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ORIGINAL ARTICLE

Pharmacokinetics and safety of olaparib tablets as monotherapy and in combination with paclitaxel: results of a Phase I study in Chinese patients with advanced solid tumours

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Abstract

Purpose Chinese patients have been enrolled in multiple Phase III trials of the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (Lynparza); however, the pharmacokinetic (PK) profile of olaparib has not been investigated in this population. This two-part, open-label Phase I study was, therefore, carried out to determine the PK and safety profile of olaparib (tablet formulation) in Chinese patients with advanced solid tumours as monotherapy and in combination with paclitaxel (NCT02430311).

Methods The PK profile of olaparib 300 mg (twice daily [bid]; Cohort 1) as monotherapy after a single dose and at steady state, and 100 mg (bid; Cohort 2) as monotherapy (single dose and at steady state) and in combination (at steady state) with weekly paclitaxel (80 mg/m^2) was assessed during Part A. Patients could continue to receive treatment (monotherapy, Cohort 1; combination therapy, Cohort 2) in Part B, which assessed safety and tolerability.

Results Twenty and 16 patients were enrolled into Cohorts 1 and 2, respectively. Steady-state olaparib exposure increased slightly less than proportionally with increasing monotherapy dose and inter-patient variability was high. A statistically significant decrease in olaparib exposure was seen when given in combination with paclitaxel. Discontinuation due to adverse events (AEs) was rare and haematological AEs were more common in patients receiving combination treatment.

Conclusions The PK and safety profile of olaparib monotherapy in Chinese patients is consistent with that seen previously in Western and Japanese patients, and the recommended Phase III monotherapy tablet dose (300 mg bid) is suitable for use in this population.

Keywords Chinese patients · Olaparib · Paclitaxel · PARP inhibitor · Pharmacokinetics · Safety

Introduction

Olaparib (Lynparza™) is a potent oral poly(ADP-ribose) polymerase (PARP) inhibitor that blocks base-excision repair of single-strand DNA breaks by trapping PARP at sites of DNA damage, resulting in synthetic lethality. This

Kate Hsu is no longer employed by AstraZeneca.

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is most notable in tumours with deficiencies in homologous recombination repair (HRR) pathways such as those with a *BRCA1/2* mutation (*BRCA*m) or tumours that are ataxia-telangiectasia-mutated protein negative [1–3].

The tablet formulation of olaparib is approved in the EU and USA for the treatment of advanced ovarian cancer patients and in the USA for the treatment of patients with human epidermal growth factor receptor type 2 (HER2)-negative metastatic breast cancer and a germline *BRCA*m [4, 5].

Olaparib (capsule, 200 mg twice daily [bid]) plus weekly paclitaxel (90 mg/m^2) has previously demonstrated antitumor activity in breast cancer patients [6]. Olaparib (tablet, 100 mg bid) in combination with weekly paclitaxel (80 mg/m^2) followed by olaparib maintenance (200 mg bid) was reported to improve overall survival (OS) compared with placebo plus paclitaxel in a Phase II study of Asian patients with metastatic gastric cancer and tumours with low ATM expression [7]. The Phase III GOLD study of olaparib (tablet, 100 mg bid) plus weekly paclitaxel (80 mg/m^2) in Asian patients with advanced gastric cancer did not meet its primary objective of demonstrating a statistically significant improvement in OS compared with placebo plus paclitaxel; however, OS was longer in both the overall and low ATM expression populations [8]. In these studies, a lower dose of olaparib (capsule or tablet formulation) than the approved monotherapy dose was used based on results from Phase I studies that have shown a need to reduce the dose of olaparib when given in combination with cytotoxic chemotherapy; however, standard weekly doses of paclitaxel were used [6, 9].

Studies in Western and Japanese patients have shown that the PK of olaparib tablets is characterized by rapid absorption following single and multiple dosing, with plasma concentrations declining biphasically after single dosing [10, 11]. Following oral dosing of ^{14}C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70%) and was the major component found in both urine and faeces (15% and 6% of the dose, respectively) [4]. In vitro, cytochrome P450 (CYP) 3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib [4]. In vivo, exposure to olaparib was increased following a single olaparib dose given in combination with the CYP3A4 inhibitor, itraconazole; conversely, olaparib exposure was decreased when a single dose was given in combination with the CYP3A4 inducer, rifampin [12]. It is known that there are ethnic differences because of genetic variability in drug-metabolizing enzymes such as CYP [13]. For example, it has been reported that only a small percentage of Western subjects, but considerably larger fractions of Asians and Africans, have a functional copy of the *CYP3A5* gene and in these individuals, CYP3A5 could make a significant contribution to drug metabolism [14]. Therefore, it is important to evaluate the PK of drugs metabolized by CYP enzymes, such as olaparib, in patients of different ethnic backgrounds.

Although Chinese patients have been recruited into several Phase III trials of olaparib (tablet formulation) [15, 16], the PK of olaparib has not yet been investigated in this population. This Phase I study was performed to characterize the PK profile, safety and tolerability profile of olaparib tablets as monotherapy and in combination with paclitaxel in Chinese patients with advanced solid tumours.

Methods

Study design

This was a Phase I, open-label, two-part study (NCT02430311). Part A of the study assessed the PK of olaparib (tablet; Fig. 1) using two patient cohorts. In Cohort 1, single- and multiple-dose PK of olaparib monotherapy (300 mg bid) were evaluated. In Cohort 2, single- and multiple-dose PK of olaparib (100 mg bid) monotherapy and multiple-dose PK in the presence of co-administered paclitaxel were assessed. On multiple-dose days, patients received olaparib 100 mg bid as monotherapy for 8 days and then continued olaparib treatment in combination with paclitaxel 80 mg/m^2 (administered on days 9, 16 and 23). Part B of the study assessed the safety of olaparib monotherapy (300 mg bid; Cohort 1) and in combination with weekly paclitaxel (olaparib 100 mg bid; paclitaxel 80 mg/m^2 weekly; Cohort 2). Patients in Cohort 1 could continue to receive olaparib monotherapy for as long as it was considered beneficial by the investigator; patients in Cohort 2 could receive olaparib in combination with paclitaxel for a total of 6–9 cycles across the whole study and could receive olaparib as monotherapy (300 mg bid) on completion or discontinuation of paclitaxel. Patients in Cohort 2 received pre-medication (prior to paclitaxel administration to prevent severe hypersensitivity reactions), such as dexamethasone, diphenhydramine (or equivalent), and cimetidine or ranitidine per local standard practice. No efficacy information was collected. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca Policy on Bioethics [17].

Study objectives

The primary objectives were: to characterize the single-dose PK of olaparib following a 300-mg and 100-mg monotherapy dose, and the steady-state PK of olaparib as monotherapy (300 mg bid and 100 mg bid) and as combination therapy (100 mg bid) with weekly paclitaxel (80 mg/m^2 weekly) in Chinese patients. Secondary objectives were to evaluate the effect of co-administration of paclitaxel on the

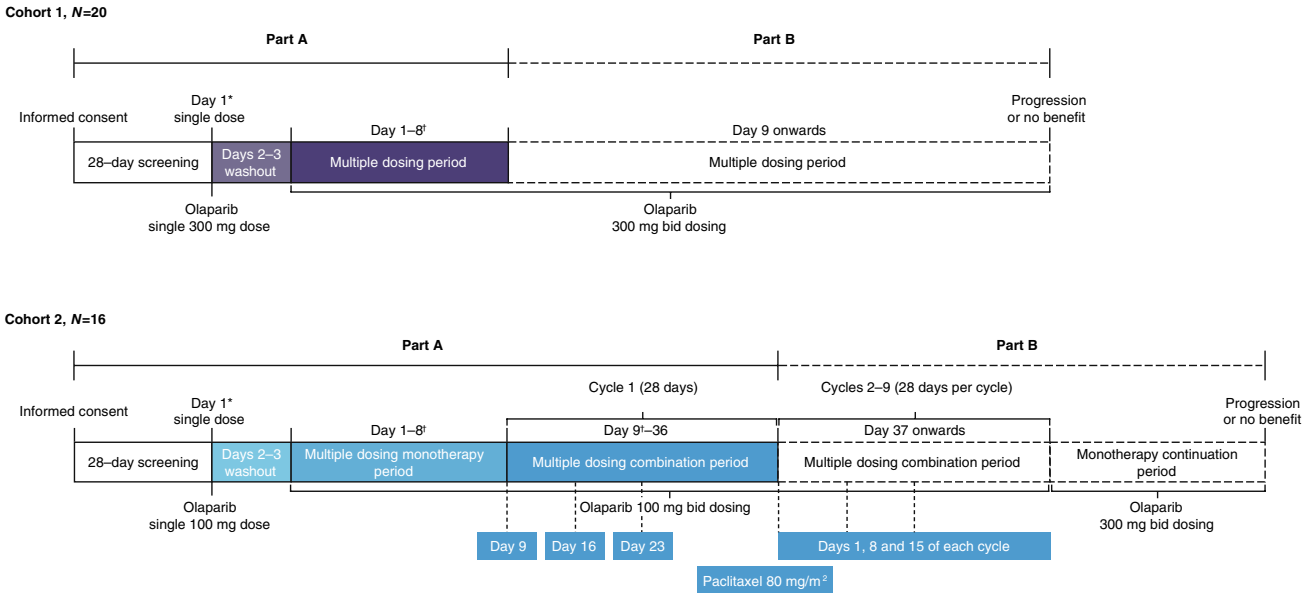

Fig. 1 Study design. *Blood samples for analysis of olaparib plasma concentrations were taken pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 h' post-dose on single-dose day 1. †Blood samples for analysis of olaparib plasma concentrations were taken pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h' post-morning olaparib dose on multiple-dose day 8 and day 9 (Cohort 2 only in combination with the first dose of paclitaxel). *Bid* twice daily

steady-state exposure to olaparib and to determine the safety and tolerability of olaparib monotherapy and in combination with paclitaxel.

Study population

Eligible patients were aged ≥ 18 years and had a confirmed (histologically or, where appropriate, cytologically) malignant solid tumour, refractory or resistant to standard therapy or for which no suitable standard therapy exists. Patients were required to have a life expectancy of ≥ 12 weeks, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, adequate bone marrow and organ function (defined as: haemoglobin ≥ 10.0 g/dL; absolute neutrophil count ≥ 1.5×10^9/L; white blood cell count > 3×10^9/L; platelet count ≥ 100×10^9/L; total bilirubin ≤ 1.5 × institutional upper limit of normal [ULN]; aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × ULN or ≤ 5 × ULN in the presence of liver metastases; serum creatinine ≤ 1.5 × ULN and serum creatinine clearance > 50 mL/min [using Cockroft Gault or 24-h urine collection]) measured within 28 days prior to administration of olaparib, and on a stable concomitant medication regimen (no changes in medication or in dose within 2 weeks prior to the start of olaparib dosing, except for bisphosphonates, denosumab or corticosteroids, which should be stable for at least 4 weeks prior to the start of olaparib dosing). Patients in Cohort 2 were required to be eligible for paclitaxel treatment.

Patients were excluded if they had received any prior treatment with a PARP inhibitor, treatment with systemic chemotherapy or radiotherapy within 4 weeks of olaparib dosing, were unable to swallow orally administered medication, had disorders likely to interfere with absorption of olaparib or paclitaxel and had any ongoing toxicities (Grade > 2). Concomitant medication with modulators of cytochrome P450 3A4 (CYP3A4) was not permitted; however, patients in Cohort 2 could receive cimetidine (a moderate CYP3A4 inhibitor) or dexamethasone (a weak CYP3A4 inducer [however, physiologically-based pharmacokinetic modelling has shown dexamethasone to have no effect on olaparib PKs when co-administered [18]]) as pre-medication ahead of paclitaxel administration. A protocol amendment was made following the initiation of patient recruitment to exclude patients with gastric or intestinal cancer, or with prior surgical procedures such as full or partial gastrectomy.

Pharmacokinetic assessments

Blood samples for analysis of olaparib concentrations were taken pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 h post-dose on single-dose day 1 (Cohorts 1 and 2) and pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h post-morning olaparib dose on multiple-dose days 8 (Cohort 1 and 2) and 9 (Cohort 2 only; Fig. 1). Blood samples were centrifuged at 4 °C for 10 min and at 1500*g* within 30 min of collection, to provide plasma samples for olaparib analysis. These were stored at ≤ − 20 °C and transported to Covance

(Shanghai, China), where concentrations of olaparib were determined by solid-phase extraction and analysis using reversed-phase high-performance liquid chromatography (HPLC) with turbo ion spray tandem mass spectrometric (MS)/MS detection (positive ion mode) [18]. PK parameters were determined using standard, noncompartmental analysis performed using Phoenix™ WinNonlin™ software version 6.3 (Pharsight Corporation, CA). The PK parameters determined for single-dose olaparib were: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the plasma concentration–time curve from zero to infinity (AUC), AUC from zero to 12 h post-dose (AUC_{0-12}), apparent volume of distribution (V_z/F), apparent oral clearance (CL/F) and terminal half-life ($t_{½}$,λ_z). For multiple-dose olaparib, both as monotherapy and in combination with paclitaxel, the following PK parameters were determined at steady state (ss): $C_{max,ss}$, minimum plasma concentration ($C_{min,ss}$), $t_{max,ss}$, AUC across the dosing interval (AUC_{ss}) and CL_{ss}/F. An accumulation ratio (R_{AC}; calculated as AUC_{ss}/AUC_{0-12}) and temporal change parameter (TCP; calculated as AUC_{ss}/AUC) were determined for multiple-dose olaparib monotherapy only.

Safety and tolerability assessments

Safety and tolerability were assessed by recording AEs, physical examination results, vital signs, electrocardiogram (ECG) and laboratory findings. Safety data were recorded for the duration of study treatment and for a 30-day follow-up period post-discontinuation. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analyses

A total of 30 patients were to be recruited to the study (15 patients in each cohort) to obtain evaluable single- and multiple-dose PK data from eight to 12 evaluable patients per cohort based on the China Food and Drug Administration guidance [19]. Based on an estimate of within-patient standard deviation (SD) of 0.238 for log AUC (as seen in Western patients from NCT02093351 taking olaparib tablet 300 mg bid) [20], 12 evaluable patients were required in Cohort 2 to provide sufficient power to detect a 30% change in log-transformed $C_{max,ss}$ and AUC_{ss} of olaparib in the presence of single-dose paclitaxel.

The PK analysis set included all patients who received an olaparib dose and provided evaluable PK profiles in at least one treatment period and who had no AEs or protocol deviations that could have impacted olaparib PK; if a patient had either of these for all the PK sampling days, the patient was excluded from the PK analysis set; if at least one but not all PK sampling days were affected, the PK data only for unaffected PK sampling days were used. The safety analysis set for Part A included all patients who received at least one dose of olaparib; in Part B, the safety analysis set included all patients who received at least one dose of olaparib or paclitaxel.

The primary PK outcome variables for characterizing single-dose and steady-state PK of olaparib following monotherapy dosing, and steady-state PK of olaparib when given in combination with weekly paclitaxel were summarized using appropriate descriptive statistics. The Cohort 2 PK outcome variables of $C_{min,ss}$, $C_{max,ss}$ and AUC_{ss} were statistically analysed to investigate the effect of paclitaxel on the PK of olaparib. Following log transformation, $C_{min,ss}$, $C_{max,ss}$ and AUC_{ss} were analysed separately by a mixed-effects model with fixed effects for treatment and random effect for patients. Point estimates and adjusted 90% confidence intervals (CIs) for the difference between treatments (olaparib co-administered with paclitaxel compared with olaparib alone) for $C_{min,ss}$, $C_{max,ss}$ and AUC_{ss} were constructed. The point estimate and adjusted 90% CIs were then back-transformed to provide point and CI estimates for the ratio of geometric least squares (GLS) means. An interaction between paclitaxel and olaparib was considered to have occurred if the lower limit of the 90% CI for the ratio was <0.7 (ie $>30\%$ decrease on a log scale in olaparib PK in the presence of paclitaxel, compared with olaparib alone) or the upper limit of the 90% CI was >1.43 (ie $>30\%$ increase on a log scale), or if the 90% CIs cross over one. All summaries and statistical analyses were performed using SAS® version 9.2 or higher.

Results

Patient population

Thirty-six Chinese patients received treatment; 20 and 16 patients in Cohort 1 and Cohort 2, respectively. More patients than planned were included in Cohort 1 following the protocol amendment (which excluded patients with prior gastric surgery). Overall, 34 of 36 patients completed Part A, two patients discontinued treatment prematurely (patient decision, Cohort 1; Grade 2 AEs of increased alanine aminotransferase [ALT] and aspartate aminotransferase [AST], Cohort 2).

All patients who completed Part A continued into Part B; 19 patients in Cohort 1 and 15 patients in Cohort 2. One patient in Cohort 2 received olaparib 100 mg bid monotherapy but did not receive paclitaxel during Part B. An additional two patients in Cohort 2 received olaparib 300 mg bid monotherapy after completing or discontinuing paclitaxel treatment. At the end of Part B, all patients had discontinued olaparib because of objective disease progression ($n=26$

[76%]), patient decision ($n=5$ [15%]), severe protocol non-compliance ($n=1$ [3%]), AE (anaemia; $n=1$ [3%]), and completion of combination schedule ($n=1$ [3%]). At the end of Part B, all 14 patients who received paclitaxel had discontinued treatment because of objective disease progression ($n=9$ [64%]), patient decision ($n=3$ [21%]), maximum number of allowed paclitaxel cycles ($n=1$ [7%]), and completion of combination schedule ($n=1$ [7%]). Two patients died during the study: one receiving combination therapy during Part A and one receiving olaparib monotherapy (300 mg bid) during Part B; both due to disease progression in the investigators' opinion.

Patient characteristics and baseline demographics were not considered to have affected the outcome of this PK study (Table 1). With the exception of one patient (Cohort 1), all 34 patients in Part B took concomitant medications, the most common being traditional Chinese medicines (27 patients [79%]).

Pharmacokinetic results

Sixteen and 15 patients in Cohorts 1 and 2, respectively, were included in the PK analysis set. Five patients (four from Cohorts 1 and one from Cohort 2) with a prior history of gastrectomy were excluded from the PK analysis set.

Table 1 Summary of patient characteristics and baseline demographics

	Cohort 1 ($n=20$)	Cohort 2 ($n=16$)
Age group (years), *n* (%)		
<50	11 (55)	9 (56)
≥50–<65	9 (45)	6 (38)
≥65	0	1 (6)
Ethnic population, *n* (%)		
Chinese	20 (100)	16 (100)
Gender, *n* (%)		
Female	13 (65)	15 (94)
Male	7 (35)	1 (6)
ECOG performance status		
0	14 (70)	11 (69)
1	6 (30)	4 (25)
2	0	1 (6)
Primary tumour location, *n* (%)		
Breast	11 (55)	10 (63)
Gastric	4 (20)	1 (6)
Ovarian	2 (10)	4 (25)
Other[a]	3 (15)	1 (6)

ECOG Eastern Cooperative Oncology Group

*Cohort 1, liver ($n=2$) and neuroendocrine ($n=1$); Cohort 2, fallopian tube ($n=1$)

Olaparib PK parameters after single dosing

Single-dose plasma concentration–time profiles of olaparib were characterized by rapid absorption (Table 2; Fig. 2a). Once C_{max} had been reached, olaparib plasma concentrations declined in an apparent biphasic manner. The observed olaparib $t_{½}$, λ_z was approximately 7 h. AUC increased approximately proportionally with increasing dose, while C_{max} increased slightly less than proportionally; inter-patient variability was moderate to high for C_{max} and AUC at both doses. Olaparib clearance (CL/F) and distribution (V_z/F) were similar across both doses (Table 2).

Olaparib PK parameters after multiple dosing—steady-state olaparib monotherapy

Steady-state olaparib monotherapy plasma concentration–time profiles were characterized by a rapid absorption phase (Table 2; Fig. 2b) and $t_{max,ss}$ values were comparable with those observed following a single olaparib dose. Olaparib multiple-dose exposure ($C_{max,ss}$, $C_{min,ss}$ and AUC_{ss}) increased slightly less than proportionally with increasing dose and inter-patient variability for these parameters was moderate to high (Table 2). Three and two patients in Cohorts 1 and 2, respectively, were considered to have unusually high olaparib exposure, none of whom were administered potent inhibitors of CYP3A and all appeared to have normal liver and renal function, based on baseline creatinine levels and liver biochemistry (creatinine: range 55–84 µmol/L; total serum protein: range 63.8–81.5 g/L; total serum bilirubin: range 7–11.5 µmol/L). Olaparib steady-state clearance (CL_{ss}/F) was similar at both doses but lower than that following single olaparib dosing. Following multiple monotherapy dosing, geometric mean R_{AC} and TCP were similar for both doses and indicated some olaparib accumulation, as well as slight time-dependent PK (Table 2).

Olaparib PK parameters after multiple dosing—steady-state olaparib in combination with paclitaxel

Plasma concentration–time profiles for olaparib (100 mg bid) when co-administered with paclitaxel were characterized by a rapid absorption phase, similar to olaparib monotherapy (Table 2; Fig. 2c). Olaparib exposure was lower when given in combination with paclitaxel with significant differences in GLS means for AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$ treatment ratios (Fig. 3). Following treatment with paclitaxel, reductions in AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$ were observed for 14/15, 9/15 and 15/15 patients, respectively, compared with olaparib monotherapy. Olaparib CL_{ss}/F was increased when co-administered with paclitaxel compared with olaparib monotherapy (Table 2). Eleven patients received pre-treatment with cimetidine on a paclitaxel dosing day and

Table 2 Summary of pharmacokinetic parameters of single- and multiple-dose olaparib as monotherapy and in combination with paclitaxel in the PK analysis set

Single-dose parameters (summary statistics)	Cohort 1 olaparib 300 mg ($n=16$)	Cohort 2 olaparib 100 mg ($n=15$)
C_{max}, µg/mL (geometric mean [%GCV])	6.88 (39.7)	2.97 (41.8)
t_{max}, hours (median [range])	1.50 (0.50–4.00)	1.95 (0.98–4.00)
AUC, µg h/mL (geometric mean [%GCV])	36.5 (59.9)	12.8 (76.7)
AUC_{0-12}, µg h/mL (geometric mean [%GCV])	31.7 (53.0)	10.9 (61.6)
V_z/F, L (arithmetic mean [SD])	74.8 (75.4)	88.3 (44.0)
CL/F, L/h (arithmetic mean [SD])	8.11 (6.69)	9.22 (4.53)
$t_{½}$,λz hours (arithmetic mean [SD])	6.52 (1.35)	7.17 (2.54)

Steady-state parameters (summary statistics)	Cohort 1 olaparib 300 mg bid ($n=15$)[a]	Cohort 2 olaparib 100 mg bid ($n=15$)	Cohort 2 olaparib 100 mg bid in combination with paclitaxel ($n=15$)
$C_{max,ss}$, µg/mL (geometric mean [%GCV])	8.27 (35.0)	3.75 (41.0)	3.03 (56.1)
$C_{min,ss}$, µg/mL (geometric mean [%GCV])	0.800 (118)	0.316 (129)	0.192 (125)
$t_{max,ss}$, hours (median [range])	1.50 (0.97–3.00)	2.00 (0.97–4.02)	1.48 (0.28–5.95)
AUC_{ss}, µg h/mL (geometric mean [%GCV])	44.0 (48.4)	16.7 (61.4)	12.4 (57.5)
CL_{ss}/F, L/h (arithmetic mean [SD])	7.51 (3.42)	6.75 (2.92)	8.97 (3.73)
R_{AC} (arithmetic mean [SD])	1.44 (0.21)	1.57 (0.30)	NA
TCP (arithmetic mean [SD])	1.25 (0.22)	1.35 (0.33)	NA

AUC area under the plasma concentration–time curve from zero to infinity, AUC_{0-12} area under the plasma concentration–time curve from 0 to 12 h post-dose, AUC_{ss} area under the plasma concentration–time curve during the dosing interval at steady state, *CL/F* apparent oral clearance, CL_{ss}/F apparent oral clearance at steady state, C_{max} maximum observed plasma concentration, $C_{max,ss}$ maximum observed plasma concentration at steady state, $C_{min,ss}$ minimum observed plasma concentration at steady state, *%GCV* geometric mean coefficient of variation %, *NA* not applicable, R_{AC} accumulation ratio, *SD* standard deviation, $t_{½}$,λz terminal half-life, *TCP* temporal change parameter, t_{max} time to reach maximum observed plasma concentration, $t_{max,ss}$ time to reach maximum observed plasma concentration at steady state, V_Z/F apparent volume of distribution during the terminal phase

[a]Excluding one patient in Cohort 1 who had no multiple-dose PK samples taken

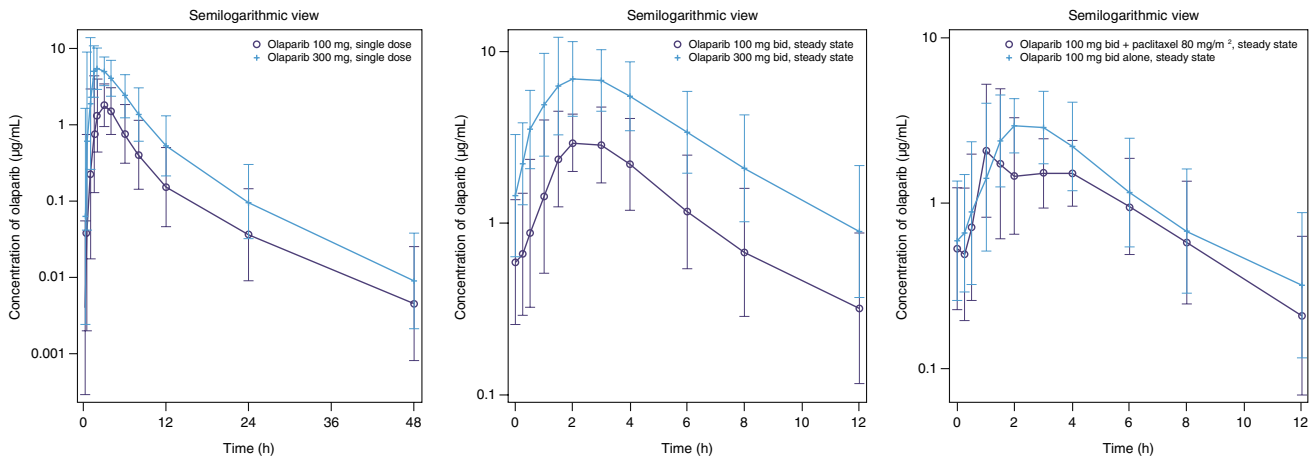

Fig. 2 Geometric mean plasma concentration–time profiles of **a** olaparib monotherapy (300 mg and 100 mg) after a single dose, **b** olaparib monotherapy (300 mg bid and 100 mg bid) after multiple dosing, and **c** olaparib monotherapy (100 mg bid) and olaparib (100 mg bid) in combination with paclitaxel at steady state after multiple dosing*. *Error bars show geometric standard deviation. Bid, twice daily

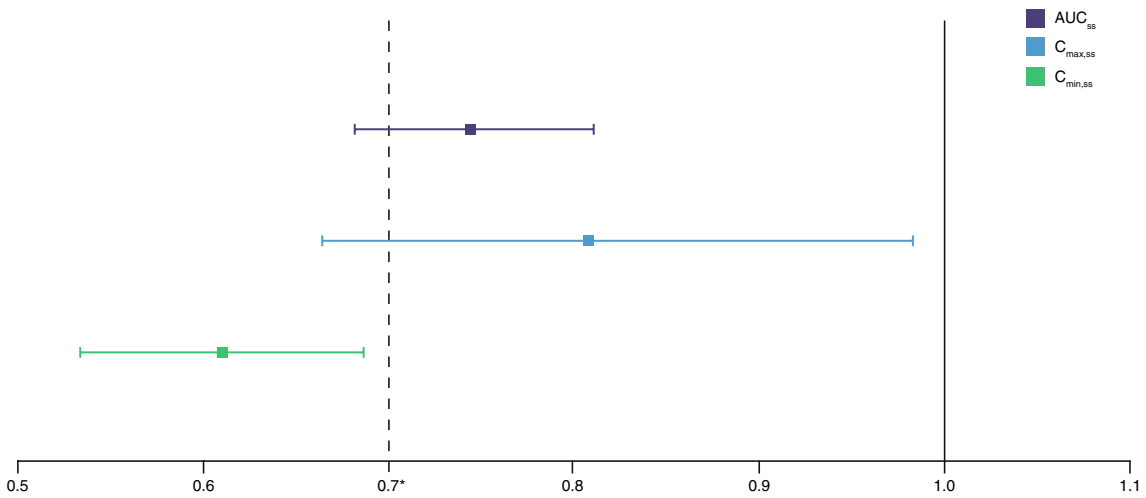

Fig. 3 Summary of GLS mean ratios and 90% CI for AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$ of olaparib monotherapy (100 mg bid), compared with olaparib (100 mg bid) in combination with paclitaxel. *An interaction between paclitaxel and olaparib was considered to have occurred if the lower limit of the 90% CI for the ratio was <0.7. *AUC_{ss}* area under the plasma concentration–time curve during the dosing interval at steady state; *CI* confidence interval, *$C_{max,ss}$* maximum observed plasma concentration at steady state, *$C_{min,ss}$* minimum observed plasma concentration at steady state, *GLS* geometric least square

these patients are included in PK analyses. Multiple-dose PK parameter ratios were calculated for combination therapy (day 9) to olaparib monotherapy (day 8). For the patients who received cimetidine, the ratios fell within the range 0.58 to 1.22 for AUC_{ss}, 0.38 to 1.46 for $C_{max,ss}$ and 0.31 to 0.98 for $C_{min,ss}$, compared with 0.58 to 0.74 for AUC_{ss}, 0.47 to 1.07 for $C_{max,ss}$ and 0.46 to 0.68 for $C_{min,ss}$ for the patients who did not receive cimetidine.

Safety results

Safety data from patients receiving olaparib monotherapy

During Part A of the study, patients in Cohort 1 received olaparib monotherapy (300 mg bid) for a median of 9.0 days (range 6–9); in Cohort 2, all patients received the planned dose of olaparib monotherapy (100 mg bid) for 9 days. During Part B, Cohort 1 patients received olaparib (300 mg bid) for a median of 59.0 days (range 17–280) with a mean compliance of 97%. Two patients in Cohort 2 went on to receive olaparib 300 mg bid monotherapy after discontinuing paclitaxel and had a total duration of exposure to olaparib of 27 and 53 days, respectively.

In Part A, the most common AEs reported following olaparib monotherapy (Cohort 1, 300 mg bid) were nausea ($n=4$), leukopenia, anaemia and thrombocytopenia ($n=3$ each) (Supplementary Table 1). In Part B, the most common AEs following olaparib in Cohort 1 were leukopenia ($n=8$; 0 grade ≥ 3), neutropenia ($n=8$; 1 grade ≥ 3) and anaemia ($n=7$; 3 grade ≥ 3) and in patients receiving olaparib monotherapy (300 mg bid) in Cohort 2 the only AEs reported were leukopenia, neutropenia and anaemia (all $n=1$; 0 grade ≥ 3) (Supplementary Table 1).

One patient (5%) who was receiving olaparib 300 mg bid had a dose interruption during Part A; this was the patient's decision. Four patients (21%) had at least one olaparib dose interruption during Part B of the study, of whom one patient (5%) interrupted olaparib due to an AE. No patients receiving olaparib monotherapy had a dose reduction.

One patient discontinued olaparib due to an AE of anaemia during Part B. AEs that led to olaparib dose modifications in > 1 patient were anaemia ($n=2$; 300 mg bid) and thrombocytopenia ($n=2$; 100 and 300 mg bid). Grade ≥ 3 AEs experienced by more than one patient during the study are reported in Supplementary Table 2; the most common of these following monotherapy was anaemia ($n=0$, Part A; $n=3$, Part B). No patients receiving olaparib monotherapy showed clinically relevant treatment-related changes in vital signs, ECG, physical findings or clinical chemistry laboratory parameters.

Safety data from patients receiving olaparib in combination with paclitaxel

Median exposure to olaparib for Cohort 2 patients during the multiple-dosing combination period (Part A) was 28.0 days (range 6–36) and all patients received all three planned paclitaxel doses. During Part B, patients in Cohort 2 received olaparib for a median of 94.0 days (range 14–345). In Cohort 2, 14 out of 15 patients (93%) received paclitaxel for a median of 4.0 cycles over 133.0 days (range 28–298).

In Parts A and B (Cohorts 2), the most common AEs were neutropenia ($n=14$, Part A; $n=14$ Part B) and leukopenia ($n=12$, Part A; $n=15$ Part B) (Supplementary Table 1). During Part A, eight patients receiving combination therapy (50%) had an olaparib dose interruption and six patients (38%) had a delay in paclitaxel dosing, all because of AEs; there were no dose reductions. During Part B, eight patients on combination therapy (53%) had at least one olaparib dose interruption, seven of which (47%) had dose interruption caused by an AE; three patients (20%) had a protocol-specified olaparib dose change. Ten patients (67%) had a delay in paclitaxel dosing, all due to AEs, and one patient (7%) had a protocol-specified paclitaxel dose change.

A greater proportion of patients on combination therapy experienced at least one AE of CTCAE Grade ≥ 3 compared with patients on olaparib monotherapy (Table 3). Adverse events that lead to olaparib dose modifications in more than one patient during Part A were neutropenia ($n=8$ [50%]) and leucopenia (n = 6 [38%]); these AEs lead to paclitaxel dose modifications in six (38%) and five (31%) patients, respectively. Similarly, in Part B, AEs that led to olaparib dose modifications in > 1 patient receiving combination therapy were neutropenia ($n=5$ [33%]) and leucopenia ($n=4$ [27%]) and these AEs lead to paclitaxel dose modifications in 7 (47%) and 6 (40%) patients, respectively. During Part A, one patient on combination therapy discontinued both treatments because of increased ALT and AST. No patients on combination therapy discontinued paclitaxel or olaparib due to an AE during Part B. Grade ≥ 3 AEs experienced by more than one patient during the study are reported in Supplementary Table 2; the most common of these occurring during combination treatment was leucopenia ($n=7$, Part A; $n=5$, Part B). There were no clinically relevant treatment-related changes in vital signs, ECG, physical findings or clinical chemistry laboratory parameters for patients on combination therapy. Serious AEs (SAEs) were reported in four patients receiving combination therapy during Part A (neutropenia, $n=3$; liver injury, $n=1$). In two patients, the neutropenia

Table 3 Summary of AEs

AE category, *n* (%)[c]	Part A[a]			Part B[b]		
	Cohort 1	Cohort 2[b]		Cohort 1	Cohort 2	
	Olaparib 300 mg bid ($n=20$)	Olaparib 100 mg bid ($n=16$)	Olaparib 100 mg bid + paclitaxel ($n=16$)	Olaparib 300 mg bid ($n=19$)	Olaparib 100 mg bid + paclitaxel[§] ($n=15$)	Olaparib 300 mg bid[d] ($n=2$)
Patients with any AE	11 (55)	8 (50)	16 (100)	18 (95)	15 (100)	2 (100)
AE causally related to both olaparib and paclitaxel	NA	2 (13)[e]	15 (94)	NA	14 (93)	1 (50)
AE causally related to olaparib only	9 (45)	6 (38)	1 (6)	17 (89)	3 (20)	1 (50)
AE causally related to paclitaxel only	NA	0	10 (63)	NA	11 (73)	0
AE of CTCAE Grade ≥ 3	2 (10)	2 (13)	10 (63)	6 (32)	9 (60)	0
AE with an outcome of death	0	0	0	0	0	0
Any SAE	0	0	4 (25)	0	1 (7)	0
AE leading to discontinuation of olaparib	0	1 (6)	0	1 (5)	0	0
AE leading to discontinuation of paclitaxel	NA	1 (6)[e]	0	NA	0	0
AE leading to dose modification of olaparib	1 (5)	1 (6)	8 (50)	3 (16)	6 (40)	0
AE leading to dose modification of paclitaxel	NA	0	6 (38)	NA	9 (60)	0

AE adverse event, *bid* twice daily, *NA* not applicable

[a]For the two patients who did not enter Part B, AEs experienced up to 30 days after the last treatment dose are reported

[b]AEs that began during the monotherapy phase are not counted in the combination therapy phase, and AEs that began during Part A are not counted in Part B

[c]Patients with multiple events in one category are counted only once in that category

[d]Two patients in Cohort 2 switched from olaparib 100 mg bid in combination with paclitaxel to olaparib 300 mg bid monotherapy during Part B. AE data for these patients are reported in both Part B Cohort 2 columns

[e]AEs began before administration of paclitaxel, but continued during paclitaxel dosing

SAE was ongoing in Part B of the study and one of these patients went on to experience a second neutropenia SAE. One additional patient on combination therapy developed a SAE during Part B (fatigue, which began during Part A, and became serious during Part B). This patient went on to receive olaparib monotherapy (300 mg bid) after discontinuing paclitaxel.

Discussion

This Phase I, non-randomized, open-label study was conducted to investigate the PK and safety profile of olaparib following single or multiple doses of the tablet formulation in Chinese patients with advanced solid tumours and to determine whether co-administration of olaparib with paclitaxel affected the PK of olaparib in these patients.

In line with the China Food and Drug Administration guidance, more than 12 patients were evaluable for PK analysis in each cohort [19]. No clinically significant differences were noted between the two cohorts at study entry, and patient characteristics and baseline demographics were representative of the intended patient population for this trial.

The results from this study have demonstrated that the PK of olaparib in Chinese patients are consistent with those previously reported for Western and Japanese populations with rapid absorption of olaparib observed after single dosing (median t_{max}: Chinese patients, olaparib 100 mg and 300 mg, 1.95 and 1.50 h, respectively; Western patients, olaparib 100 mg and 300 mg, 1.03 and 1.49 h, respectively; Japanese patients, olaparib 300 mg, 1.98 h) and multiple dosing (median $t_{max,ss}$: Chinese patients, olaparib 100 mg bid and 300 mg bid, 2.00 and 1.50 h, respectively; Western patients, olaparib 300 mg bid, 1.50 h; and Japanese patients, olaparib 300 mg, 3.00 h) [11, 12]. These observations are in line with the population PK analyses for pooled studies using both capsule and tablet formulations which did not identify race, gender, age or body weight as significant covariates [21].

Although high inter-patient variability in exposure was observed across all dose levels, an approximately dose-proportional increase in olaparib exposure (AUC) was seen following a three-fold increase in olaparib single dose from 100 mg to 300 mg (12.8 and 36.5 µg.h/mL, respectively). Slightly less than proportional increases in exposure were observed for single dose C_{max} (olaparib 100 mg and 300 mg, 2.97 and 6.88 µg/mL, respectively) and steady-state exposure (AUC_{ss} [olaparib 100 mg and 300 mg, 16.7 and 44.0 µg.h/mL, respectively], $C_{max,ss}$ [3.75 and 8.27 µg/mL] and $C_{min,ss}$ [0.32 and 0.80 µg/mL]). Less than dose-proportional increases in C_{max} and $C_{max,ss}$ were observed, possibly as a result of faster dissolution of the 100-mg tablet compared with the 150-mg tablet used for the 300-mg dose. This finding is consistent with Western patients (C_{max} olaparib 50 and 250 mg, 2.22 and 8.81 µg/mL, respectively [$C_{max,ss}$ was only evaluated at one olaparib tablet dose in this study]) [10]. When compared with single-dose olaparib, at steady state a small increase in exposure and accumulation of olaparib was observed following both 100 mg and 300 mg bid dosing. Studies in Western patients have previously shown that the optimal olaparib tablet monotherapy dose is 300 mg bid and the consistency between the PK results reported here and those observed in Western patients (olaparib 300 mg bid: AUC_{ss}, 58.32 µg.h/mL and 55.45 µg.h/mL, $C_{max,ss}$, 9.17 µg/mL and 8.44 µg/mL and $C_{min,ss}$, 1.76 µg/mL and 1.61 µg/mL) suggest that no dose change is required for Chinese patients [12, 22]. A slight time-dependent PK profile was indicated by the mean TCP values of greater than one for both the olaparib 100 mg and 300 mg doses. This finding was in line with that previously observed following In vitro analyses, as well as physiologically-based PK modelling and clinical data from Western patients (unpublished data from NCT02093351 and NCT01921140), which demonstrated that weak inhibition of CYP3A by olaparib is time-dependent [23]. Individual patients with an unusually high exposure to olaparib appeared to have normal renal and hepatic function (based on normal creatinine levels and normal liver biochemistry) and were not receiving any concomitant potent inducers or inhibitors of CYP3A; therefore, the increased exposure observed in these patients could be attributed to the high PK variability of olaparib.

We found a statistically significant decrease in steady-state exposure of olaparib at the 100-mg bid dose when administered in combination with paclitaxel compared with monotherapy (GLS mean treatment ratios of 0.744, 0.808 and 0.606 for AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$, respectively). In addition to the fact that patients on combination treatment received a lower dose of olaparib (100 mg bid), this suggests that patients receiving olaparib concomitantly with paclitaxel experience considerably lower olaparib exposure than those receiving the recommended monotherapy dose (300 mg bid).

Olaparib is known to be metabolized by CYP3A, although physiologically-based PK modelling has indicated that weak CYP3A inhibitors would have a minimal effect on the PK of olaparib [23, 24]. It is worth noting, however, that ethnic differences because of genetic variability in drug-metabolizing enzymes such as CYP can occur [25]. In the current study, the PK of olaparib was characterized immediately following co-administration of a single dose of paclitaxel; therefore, it is unlikely that CYP3A enzyme induction was the cause of the observed decrease in olaparib exposure. Although paclitaxel has been reported to be an inducer of CYP3A In vitro, co-administration of paclitaxel was shown to have no effect on the PK of the CYP3A substrate everolimus In vivo [26, 27]. In vitro study results have suggested

that an excipient included in paclitaxel formulation, macrogolglycerol ricinoleate, may reduce olaparib plasma protein binding, which may result in increased clearance In vivo (data on file). Ricinoleate has been reported to interact with the efflux transporter P-glycoprotein (P-gp) [28]. In vitro olaparib is a substrate for P-gp, but given olaparib's high solubility in human intestinal fluid (0.16 mg/mL) [18], P-gp transport activity is expected to be saturated at the therapeutic olaparib dose of 300 mg bid. Therefore, there is low potential for P-gp transporter interaction to significantly influence the overall drug absorption and the systemic exposure to olaparib. In vitro data also show that olaparib is not a substrate for organic anion transport polypeptide (OATP)-1B1, OATP1B3, organic cation transporter-1 (OCT1), breast cancer resistance protein (BCRP) or multi-drug resistance protein 2 (MRP2) [29].

Co-administration of potent CYP3A inhibitors and inducers was prohibited during the study; however, the moderate CYP3A4 inhibitor cimetidine was allowed as an injection for patients in Cohort 2 on the days they received paclitaxel. Eleven of 15 patients received cimetidine on a paclitaxel dosing day. These patients were not excluded from the PK analysis and the change in olaparib exposure from monotherapy to combination therapy was comparable to those who had not received cimetidine. It is also noteworthy that with the exception of one patient (Cohort 1), all 34 patients in Part B took concomitant medications, the most common being traditional Chinese medicines (79% of patients). It has been reported that traditional Chinese medicines can result in the induction of CYP3A4, leading to a reduced efficacy of drugs that are CYP3A4 substrates [30], therefore, it is possible that Chinese medicines may have the potential to affect the PK of olaparib.

No new safety findings were observed for olaparib during the study and safety data were consistent with the known tolerability profiles of olaparib and paclitaxel. The majority of Grade ≥ 3 AEs were haematological and these were more frequent in patients who received combination therapy. No clinically relevant differences in vital signs, ECG or physical findings were observed.

The administration of olaparib tablets to Chinese patients at doses of 300 mg bid showed a similar safety and tolerability profile to that observed in olaparib studies in wider patient populations; therefore, it is recommended that olaparib tablets can be taken without dose adjustment in this population [5, 31, 32]. Haematological laboratory variables did not change significantly in the majority of patients receiving olaparib monotherapy, and abnormalities that were recorded were generally mild to moderate in severity. However, increased haematological toxicities were observed in laboratory parameters for patients who received olaparib in combination with paclitaxel. This is consistent with expectations based on the known tolerability profile of paclitaxel monotherapy and no cumulative toxicities were observed; therefore, an olaparib dose of 100 mg bid in combination with paclitaxel 80 mg/m^2 is considered well tolerated [33].

Conclusions

In conclusion, the PK of olaparib tablets following administration as monotherapy to Chinese patients with advanced solid tumours are consistent with those observed in Western and Japanese patient populations [10, 11]. Similarly, the tolerability profile of olaparib tablet monotherapy (300 mg bid) is consistent with that previously identified and no new safety signals have been identified for Chinese patients [5]. Administration of olaparib tablets (100 mg bid) in combination with paclitaxel results in a significant decrease in olaparib exposure and the tolerability profile of the combination is consistent with the known safety profiles of olaparib and paclitaxel [5, 33]; further studies should evaluate olaparib tablet at 300 mg in combination with paclitaxel. Based on the PK and safety data reported here, the 300 mg bid tablet monotherapy dose of olaparib is recommended for further evaluation in Chinese patients, consistent with the dose used in completed and ongoing Phase III olaparib trials that have recruited, or will recruit, Chinese patients (SOLO1 [NCT01844986], SOLO2 [NCT01874353], OlympiAD [NCT02000622], OlympiA [NCT02032823] and PROfound [NCT02987543]) [15, 16, 31, 32, 34].

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Compliance with ethical standards

Conflict of interest WB is employed by Covance Clinical Research Unit. KH was employed by AstraZeneca during manuscript development. ML is currently employed by AstraZeneca and owns stock. MZ is currently employed by AstraZeneca. All other authors report no conflicts of interest.

Ethical approval 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.

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

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