy. Patients should not have received >2 previous courses of 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/or paclitaxel. Secondary objectives included assessment of the PK of olaparib monotherapy and in combination with carboplatin and/or paclitaxel, and to assess the preliminary efficacy of olaparib in combination with carboplatin and/or paclitaxel.

Safety assessments

All AEs were monitored and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [31].

A DLT was defined as any of the following drug-related events experienced during the first treatment cycle: thrombocytopenia with platelets $< 25 \times 10^9$ /L or grade 4 neutropenia lasting ≥ 7 days; grade 3 or 4 febrile neutropenia; grade ≥ 3 non-hematologic 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

Blood samples were taken for olaparib PK analysis in all study parts pre-dose and at 0.5, 1, 2, 3, 4, 6 and 8 h post-dose on days 4 (olaparib monotherapy) and 8 (olaparib in combination with carboplatin and/or paclitaxel) 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 detection (positive-ion mode) [32].

The first 10 patients dosed in Part A had a single blood sample taken 24 h after administration of the cycle 1 day 8 carboplatin infusion to enable the free carboplatin area under the plasma concentration–time curve (AUC) to be estimated in the presence of olaparib by the Ghazal-Aswad method [33]. Subsequently, blood samples were taken for carboplatin PK analysis in the remaining patients in Parts A and B pre-dose, at the end of the infusion and at 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h following the end of the infusion on day 8 of cycle 1. Samples were not processed to determine free (unbound) platinum, thus only total platinum concentrations were analyzed using an inductively coupled plasma atomic emission spectroscopic method [34]. AUC values were corrected for plasma protein binding using the protein data in section 5.2 of the carboplatin summary of product characteristics [35].

Blood samples were taken for paclitaxel PK analysis in Parts B and C pre-dose, 1 h after the start of the infusion, at the end of the infusion, and at 6 and 24 h after the end of the infusion on day 8 of cycle 1. Paclitaxel concentrations were analyzed by liquid/liquid extraction followed by liquid chromatography/tandem mass spectrometry [36].

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

Efficacy evaluations

Tumor assessments were performed by CT/MRI at baseline and at the end of every two cycles. Tumor response in patients with measurable disease was assessed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.0 [37]. 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. PK parameters were calculated for all patients receiving continuous olaparib dosing for whom PK data were available. No formal statistical analyses were performed on safety, PK and efficacy data.

Results

Patient population

A total of 57 patients were enrolled into Parts A–C of the study (10 cohorts in total; Table 1). Patient demographics and baseline characteristics are shown in Table 2. Approximately half of the patients were male (54%), and the most common tumor types were breast cancer (21%), melanoma and lung/bronchus cancer (9% each). Most patients were heavily pre-treated with surgery, radiotherapy and several lines of prior chemotherapy.

Safety

Two patients experienced DLTs, both in Part A, cohort 2 (olaparib 100 mg bid plus carboplatin AUC 4): grade 1 thrombocytopenia with grade 2 neutropenia lasting for 16 days, which led to discontinuation of study drug, and grade 2 neutropenia lasting for 7 days, resulting in a dose interruption.

All patients were evaluable for safety, the majority of whom (97%) experienced a treatment-emergent adverse event (TEAE). Table 3 reports TEAEs occurring in each

Table 2 Patient demographics and baseline characteristics

	Part A (O + C)	Part B (O + C + P)	Part C (O + P)	Overall
Number of patients	25	20	12	57
Sex, n (%)				
Male	16 (64)	9 (45)	6 (50)	31 (54)
Female	9 (36)	11 (55)	6 (50)	26 (46)
Mean age, years (range)	55 (24–70)	49 (25–74)	48 (30–63)	51 (24–74)
Ethnic origin, n (%)				
Caucasian	24 (96)	19 (95)	12 (100)	55 (96)
Asian	1 (4)	0	0	1 (2)
Black	0	1 (5)	0	1 (2)
Other	0	0	0	0
ECOG performance status, n (%)				
0	10 (40)	10 (50)	4 (33)	24 (42)
1	14 (56)	9 (45)	8 (67)	31 (54)
2	1 (4)	1 (5)	0	2 (4)
Unknown	0	0	0	0
Primary site of disease, n (%)				
Breast	3 (12)	6 (30)	3 (25)	12 (21)
Melanoma	1 (4)	3 (15)	1 (8)	5 (9)
Ovary	1 (4)	0	2 (17)	3 (5)
Lung and bronchus	1 (4)	2 (10)	2 (17)	5 (9)
Uveal melanoma	3 (12)	1 (5)	0	4 (7)
Prostate	3 (12)	1 (5)	0	4 (7)
Large intestine	0	3 (15)	0	3 (5)
Other	11 (44)	3 (15)	4 (33)	18 (32)
Unknown	2 (8)	1 (5)	0	3 (5)
Mutation status, n (%)				
Wild type	2 (8)	2 (10)	0	4 (7)
<i>BRCA1</i>	1 (4)	2 (10)	2 (17)	5 (9)
<i>BRCA2</i>	0	1 (5)	2 (17)	3 (5)
Unknown	22 (88)	15 (75)	8 (67)	38 (67)
Mean duration of disease, months (range)	37 (1–104)	36 (3–122)	38 (10–105)	37 (1–122)
Prior therapies, n (%)				
Surgery*	24 (96)	20 (100)	12 (100)	56 (98)
Chemotherapy	19 (76)	19 (95)	12 (100)	50 (88)
Radiotherapy	12 (48)	8 (40)	5 (42)	25 (44)

*Including biopsies for diagnosis. C, carboplatin; ECOG, Eastern Cooperative Oncology Group; O, olaparib; P, paclitaxel

The bold merely signifies the overall statistics

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

TEAE, <i>n</i> (%)	Part A (O + C) (<i>n</i> = 25)	Part B (O + C + P) (<i>n</i> = 20)	Part C (O + P) (<i>n</i> = 12)	Overall (<i>n</i> = 57)
Blood and lymphatic system disorders				
Neutropenia				
All grades	12 (48)	11 (55)	6 (50)	29 (51)
Grade ≥ 3	5 (20)	10 (50)	5 (42)	20 (35)
Thrombocytopenia				
All grades	8 (32)	6 (30)	0	14 (25)
Grade ≥ 3	4 (16)	0	0	4 (7)
Anemia				
All grades	8 (32)	4 (20)	2 (17)	14 (25)
Grade ≥ 3	1 (4)	1 (5)	0	2 (4)
Gastrointestinal disorders				
Nausea	9 (36)	9 (45)	5 (42)	23 (40)
Constipation	10 (40)	3 (15)	3 (25)	16 (28)
Diarrhea	6 (24)	4 (20)	5 (42)	15 (26)
Vomiting	5 (20)	3 (15)	5 (42)	13 (23)
Stomatitis	1 (4)	5 (25)	4 (33)	10 (18)
General disorders				
Fatigue				
All grades	19 (76)	14 (70)	7 (58)	40 (70)
Grade ≥ 3	2 (8)	0	0	2 (4)
Dyspnea	6 (24)	5 (25)	0	11 (19)
Pyrexia	2 (8)	6 (30)	3 (25)	11 (19)
Nervous system disorders				
Peripheral sensory neuropathy	2 (8)	3 (15)	7 (58)	12 (21)
Infections				
Nasopharyngitis	5 (20)	6 (30)	8 (67)	19 (33)
Skin and subcutaneous tissue disorders				
Alopecia	0	10 (50)	7 (58)	17 (30)
Dry skin	0	0	4 (33)	4 (7)
Dose modifications due to TEAEs, <i>n</i> (%)				
Olaparib dose reduction	2 (8)	6 (30)	3 (25)	11 (19)
Olaparib dose interruption	5 (20)	6 (30)	5 (42)	16 (28)
Carboplatin dose reduction	1 (4)	—	—	1 (2)
Carboplatin dose delay	12 (48)	6 (30)	—	18 (40*)
Paclitaxel dose reduction	—	—	—	—
Paclitaxel dose delay	—	7 (35)	6 (50)	13 (41*)
TEAEs leading to discontinuation	4 (16)	5 (25)	—	9 (16)

*Percentages determined out of the total number of patients who received carboplatin (*n* = 45) or paclitaxel (*n* = 32). C, carboplatin; O, olaparib; P, paclitaxel; TEAE, treatment-emergent adverse event

The bold merely signifies the overall statistics

part of the study, and Table 4 reports TEAEs occurring in each cohort of the study. The most frequently occurring TEAEs overall were fatigue (70% of patients), neutropenia (51%), nausea (40%), nasopharyngitis (33%) and alopecia (30%). In total, 32 patients (56%) experienced a TEAE of grade 3 or higher in severity, the majority of

which were hematologic in nature, with neutropenia (35%; Table 3) being the most common. Grade ≥ 3 thrombocytopenia only occurred in patients receiving olaparib plus carboplatin.

There was a relatively high incidence of bone marrow suppression, most commonly neutropenia (51% overall), which occurred in a similar proportion of patients in each treatment regimen

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

TEAE, n (%)	Part A treatment cohort (olaparib dose, mg bid/carboplatin dose, AUC) [n]				Part B treatment cohort (olaparib dose, mg bid/carboplatin dose, AUC/paclitaxel dose, mg/m ²) [n]				Part C treatment cohort (olaparib dose, mg bid/ paclitaxel dose, mg/m ²) [n]	
	1 (50/4) [3]	2 (100/4) [14]	3 (50/5) [4]	7 (200/4) [4]	4 (50/4/90) [4]	5 (50/4/135) [5]	8 (50/4/175) [5]	9 (100/4/175) [6]	6 (100/80) [6]	10 (200/80) [6]
Any TEAE	3 (100)	13 (93)	4 (100)	4 (100)	4 (100)	5 (100)	5 (100)	6 (100)	6 (100)	5 (83)
Blood and lymphatic system disorders										
Anemia	1 (33)	3 (21)	3 (75)	1 (25)	0	1 (20)	0	3 (50)	2 (33)	0
Neutropenia	2 (67)	6 (43)	2 (50)	2 (50)	2 (50)	3 (60)	2 (40)	4 (67)	2 (33)	4 (67)
Thrombocytopenia	2 (67)	4 (29)	1 (25)	1 (25)	0	2 (40)	1 (20)	3 (50)	0	0
Cardiac disorders										
Tachycardia	2 (67)	4 (29)	2 (50)	1 (25)	1 (25)	0	0	3 (50)	2 (33)	1 (17)
General disorders and administration site conditions										
Constipation	2 (67)	6 (43)	2 (50)	0	0	1 (20)	1 (20)	1 (17)	0	3 (50)
Diarrhea	0	5 (36)	1 (25)	0	2 (50)	0	0	2 (33)	2 (33)	3 (50)
Nausea	2 (67)	5 (36)	0	2 (50)	1 (25)	3 (60)	3 (60)	2 (33)	2 (33)	4 (50)
Stomatitis	0	1 (7)	0	0	1 (25)	1 (20)	2 (40)	1 (17)	1 (17)	3 (50)
Vomiting	2 (67)	3 (21)	0	0	0	1 (20)	0	2 (33)	3 (50)	2 (33)
General disorders										
Fatigue	3 (100)	10 (71)	3 (75)	3 (75)	4 (100)	3 (60)	3 (60)	4 (67)	3 (50)	4 (67)
Influenza-like illness	2 (67)	2 (14)	0	0	0	0	0	0	1 (17)	2 (33)
Peripheral edema	0	0	0	0	0	0	1 (20)	0	2 (33)	1 (17)
Pyrexia	1 (33)	1 (7)	0	0	2 (50)	1 (20)	0	3 (50)	2 (33)	1 (17)
Infections and infestations										
Nasopharyngitis	1 (33)	2 (14)	0	2 (50)	2 (50)	1 (20)	1 (20)	2 (33)	5 (83)	3 (50)
Musculoskeletal and connective tissue disorders										
Myalgia	0	0	0	1 (25)	1 (25)	0	0	1 (17)	0	3 (50)
Nervous system disorders										
Headache	0	0	0	1 (25)	0	0	0	1 (17)	1 (17)	2 (33)
Peripheral sensory neuropathy	2 (67)	0	0	0	1 (25)	0	1 (20)	1 (17)	4 (67)	3 (50)
Respiratory, thoracic and mediastinal disorders										
Dyspnea	0	2 (14)	2 (50)	2 (50)	0	0	2 (40)	3 (50)	1 (17)	1 (17)
Epistaxis	1 (33)	1 (7)	0	0	0	0	0	1 (17)	1 (17)	2 (33)
Skin and subcutaneous tissue disorders										
Alopecia	0	0	0	0	2 (50)	2 (40)	2 (40)	4 (67)	3 (50)	4 (67)
Dry skin	0	0	0	0	0	0	0	0	4 (67)	0
Nail disorder	0	0	0	0	0	0	0	0	2 (33)	1 (17)
Rash	0	0	0	0	0	0	0	0	2 (33)	1 (17)

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

(Table 3). However, the frequency of thrombocytopenia and anemia was lower in Part C cohorts, in which olaparib was combined with paclitaxel. Although hematologic toxicities did not result in DLTs in most cases, many cohorts were declared intolerable because of the prolonged bone marrow suppression. Dose modifications (interruptions, delays and/or reductions) were required in a number of patients to allow their hematologic laboratory values to

recover back to grade 1, and some patients required repeated treatment with granulocyte colony-stimulating factor (G-CSF). However, bone marrow suppression only led to treatment discontinuation in five patients overall (9%; one patient in cohort 1 [olaparib 50 mg bid and carboplatin AUC 4], one patient in cohort 2 [olaparib 100 mg bid and carboplatin AUC 4], two patients in cohort 5 [olaparib 50 mg bid, carboplatin AUC 4 and paclitaxel

135 mg/m²] and one patient in cohort 8 [olaparib 50 mg bid, carboplatin AUC 4 and paclitaxel 175 mg/m²]. Throughout the study, dose reductions and interruptions/delays were required for olaparib in 19% and 28% of patients, for carboplatin in 2% and 32% of patients, and for paclitaxel in 0% and 23% of patients, respectively (Table 3). Study treatment discontinuations were required for 16% of patients receiving olaparib plus carboplatin, 25% of patients receiving olaparib plus carboplatin and paclitaxel, and no patients receiving olaparib plus paclitaxel.

When further evaluating dose modifications, it was clear that some regimens appeared tolerable for up to three cycles, with increased toxicity with later cycles. In two cohorts (cohort 3: olaparib 50 mg bid, carboplatin AUC 5; cohort 4: olaparib 50 mg bid, carboplatin AUC 4, paclitaxel 90 mg/m²), few dose adjustments were required and the treatment doses appeared tolerable for at least three cycles. In cohort 8 (olaparib 50 mg bid, carboplatin AUC 4, paclitaxel 175 mg/m²), one patient required a treatment interruption because of neutropenia, but did not require any other dose modification up to seven cycles of treatment.

Pharmacokinetics

PK parameters for olaparib, carboplatin and paclitaxel are summarized in Table 5, and Fig. 1 shows the plasma concentration–time curves of olaparib alone and in combination with carboplatin and/or paclitaxel.

Patients in the PK evaluable population were required to have a reportable area under the plasma concentration–time curve up to 8 h post-dose (AUC_{0–8}) and a reportable maximum steady-state plasma concentration (C_{max,ss}) for olaparib on both the day dosed without chemotherapy (day 4) and the day dosed with chemotherapy (day 8). Overall, 50 patients were evaluable for olaparib PK assessments. Geometric mean plasma concentration–time profiles were similar for olaparib alone and in the presence of carboplatin in all cohorts of Part A. Although some variability was observed in the exposure (AUC_{0–8} and C_{max,ss}) ratios for olaparib alone and in combination with chemotherapy within all the treatment groups, and the number of patients in each cohort was small, there was no evidence of any marked effect on olaparib exposure when dosed in combination with carboplatin compared with that when olaparib was dosed alone, with the geometric mean treatment ratios for all four groups falling between 0.795 and 1.05. However, exposure to olaparib (AUC_{0–8}) was reduced in nearly all the evaluable patients when co-administered with paclitaxel alone (Part C) and in combination with carboplatin and paclitaxel (Part B), with a mean reduction in olaparib exposure of 40–43% and 22–45%, respectively.

The first 10 patients dosed in Part A of the study had a single PK sample collected 24 h after the cycle 1 day 8 carboplatin infusion to evaluate the estimated free carboplatin AUC in the presence of olaparib. The free carboplatin AUC

was determined to be ~25% higher (range, 9% lower to 57% higher) than the target AUC of 4 mg·min/mL, with a range of 3.7–6.3 mg·min/mL. Subsequently, carboplatin exposure was evaluated when given in combination with olaparib in 25 patients over a 48-h period following carboplatin treatment, and the mean carboplatin exposure (free AUC_{0–48.5}) was determined to be lower on average than the AUC target of 4 mg·min/mL (range, 48% lower to 10% higher) or 5 mg·min/mL (range, 31% lower to 3.8% higher) across all treatment regimens, either when in combination with olaparib in Part A or with olaparib plus paclitaxel in Part B.

In total, 20 patients were evaluable for exposure to paclitaxel (AUC_{0–27}) when given in combination with olaparib. Variability in exposure was relatively high, with a coefficient of variation ranging from 9% to 246%; however, as the number of patients in each cohort was small and the variability between the patients high, these data should be interpreted with caution.

Antitumor activity

In total, 44 patients had measurable disease at baseline (Table 6). Two patients with ovarian and breast cancer who both received olaparib in combination with paclitaxel (Part C) achieved a CR, and three patients (one with nasopharyngeal and two with breast cancer), one of whom received olaparib plus carboplatin (Part A) and two of whom received olaparib plus carboplatin and paclitaxel (Part B), achieved a PR, resulting in an ORR of 11%. Additionally, there was one unconfirmed PR, and 22 patients experienced stable disease for at least two cycles of treatment.

Discussion

This Phase I study was originally designed to determine the safety and tolerability of combining continuous olaparib dosing with carboplatin. While the frequency of non-hematologic toxicities was in line with that seen when giving carboplatin with paclitaxel, the frequency, severity and duration of myelosuppression (neutropenia 51%; thrombocytopenia 25%) was higher than previously reported for carboplatin alone in patients with advanced ovarian cancer [23, 38, 39]. As such, the study protocol was revised to add paclitaxel to the regimen with the aim of reducing the incidence of thrombocytopenia [40]. The combination of olaparib with paclitaxel alone did not result in thrombocytopenia; however, the incidence of neutropenia (50%; of which 42% was grade ≥ 3) was similar to that observed with olaparib plus carboplatin and was greater than that published following paclitaxel monotherapy (12% grade 2, no grade ≥ 3) [41]. The addition of paclitaxel to olaparib and carboplatin also had no significant effect on reducing the rate of myelosuppression, which remained the

Table 5 Pharmacokinetic parameters of (a) olaparib monotherapy at steady state and in combination with carboplatin and/or paclitaxel, (b) carboplatin in combination with olaparib or olaparib plus paclitaxel, and (c) paclitaxel in combination with olaparib or olaparib plus carboplatin and published pharmacokinetic data for paclitaxel monotherapy

a) Pharmacokinetic parameters of olaparib monotherapy at steady state and in combination with carboplatin and/or paclitaxel									
Steady state	Olaparib dose, mg bid	Carboplatin AUC, mg·min/mL	Paclitaxel dose, mg/m ²	Patients, n	C _{max} , µg/mL	Olaparib monotherapy Gmean (%CV)	Olaparib in combination Gmean (%CV)	Mean ratio (range)	
Cohorts with carboplatin (Part A)									
1	50	4	x	3	2.03 (18)		2.03 (18)	1.03 (0.68–1.3)	
2	100	4	x	13	3.75 (63)		3.20 (72)	0.88 (0.47–1.2)	
3	50	5	x	3	3.20 (43)		2.68 (23)	0.85 (0.75–1.0)	
7	200	4	x	4	4.95 (40)		4.10 (31)	0.85 (0.62–1.2)	
Cohorts with carboplatin and paclitaxel (Part B)									
4	50	4	90	4	1.70 (48)		1.71 (54)	1.01 (0.85–1.1)	
5	50	4	135	4	2.58 (70)		2.29 (74)	0.94 (0.64–1.5)	
8	50	4	175	3	1.62 (19)		0.801 (38)	0.52 (0.35–0.77)	
9	100	4	175	5	4.64 (42)		2.99 (76)	0.70 (0.28–0.97)	
Cohorts with paclitaxel (Part C)									
6	100	x	80	6	4.06 (69)		2.96 (78)	0.75 (0.47–0.95)	
10	200	x	80	5	4.54 (43)		3.13 (40)	0.69 (0.65–0.75)	
b) Pharmacokinetic parameters of carboplatin in combination with olaparib or olaparib plus paclitaxel									
Olaparib dose, mg bid	Carboplatin AUC, mg·min/mL	Paclitaxel dose, mg/m ²	Patients, n	Free AUC estimated from 24-h total platinum, mg·min/mL	Free AUC _{0–48.5} , mg·min/mL	Gmean (%CV)			
Cohorts with olaparib (Part A)									
1	50	4	X	3			4.99 (28)	X	
2	100	4	X	7/5			4.96 (12)	3.69 (16)	
3	50	5	X	1			X	3.47	
7	200	4	X	3			X	2.98 (8)	
Cohorts with olaparib and paclitaxel (Part B)									
4	50	4	90	4			X	3.26 (13)	
5	50	4	135	4			X	3.40 (16)	
8	50	4	175	4			X	2.93 (15)	
9	100	4	175	4			X	2.67 (22)	
c) Pharmacokinetic parameters of paclitaxel in combination with olaparib or olaparib plus carboplatin and published pharmacokinetic data for paclitaxel monotherapy									
Olaparib dose, mg bid	Carboplatin dose (AUC), mg·min/mL	Paclitaxel dose, mg/m ²	Patients, n	C _{inf} , µg/mL	Gmean (%CV)	Range	AUC _{0–27} , µg·h/mL	Gmean (%CV)	Range
Cohorts with olaparib and carboplatin (Part B)									
4	50	4	90	4	2.91 (319)	0.85–26.3	15.0 (246)		5.03–11.1
5	50	4	135	4/3	2.26 (51)	1.26–3.98	13.5 (54)		8.37–22.8
8	50	4	175	4/2	3.20 (61)	1.42–5.20	NA		20.8–28.4
9	100	4	175	4	4.38 (11)	3.92–4.85	23.5 (9)		21.2–25.9
Cohorts with olaparib (Part C)									
6	100	X	80	3	1.00 (17)	0.87–1.20	6.22 (30)		5.12–8.66
10	200	X	80	5/4	0.93 (8)	0.87–1.06	5.66 (15)		4.98–6.64
Published data for paclitaxel [50, 54]									
X	X	X	135	X	2.13	X	7.83*	X	X
X	X	X	150	X	3.04	X	11.7*	X	X
X	X	X	175	X	3.41	X	14.3*	X	X
X	X	X	200	X	5.88	X	19.2*	X	X

*AUC_{0–∞}, AUC, area under the concentration–time curve; AUC_{0–27}, area under the concentration–time curve from time 0 to 27 h; AUC_{0–48.5}, area under the concentration–time curve from time 0 to 48.5 h; C_{inf}, plasma concentration at the end of the infusion; C_{max}, maximum plasma concentration; CV, coefficient of variation; Gmean, geometric mean; NA, not available

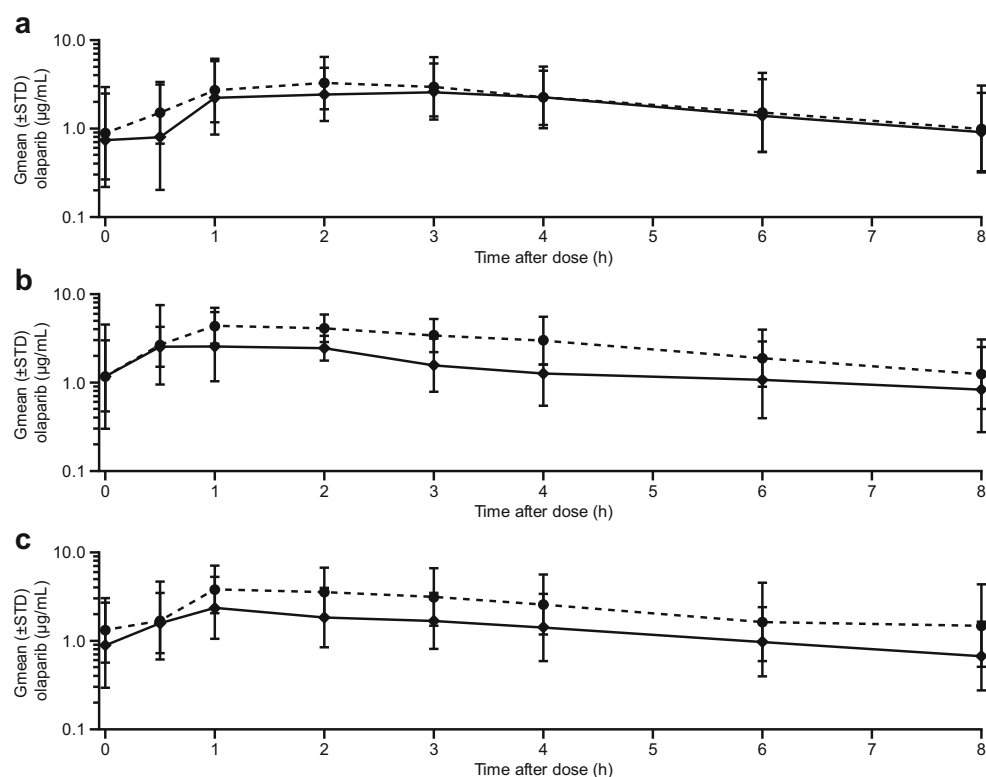


Fig. 1 Plasma concentration–time curves of (a) olaparib monotherapy at steady state and in combination with carboplatin (Part A), (b) olaparib monotherapy at steady state and in combination with paclitaxel (Part B), and (c) olaparib monotherapy at steady state and in combination with carboplatin and paclitaxel (Part C). a) Cohort 2 ($n = 13$), olaparib 100 mg alone (day 4) and in combination with carboplatin AUC 4 (day 8). b) Cohort 9 ($n = 5$), olaparib 100 mg alone (day 4) and in combination

with carboplatin AUC 4 and paclitaxel 175 mg/m² (day 8). c) Cohort 6 ($n = 6$), olaparib 100 mg alone (day 4) and in combination with paclitaxel 80 mg/m² (day 8). Solid lines, olaparib monotherapy at steady state; dotted lines, olaparib monotherapy at steady state in combination with carboplatin and/or paclitaxel. Gmean, geometric mean; STD, standard deviation

cause of many dose modifications. Analyses of all dose combinations and levels evaluated revealed that at least two dose levels (cohorts 3 and 4) with continuous dosing of olaparib 50 mg bid did not result in any dose modifications for up to three cycles.

The enhancement of myelosuppression following olaparib treatment has been observed in other Phase I trials in which

olaparib was added to other chemotherapeutics, such as dacarbazine [42], topotecan [43] and cisplatin/gemcitabine [44]. A possible explanation for this is that olaparib, in addition to its effect in tumor cells, may also enhance the toxic effects of chemotherapies on bone marrow cells. Accordingly, when exposed to ionizing radiation, bone marrow cells in PARP-null mice were shown to have an increased rate of chromatid breaks, suggesting a serious DNA-repair deficiency [45].

The exacerbated myelosuppression could also be caused by a lower tolerability threshold of immature hematopoietic progenitor cells. Although normal bone marrow progenitors do not have DNA-repair deficiencies *per se*, immature progenitors, which are ultimately responsible for replenishing mature blood cells, exhibit reduced capacity for DNA lesions, including SSBs, and are at higher risk of undergoing apoptosis [46]. There is also evidence to suggest a role for PARP2 in sustaining erythropoiesis and bone marrow recovery following DNA damage induced by ionizing radiation, which may be affected by olaparib treatment and accentuated when it is combined with chemotherapy [47, 48]. Additionally, myelosuppression can be further compounded by the reduced self-renewal capability of hematopoietic stem cells resulting from accumulated DNA damage and consequently limited bone marrow

Table 6 Antitumor activity of olaparib in combination with carboplatin and/or paclitaxel in patients evaluable for efficacy

	Patients with measurable disease, n	CR, n (%)	PR, n (%)	SD for at least two cycles, n (%)	PD, n (%)	NE, n (%)
Part A	17	0	1 (6)	11 (65)	5 (29)	0
Part B	17	0	2 (12)	7 (41)	6 (35)	2 (12)
Part C	10	2 (20)	0	4 (40)*	4 (40)	0
Overall	44	2 (5)	3 (7)	22 (50)	15 (34)	2 (5)

*Unconfirmed responses: one partial response in Part C. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

The bold merely signifies the overall statistics

repopulation, potential in elderly patients or those exposed to multiple rounds of chemotherapy, which many patients in the current study had undergone.

Routine use of GCSF was not permitted during the first cycle of study treatment, while DLTs were assessed. Following completion of cycle 1, GCSF could be used therapeutically if clinically indicated. However, data for GCSF use were irregularly recorded and thus any possible benefit of the addition of GCSF could not be determined in this trial.

While the number of patients was small and variability within treatment groups high, there was no evidence that carboplatin had a marked effect on the exposure to olaparib at steady state. However, when olaparib was co-administered with paclitaxel alone or in combination with both paclitaxel and carboplatin, the steady-state exposure to olaparib was reduced, by up to 45%. While paclitaxel is also metabolized by CYP3A4, the enzyme primarily involved in the oxidative metabolism of olaparib, it is not a known inducer of this CYP enzyme. The reason behind this mechanism is unclear and might be elucidated with more observations in future studies.

When 24-h platinum PK samples were evaluated, the estimated free carboplatin AUC appeared to be approximately 25% higher than that based on the calculated AUCs employing Calvert's formula [49]. When samples were collected across the whole PK profile, the estimated free platinum AUC_{0–48.5} was determined to be lower than the target exposure (AUC) across all cohorts. However, it is important to note that these observations have to be viewed with caution. The number of patients was small, the free platinum AUC values were not determined directly and the carboplatin AUC values in the absence of olaparib were not determined.

It appeared that paclitaxel exposure was higher in the presence of olaparib in this study compared with published data [39, 50]. However, this implication should also be considered with caution as patient numbers were small, variability was high and paclitaxel concentrations alone were not determined, making it difficult to make intra- and inter-patient comparisons.

The overall ORR seen in this study was 11%. This is low compared with other studies in which olaparib was combined with chemotherapeutic agents [51, 52]. However, it is important to note that at the start of this study, the population was not yet enriched with patients carrying BRCA mutations, in whom responses are most likely to be observed [10].

In conclusion, because of the increased frequency, severity and duration of myelosuppression, it was difficult to find a tolerable dosing regimen for olaparib in combination with carboplatin and/or paclitaxel. None of the regimens explored in this part of the study could be given for multiple cycles without the need for dose modification within six cycles of treatment. However, some dosing regimens could be given for up to at least three cycles without any dose modifications for myelosuppression; these regimens included the relatively low dose of continuous olaparib (50 mg bid). However,

pharmacodynamic data from a Phase I study of olaparib monotherapy demonstrated that the olaparib exposure (AUC) following a dose of 100 mg was sufficient to inhibit PARP in peripheral blood mononuclear cells [53]. Further studies are needed to elucidate how to optimally combine olaparib with these chemotherapeutics without decreasing its potentiating antitumor effects. Part 2 of the study further evaluates the safety and efficacy of olaparib in combination with carboplatin and paclitaxel (see companion article, <https://doi.org/10.1007/s10637-019-00857-6>).

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Compliance with ethical standards

Conflict of interest Ilian Tchakov was an employee of AstraZeneca at the time of this study.

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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