Effect of itraconazole and rifampin on the pharmacokinetics of olaparib in patients with advanced solid tumors: results of two Phase I open-label studies

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Abstract

Purpose: The metabolism of olaparib, a potent inhibitor of poly(ADP-ribose) polymerase (PARP) with demonstrated efficacy in patients with *BRCA*-mutated ovarian cancer, is mediated by cytochrome P450 (CYP) enzymes (predominantly CYP3A4/5). We assessed the potential of a CYP3A4 inhibitor (itraconazole) and inducer (rifampin) to alter the pharmacokinetic (PK) profile of olaparib following single oral tablet doses.

Methods: Two Phase I, open-label, non-randomized trials were conducted in patients with advanced solid tumors. In Study 7 (NCT01900028) patients received olaparib alone and co-administered with itraconazole, and in Study 8 (NCT01929603) olaparib alone and co-administered with rifampin. No interaction between itraconazole and olaparib was to be concluded if 2-sided 90% confidence intervals (CIs) for the treatment ratios of area under the curve (AUC; and/or AUC_{0-t}) and maximum plasma concentration (C_{max}) fell within the bioequivalence range of 0.80–1.25. An interaction between rifampin and olaparib was to be concluded if the lower limit of the 90% CI for the treatment ratios was <0.5 (ie, >50% decrease in olaparib AUC or C_{max} in the presence of rifampin compared with olaparib alone).

Findings: In Study 7 (N=59 patients), 56 and 53 patients were evaluable for PK analysis following treatment with olaparib alone and olaparib plus itraconazole, respectively. In Study 8 (N=22), all patients were evaluable for PK. Co-administration of olaparib with itraconazole resulted in a statistically significant increase in the relative bioavailability of olaparib: C_{max} treatment ratio 1.42 (90% CI: 1.33, 1.52) and mean AUC treatment ratio 2.70 (90% CI: 2.44, 2.97). The mean apparent plasma clearance (CL/F) and apparent volume of distribution (Vz/F) were reduced (8.16 vs 3.05 L/hour, and 192 vs 75.1 L, respectively) although mean $t_{½}$ was unchanged (15.0 vs 15.6 hours). Co-administration of olaparib with rifampin resulted in a statistically significant decrease in the relative bioavailability of olaparib: C_{max} treatment ratio 0.29 (90% CI: 0.24, 0.33) and mean AUC treatment ratio 0.13 (90% CI: 0.11, 0.16). CL/F and Vz/F were increased when olaparib and rifampin were co-administered (6.36 vs 48.3 L/hour and 112 vs 1076 L, respectively); however, mean $t_{½}$ was unchanged (13.0 vs 15.8 hours). Safety data for olaparib following tablet dosing were consistent with the known safety profile.

Implications: Exposure to olaparib was significantly increased when co-administered with the CYP3A4 inhibitor, itraconazole, and significantly decreased when co-administered with the CYP3A4 inducer, rifampin, compared with olaparib alone. CYP3A4 enzyme inhibitors and inducers should be avoided during olaparib treatment.

Study registry identification number: NCT01900028 (referred to as Study 7) and NCT01929603 (referred to as Study 8).

Word count: 397 (limit 400)

Key words (4–6): olaparib, pharmacokinetic, CYP3A4, itraconazole, rifampin

Abbreviations: AE, adverse event; ANOVA, Analysis of Variance; AUC, area under the plasma concentration time curve; AUC_{0-t}, AUC from zero to time of last quantifiable sample; AUC_{tau}, AUC for a dosing interval; BMI, body mass index; *BRCA1/2*m, *BRCA1/2* mutations; CI, confidence interval; CL/F, mean apparent plasma clearance; C_{max}, maximum plasma concentration; CTCAE, common terminology criteria for adverse events; CYP, cytochrome P450; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; g*BRCA*m, germline *BRCA*m; GCV, geometric coefficient of variation; GLS, geometric least squares; HRR, homologous recombination repair; NCI-CTC, National Cancer Institute Common Terminology Criteria; ND, not determined; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PK, pharmacokinetic; SAE, serious adverse event; SD, standard deviation; t_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal half-life; V_z/F, apparent volume of distribution

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.[1] PARP inhibitors also impair, via other mechanisms, high fidelity repair of double-strand DNA breaks in tumor cells with deficiencies in homologous recombination repair (HRR), such as *BRCA1/2* mutations (*BRCA1/2*m).[2,3] Impaired DNA repair in tumor cells with HRR deficiencies leads to irreparable double-strand breaks being formed that result in tumor cell death by synthetic lethality.[4] PARP inhibitors can also induce lethality in tumor cells that have deficiencies in DNA damage repair mechanisms other than HRR deficiencies.

In 2014 olaparib (capsule formulation) became the first PARP inhibitor approved for treatment when the United States Food and Drug Administration (FDA) granted accelerated approval of olaparib for the monotherapy treatment of patients with relapsed germline *BRCA*m (g*BRCA*m) ovarian cancer who have received three or more lines of chemotherapy.[5] The European Medicines Agency (EMA) also granted approval of olaparib as monotherapy maintenance treatment of adult patients with platinum-sensitive, relapsed *BRCA*m (germline and/or somatic) ovarian cancer who are in response to platinum-based chemotherapy based on Study 19 data.[6] In patients with platinum-sensitive, recurrent serous ovarian cancer, maintenance monotherapy with a capsule formulation of olaparib 400 mg bid significantly prolonged progression-free survival (PFS) versus placebo.[7] Further analysis of this patient population has shown that patients with a *BRCA*m receive greater treatment benefit.[8] In a study of patients with a germline *BRCA1/2*m and solid tumors refractory to standard therapy, treatment with a capsule formulation of olaparib 400 mg bid prolonged tumor responses across a spectrum of malignancies, including ovarian, breast, pancreatic, and prostate cancers.[9] To receive the recommended 400 mg bid dose of olaparib, patients are required to take 16 x 50 mg large capsules per day and consequently patient compliance may be compromised. A tablet formulation has therefore been developed to deliver a therapeutic dose in fewer and smaller units. A recommended tablet dose of 300 mg bid has been determined in a Phase I trial (Study 24, NCT00777582) for administration in Phase III studies. [Study 24 primary manuscript to be cited when appropriate][10]

In vitro data have shown the metabolism of olaparib is mediated by cytochrome P450 (CYP) enzymes (predominantly CYP3A4/5), therefore, co-administration with potent inhibitors or inducers of CYP3A4 would be expected to alter the pharmacokinetics (PK)

of olaparib [McCormick & Swaisland, *in preparation*]. Since patients receiving olaparib are likely to be taking multiple medications, significant PK drug–drug interactions could lead to alterations in plasma concentrations of olaparib, potentially resulting in a reduction in efficacy or an increase in drug-related toxicity.

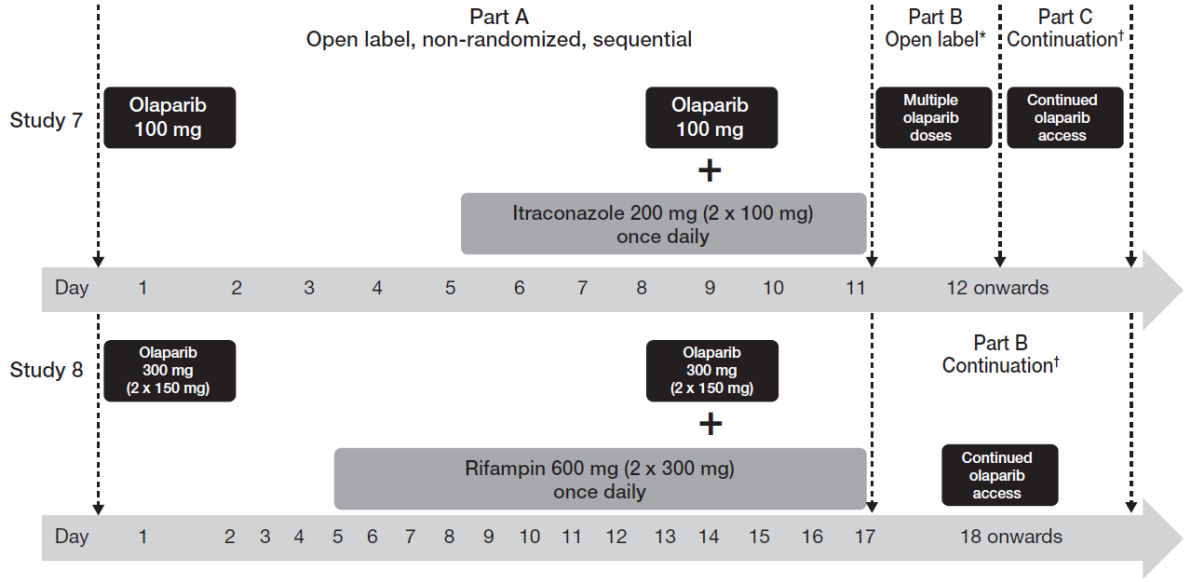
The results of two clinical studies, which investigated the potential for PK interactions between either olaparib (tablet formulation) and itraconazole, an antifungal agent and potent CYP3A4 inhibitor (Study 7), or olaparib and rifampin, a bactericidal antibiotic and potent CYP3A4 inducer (Study 8) are reported.

Patients and methods

Study design

Both studies were Phase I, open-label, non-randomized, multicenter trials in patients with advanced solid tumors (Study 7: NCT01900028 [D0816C00007] and Study 8: NCT01929603 [D0816C00008]). Study 7 consisted of three parts (A–C) and Study 8 two parts (A and B) (Figure 1).

Figure 1. Study designs



In both studies, Part A assessed the effect of either the CYP3A4 inhibitor (Study 7) or CYP3A4 inducer (Study 8) on the PK profile of olaparib following single dosing of the tablet formulation, and only data from this part of each study are reported in this manuscript. Data from Study 7 Part B (assessment of the effect of olaparib on the QT interval following multiple oral dosing of olaparib tablets) and Part C (long-term safety), and from Study 8 Part B (long-term safety), will be reported separately.

In Study 7, Part A consisted of a non-randomized, open-label, sequential, two-treatment design. Patients received a single oral dose of olaparib 100 mg (1 x 100 mg tablet) on day 1 after a 10-hour fast, and a single oral dose of olaparib 100 mg (1 x 100 mg tablet) administered concurrently with itraconazole 200 mg (2 x 100 mg tablets) on day 9 after

an overnight fast. Itraconazole 200 mg was administered once daily on days 5–11 with a full meal (except for the dose on day 9).

In Study 8, Part A also consisted of a non-randomized, open-label, sequential, two-treatment design. Patients received a single oral dose of olaparib 300 mg (2 x 150 mg tablets) on day 1, and a single oral dose of olaparib 300 mg (2 x 150 mg tablets) administered concurrently with rifampin 600 mg (2 x 300 mg tablets) on day 14. The treatments on days 1 and 14 were administered following an overnight fast, and patients remained fasting for 2 hours post-dose. Rifampin 600 mg (2 x 300 mg tablets) was administered once daily following an overnight fast on days 5–17.

Study population

In both studies, 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 a life expectancy of ≥16 weeks, an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and adequate organ and bone marrow function measured within 28 days prior to administration of olaparib. Patients were excluded if they had recently received or were receiving medications known to be inhibitors or inducers of CYP3A4. Additionally, any intake of grapefruit or Seville oranges, or products containing these components was not permitted within 7 days prior to olaparib dosing. Patients were required to be on a stable concomitant medication regimen (with the exception of electrolyte supplements), defined as no changes in medication or in dose within 2 weeks prior to olaparib dosing, except for bisphosphonates, denosumab and corticosteroids, which needed to be stable for at least 4 weeks prior to the start of olaparib dosing.

The institutional review boards or independent ethics committees of all investigational sites approved both protocols, and the studies were performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on Bioethics.[11] All patients provided written informed consent.

Study objectives

Primary and secondary objectives included investigation of the effect of itraconazole (Study 7) or rifampin (Study 8) on the PK profile of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumors; to demonstrate exposure to itraconazole and its metabolite hydroxyitraconazole (Study 7); to demonstrate exposure to rifampin and induction of CYP by rifampin (assessed by determining plasma concentrations of 4β-hydroxycholesterol, a biomarker for CYP3A4 activity)[12,13] (Study 8); and to further investigate the safety and tolerability of olaparib tablets in patients with advanced solid tumors (both studies).

Pharmacokinetic assessment

Blood samples for determination of olaparib concentrations were taken on days 1 and 9 for Study 7, and on days 1 and 14 for Study 8 as follows: pre-dose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post-dose.

Blood samples for determination of itraconazole and hydroxyitraconazole concentrations were taken on day 9, pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose. Blood samples for determination of rifampin concentrations were taken on days 5, 9, 14 and 17 at 2 hours post-dose and blood samples for determination of 4β-hydroxycholesterol were taken on days 5, 9, 14 and 17 prior to administration of rifampin.

The determination of drug concentrations (olaparib, itraconazole/metabolite, rifampicin) and the PK analyses of these concentrations were conducted by Covance Laboratories in Harrogate, UK and Alnwick, UK, respectively.[14] Analyses of 4β-hydroxycholesterol were conducted by PRA International, Assen, The Netherlands.[15] PK parameters were determined using standard, non-compartmental analysis: maximum plasma concentration (C_{max}), area under the plasma concentration time curve (AUC) from zero (pre-dose) to infinity, AUC from zero to time of last quantifiable sample (AUC_{0-t}), time to maximum plasma concentration (t_{max}), terminal half-life ($t_{½}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F). PK parameters determined for itraconazole included C_{max}, AUC over the dosing interval AUC_{tau}, $t_{max,}$ and CL/F, and for hydroxyitraconazole included C_{max}, AUC_{tau}, and t_{max}. PK computations were performed using Phoenix™ for WinNonlin. Plasma concentrations of rifampin and 4β-hydroxycholesterol were summarized.

Patients were monitored for adverse events (AEs) throughout both studies. AEs were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4. All serious AEs (SAEs) and AEs related to treatment were followed up to resolution. For both studies, AEs were summarized separately for the olaparib alone and olaparib plus itraconazole/rifampin dosing periods. For the olaparib plus itraconazole/rifampin dosing period, only new AEs occurring from the first dose of olaparib plus itraconazole/rifampin were included; ongoing AEs from the olaparib-alone dosing period were not included. Clinical laboratory, vital signs and physical examination parameters were also evaluated.

Statistical analyses

The PK analysis set included all patients who received an olaparib dose and provided evaluable PK profiles in at least one treatment period, ie, olaparib or olaparib plus itraconazole/rifampin. The safety analysis set (patients evaluable for safety) included all patients who received at least one dose of olaparib and for whom any post-dose data were available. Safety data are presented descriptively.

In both studies, the primary PK outcome variables of olaparib AUC, or AUC_{0-t} if AUC was not adequately estimable, and C_{max} were statistically analyzed to investigate the effect of itraconazole or rifampin on the PK of olaparib. Following log-transformation, C_{max}, AUC, and AUC_{0-t} were analyzed separately by mixed-effect analysis of variance (ANOVA), fitting terms for treatment as a fixed effect and patient as a random effect. Point estimates and adjusted 90% confidence intervals (CIs) for the difference between treatments (olaparib co-administered with itraconazole or rifampin compared with olaparib alone) for C_{max}, AUC, and AUC_{0-t} were constructed. The point estimate and adjusted 90% CIs were then exponentially back transformed to provide point and CI estimates for the ratio of interest.

An analysis of t_{max} using the Wilcoxon signed rank test, and the Lehman median estimator of difference, (olaparib co-administered with itraconazole or rifampin compared with olaparib alone) and 90% CIs were also presented. All summaries and statistical analyses were performed using SAS® version 8.1 or higher.

Determination of sample size

In Study 7, recruitment of approximately 48 patients was planned to ensure 42 evaluable patients completed the study. This sample size of 42 patients was required to give 90%

power to rule out a 20% change in log-transformed AUC (and/or AUC_{0-t}) and C_{max} of olaparib, ie, if the true effect of itraconazole on olaparib exposure was minimal, the 90% CI treatment ratio would be entirely within the bioequivalence range of 0.80 to 1.25. Accordingly, no interaction of itraconazole on the PK of olaparib was to be concluded if the 2-sided 90% CIs for the treatment ratios of AUC (and/or AUC_{0-t}) and C_{max} fell entirely within the bioequivalence range of 0.80 to 1.25.

In Study 8, recruitment of approximately 18 patients was planned to ensure 16 evaluable patients completed the study; 16 evaluable patients were required to give 90% power to rule out a halving of log-transformed AUC (and/or AUC_{0-t}) and C_{max} of olaparib in the presence of rifampin, indicated by a 90% CI for the treatment ratio entirely above 0.5. Accordingly, no interaction between olaparib and rifampin was to be considered to have occurred if the lower limit of the 90% CI for the treatment ratios was greater than 0.5 (ie, less than a 50% decrease in olaparib AUC or C_{max} in the presence of rifampin, compared with olaparib alone).

Results

Patients

Table 1 shows the demographics and baseline characteristics of patients in Study 7 and 8. Between 2013 and 2014, 59 patients (17 male and 42 female) were assigned to Study 7, received at least one dose of olaparib, and completed Part A; patients were recruited from 11 centers in four countries. Between 2013 and 2014, 22 patients (4 male and 18 female) were assigned to treatment into Part A and received at least one dose of olaparib in Study 8; patients were recruited from five centers in two countries.

In both studies the majority of patients had an ECOG performance status ≤1 and the most common primary tumor type was ovarian (Table 1).

Table 1. Summary of patient demographics and baseline clinical characteristics (safety analysis set)

	Study 7 N=59	**Study 8 N=22**
Median age (range), years	61.0 (34–82)	59.0 (31–79)
Gender, n (%)		
Male	17 (28.8)	4 (18.2)
Female	42 (71.2)	18 (81.8)
Race, n (%)		
White	55 (93.2)	22 (100)
Asian	2 (3.4)	0
Black/African American	1 (1.7)	0
Other	1 (1.7)	0
Weight, mean, kg (SD)	74.6 (19.4)	74.2 (14.0)
BMI, mean, kg/m^2 (SD)	26.6 (5.7)	26.2 (4.4)
ECOG performance status, n (%)*****		
0	25 (42.4)	7 (31.8)
1	32 (54.2)	11 (50.0)
2	2 (3.4)	3 (13.6)
Tumor type, n (%)		
Ovarian (including fallopian tube)	21 (35.6)	7 (31.8)
Colorectal	10 (16.9)	3 (13.6)
Pancreatic	7 (11.9)	0
Breast	3 (5.1)	5 (22.7)

Lung	3 (5.1)	0
Cervical	3 (5.1)	0
Peritoneal	2 (3.4)	0
Head and neck	2 (3.4)	0
Biliary tract	2 (3.4)	0
Uterine	2 (3.4)	0
Bladder (including urethra)	1 (1.7)	3 (13.6)
Other†‡	2 (3.4)	4 (18.2)
Disease classification, n (%)		
Metastatic	53 (89.8)	20 (90.9)
Locally advanced	6 (10.2)	2 (9.1)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.
*Data were missing for one patient in Study 8 who had metastatic well differentiated (G1) colon cancer; †Data were missing for one patient in Study 7; ‡Other primary tumor locations were central nervous system, and bilio-pancreas in Study 7. Adrenal and prostate in one patient each, and cancer of unknown primary in two patients in Study 8; ECOG performance status and overall disease classification were based on assessments at baseline. Primary tumor types are based on assessments at diagnosis.

Pharmacokinetics

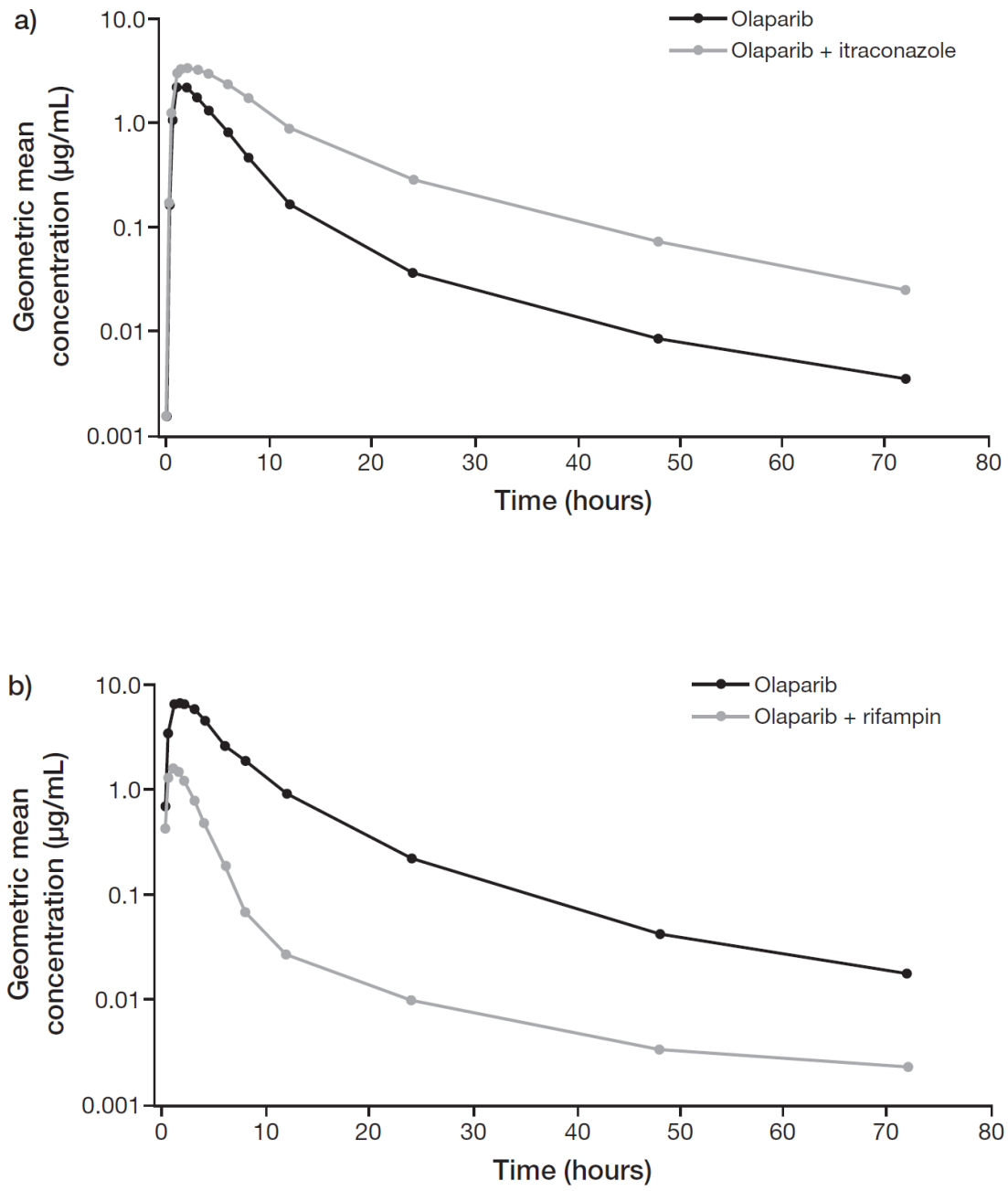
Study 7 (CYP3A4 inhibition)

Out of the 59 patients assigned to treatment, 56 and 53 patient profiles were evaluable for the olaparib-alone dosing period and the olaparib and itraconazole dosing period, respectively. Three patients were excluded from both dosing periods due to a disallowed surgical procedure (having previously had a gastric band fitted), baseline creatinine >50 mL/min, and incorrect sample handling. Three additional patients were excluded from the olaparib and itraconazole dosing period due to a full itraconazole dose not being administered, incorrect formulation of itraconazole used (liquid rather than tablet), and PK samples not provided. Although the protocol planned to enrol 48 evaluable patients, 11 additional patients were recruited and randomized to treatment to ensure sufficient patient numbers were available for a later part of the study (effect of olaparib on the QT interval – to be reported separately).

Following a single oral administration of olaparib alone (100 mg tablet) in fasted conditions, the drug appeared rapidly in plasma, with peak concentrations typically observed 1 hour after dosing. Following dosing in combination with itraconazole, median t_{max} was slightly later (1.5 hours). Beyond the peak, plasma concentrations in both treatment arms generally declined in a biphasic manner, remaining above the limit of

quantification of the assay for up to 72 hours after dosing in the majority of patients where sampling continued to that point (Figure 2).

Figure 2. Geometric mean plasma concentration of olaparib over time following a single dose of olaparib alone, or in combination with (a) itraconazole or (b) rifampin



Consistent with the increase in AUC, mean apparent plasma clearance (CL/F) and apparent volume of distribution (Vz/F) were reduced when olaparib was dosed in

combination with itraconazole, 8.16 L/hour vs 3.05 L/hour, and 192 L vs 75.1 L, respectively. However, the mean $t_{½}$ of olaparib was unchanged, 15.0 hours vs 15.6 hours, respectively for olaparib alone versus olaparib co-administered with itraconazole (Table 2).

Table 2. Pharmacokinetic parameters of single-dose olaparib alone or in combination with itraconazole or rifampin

	Study 7 (itraconazole) N=57		**Study 8 (rifampin) N=22**	
PK parameter	**Olaparib alone (100 mg)**	**Olaparib (100 mg) plus itraconazole (200 mg)**	**Olaparib alone (300 mg)**	**Olaparib (300 mg) plus rifampin (600 mg)**
n	56	53	22	18
$C_{max,}$ µg/mL (GCV, %)	2.99 (48.2)	4.24 (37.7)	8.05 (24.3)	2.24 (53.4)
n	56	53	22	18
$t_{max,}$ h (min,max)	1.03 (0.48–8.25)	1.50 (0.50–12.00)	1.49 (0.57–3.05)	0.78 (0.27–5.95)
n	53	49	21	17
AUC, µg/mL (GCV, %)	14.78 (75.4)	40.09 (72.1)	55.20 (67.4)	6.79 (46.4)
n				
$AUC_{(0–t),}$ µg/mL	52	52	22	18
(GCV, %)	15.21 (76.0)	39.52 (68.8)	54.60 (63.8)	6.19 (60.2)
n	53	49	21	17
$t_{½,}$ h (SD)	15.01 (8.23)	15.55 (6.44)	13.02 (4.16)	15.80 (9.55)
n	53	49	21	17
CL/F, L/h (SD)	8.16 (4.61)	3.05 (2.10)	6.36 (3.47)	48.3 (21.04)
n	53	49	21	17
V_z/F, L (SD)	191.8 (172.4)	75.14 (81.27)	112.1 (59.84)	1076 (868.8)

AUC, area under plasma concentration–time curve from zero to infinity; $AUC_{(0–t)}$, area under plasma concentration–time curve from zero to the last measurable time point; CL/F, apparent clearance following oral administration; C_{max}, maximum plasma concentration; t_{max}, time to maximal plasma concentration; $t_{½}$, terminal half-life; Vz/F, apparent volume of distribution. n is the number of patients with non-missing data. N is the PK analysis set (all patients who received at least one dose of study treatment and provided evaluable PK profiles in at least one treatment period). n is the number of patients with non-missing data; Data are expressed as geometric mean (CV%) for C_{max}, AUC and $AUC_{(0–t)}$; arithmetic mean (standard deviation) for CL/F, Vz/F and $t_{½}$; and median (range) for t_{max}.

Co-administration of olaparib with itraconazole resulted in a significant increase in the relative bioavailability of olaparib compared with olaparib administered alone: C_{max} treatment ratio 1.42 (90% CI: 1.33, 1.52) and mean AUC treatment ratio 2.70 (90% CI:

2.44, 2.97) (Table 3). For individual patients, the highest observed ratio for AUC was a 7-fold increase.

Table 3. Relative bioavailability of single-dose olaparib alone or in combination with itraconazole or rifampin

PK parameter	Study 7 (itraconazole)	Study 8 (rifampin)
GLS mean ratio (90% CI)	**Olaparib (100 mg) plus itraconazole (200 mg) vs olaparib (100 mg)**	**Olaparib (300 mg) plus rifampin (600 mg) vs olaparib (300 mg)**
$C_{max,}$ µg/mL	1.42 (1.33, 1.52)	0.29 (0.24, 0.33)
AUC, µg h/mL	2.70 (2.44, 2.97)	0.13 (0.11, 0.16)
$AUC_{0-t,}$ µg h/mL	2.66 (2.41, 2.93)	0.12 (0.10, 0.15)

AUC, area under plasma concentration–time curve from zero to infinity; AUC_{0-t}, area under plasma concentration–time curve from zero to the last measurable time point; C_{max}, maximum plasma concentration; GLS, geometric least squares.

C_{max} and AUC for itraconazole and hydroxyitraconazole determined after 5 days administration of itraconazole (200 mg once daily) are shown in Table 4.

Table 4. Pharmacokinetic parameters for itraconazole and hydroxyitraconazole obtained on the fifth day of itraconazole dosing (Study 7)

PK parameter	Itraconazole (n=53)	Hydroxyitraconazole (n=53)
$C_{max,}$ ng/mL (GCV, %)	245.5 (107.2)	313.3 (101.5)
$t_{max,}$ h (min,max)	3.00 (1.00–12.00)	4.00 (0.00–8.03)
$AUC_{tau,}$ µg.h/mL (GCV, %)	2702 (108.1)	5341 (127.6)
CL/F, L/h (GCV, %)	74.02 (108.1)	ND

AUC_{tau}, area under plasma concentration–time curve for a dosing interval; CL/F, apparent clearance following oral administration; C_{max}, maximum plasma concentration; GCV, geometric coefficient of variation; ND, not determined; t_{max}, time to maximal plasma concentration. n is the number of patients with non-missing data. Data are expressed as geometric mean (geometric CV%) for C_{max}, AUC_{tau}; arithmetic mean (standard deviation) for CL/F; and median (range) for $t_{max.}$

All patients in the olaparib plus itraconazole treatment arm were shown to have been exposed to itraconazole and its metabolite. Steady state exposures (C_{max} and AUC) for itraconazole and hydroxyitraconazole, determined after 5 days' administration of itraconazole (200 mg once daily), were of a similar order of magnitude to the exposures reported in other clinical PK studies utilizing a similar dosing regimen where significant interactions have been demonstrated (the mean itraconazole previously reported was 324 ng/mL).[16] In six patients, however, the plasma concentrations achieved for both itraconazole and hydroxyitraconazole appeared low, with the observed itraconazole C_{max} being less than 100 ng/mL (range 14.6 to 71.6 ng/mL). There was no clear evidence that these patients were those where the smallest effect was seen on olaparib suggesting that sufficient itraconazole exposure to inhibit CYP3A4 had still been achieved in these patients.

Study 8 (CYP3A4 induction)

All 22 patients had evaluable PK profiles with no important protocol deviations that impacted PK. The olaparib plasma concentration versus time profiles in the absence and presence of rifampin are shown in Figure 2b.

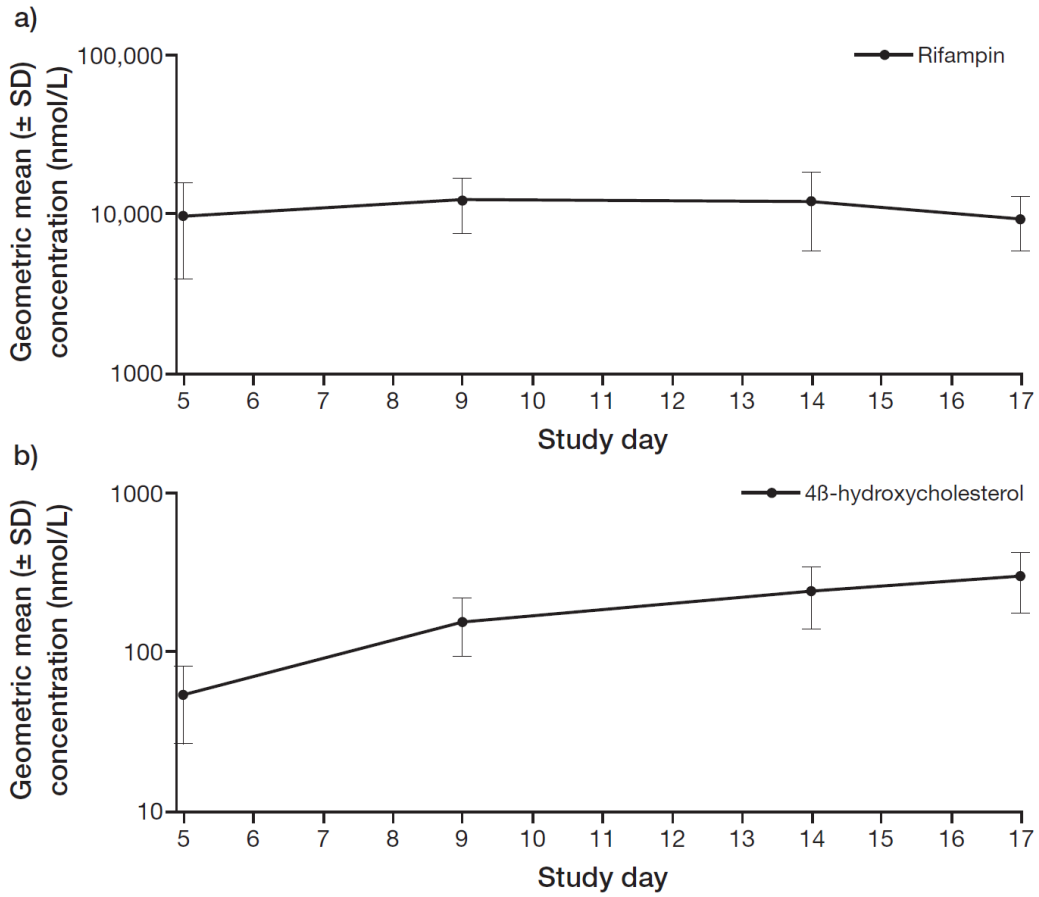
The rate of absorption of olaparib (300 mg) was increased when administered in the presence of rifampin, with a median t_{max} of 0.78 hours (range: 0.27–5.95 hours) compared with olaparib administered alone (1.49 hours, range: 0.57–3.05 hours) (Table 2). Co-administration of olaparib with rifampin resulted in a statistically significant decrease of approximately 71% in the relative bioavailability of olaparib; C_{max} treatment ratio 0.29 (90% CI: 0.24, 0.33). Mean AUC was also reduced by 87% in the presence of rifampin compared with olaparib administered alone; treatment ratio 0.13 (90% CI: 0.11, 0.16) (Table 3).

Consistent with the decrease in AUC of olaparib, mean apparent CL/F increased by 7.6-fold (6.36 vs 48.3 L/hour) and mean apparent V_z/F by 9.6-fold (112 vs 1076 L) following dosing in the presence of rifampin (Table 2). However, there was no marked change in $t_{½}$ compared with olaparib administered alone (13 hours for olaparib alone vs 15.8 hours in combination with rifampin).

Overall, mean plasma concentrations of rifampin were generally consistent on all study days, suggesting that steady-state exposures had been maintained throughout the study period (Figure 3a).

Following administration of rifampin (600 mg), mean plasma 4β-hydroxycholesterol levels increased by approximately 5-fold (from 55.2 nmol/L on day 5 to 316 nmol/L by day 17; ratio: 5.31, 90% CI: 4.68, 6.02), indicating that CYP3A4 enzyme induction had occurred (Figure 3b).

Figure 3. Geometric mean plasma concentration of (a) rifampin over time: log scale and (b) 4β-hydroxycholesterol over time: log scale



Safety and tolerability

Study 7 (CYP3A4 inhibition)

In Study 7, a total of 42 (71.2%) patients reported 135 AEs. In the olaparib-alone dosing period nine (15.3%) patients reported nine AEs considered by the investigator as causally related to olaparib (nausea, n=3; diarrhea, n=2; flushing, n=1; headache, n=1; rash, n=1; rash erythematous, n=1). In the olaparib plus itraconazole dosing period seven (11.9%) patients reported 11 AEs that were considered causally related to olaparib (constipation, n=2; diarrhea, n=2; nausea, n=2; abdominal pain, n=1; ascites, n=1; cough, n=1; headache, n=1; tinnitus, n=1). The majority of AEs were gastrointestinal in origin, and of common terminology criteria for adverse events (CTCAE) grade 2 or lower. The AEs reported by the greatest number of patients are shown in Table 5.

Table 5. Adverse events experienced by >5% of patients overall in Study 7 or Study 8*

Adverse event	Study 7 (itraconazole)		Study 8 (rifampin)	
	Olaparib (100 mg) (n=59)	**Olaparib (100 mg) plus itraconazole (200 mg) (n=59)**	**Olaparib (300 mg) (n=22)**	**Olaparib (300 mg) plus rifampin (600 mg) (n=22)**
Patients with any AE, n patients (%)	25 (42.4)	33 (55.9)	8 (36.4)	18 (81.8)
Diarrhea	4 (6.8)	4 (6.8)	1 (4.5)	3 (13.6)
Nausea	4 (6.8)	4 (6.8)	0	7 (31.8)
Constipation	2 (3.4)	6 (10.2)	1 (4.5)	2 (9.1)
Vomiting	2 (3.4)	4 (6.8)	0	6 (27.3)
Fatigue	2 (3.4)	5 (8.5)	0	2 (9.1)
Abdominal pain	1 (1.7)	2 (3.4)	1 (4.5)	3 (13.6)
Cough	1 (1.7)	3 (5.1)	0	0
Dyspepsia	1 (1.7)	2 (3.4)	0	1 (4.5)
Headache	1 (1.7)	5 (8.5)	1 (4.5)	3 (13.6)
Dyspnea	1 (1.7)	2 (3.4)	0	2 (9.1)
Hypokalemia	0	3 (5.1)	0	1 (4.5)

Back pain	0	3 (5.1)	0	0
Pain in extremity	0	2 (3.4)	0	2 (9.1)
Insomnia	0	1 (1.7)	0	2 (9.1)
Feces discolored	0	0	0	2 (9.1)
Malaise	0	0	0	2 (9.1)
Decreased appetite	0	0	1 (4.5)	3 (13.6)
Chromaturia	0	0	0	5 (22.7)

*AEs presented for olaparib alone and olaparib in combination should not be compared, as the combination data was evaluated over a longer observation period and consists primarily of administration of the putative interacting drug alone.

In total, two (3.4%) and five (8.5%) patients reported a CTCAE grade 3 AE in the olaparib-alone dosing period (diarrhea, nausea) and in the olaparib plus itraconazole dosing period (anemia, fatigue, international normalised ratio increased nausea, urinary tract obstruction, vomiting), respectively. Two patients experienced SAEs of nausea (grade 2, grade 3), both in the olaparib plus itraconazole dosing period, which were considered by the investigator to be causally related to olaparib. No AEs considered causally related to olaparib treatment resulted in discontinuation of olaparib. Overall, there were no clinically relevant differences in clinical chemistry parameters between the safety profiles of olaparib when administered alone or in combination with itraconazole.

One death was reported during the olaparib plus itraconazole dosing period. The reported primary cause of death was disease progression and was not reported as an AE.

Study 8 (CYP3A4 induction)

In total 19 (86.4%) patients experienced 90 AEs. Two patients (9.1%) reported three AEs considered causally related to olaparib (abdominal pain upper, diarrhea, headache). In the olaparib plus rifampin dosing period five patients (22.7%) reported 14 AEs considered causally related to olaparib (nausea, n=3; vomiting n=3; constipation, decreased appetite, diarrhea, gastrointestinal hypermotility, hemoglobin urine present, malaise, stomatitis, and urinary retention, all n=1). The most frequently reported AEs are shown in Table 5. Chromaturia, observed in five (22.7%) patients, is a known AE associated with rifampin treatment.[17]

Two (9.1%) patients reported two CTCAE grade 3 AEs in the olaparib-alone dosing period (decreased appetite, lymphoedema) and five (22.7%) patients reported eight CTCAE grade 3 AEs in the olaparib plus rifampin dosing period (abdominal pain, ascites, convulsion, fatigue, headache, malaise, neutropenia, thrombocytopenia). None of the SAEs reported were considered related to olaparib treatment and no AEs resulted in discontinuation of olaparib.

There was one death reported during the olaparib plus rifampin dosing period. The reported primary cause of death was disease progression and was not reported as an AE.

Discussion

Two Phase I, non-randomized, open-label studies were conducted to investigate the effect of itraconazole, a potent CYP3A4 inhibitor, or rifampin, a potent CYP3A4 inducer on the PK profile of olaparib following a single dose of the tablet formulation. Given that *in vitro* studies have shown that the metabolism of olaparib is mediated by CYP enzymes, [McCormick & Swaisland, *in preparation*] predominantly CYP3A4/5, the current Phase I studies were deemed important, as any PK interactions of olaparib with agents that inhibit or induce CYP3A4 could have clinical implications.

In Study 7, CYP3A4 was inhibited by administration of itraconazole 200 mg/day for 4 days, before dosing with a single 100 mg olaparib dose. This itraconazole regimen resulted in steady-state exposures of itraconazole and its metabolite, hydroxyitraconazole, consistent with other clinical PK studies.[16] Co-administration of olaparib with itraconazole significantly increased olaparib mean plasma AUC by 2.7-fold, whilst mean C_{max} increased 1.4-fold, indicating that an interaction had occurred. Since the treatment ratios and 90% CIs for both C_{max} and AUC were outside the predefined bioequivalence range (0.80–1.25), these findings show that itraconazole has a statistically significant and potentially clinically relevant effect on olaparib. There was no difference in $t_{½}$ of olaparib when dosed in combination with itraconazole, but both CL/F and V_z/F were decreased, reflecting the increased exposure to olaparib. The unchanged elimination $t_{½}$ of olaparib despite the decreased clearance and volume of distribution suggests that itraconazole may predominantly affect olaparib exposure by altering its bioavailability, possibly through inhibition of transporter-mediated processes in the gut, resulting in a change in the extent of olaparib absorption.

Preclinical data have shown that olaparib is a substrate for P-glycoprotein [McCormick & Swaisland, *in preparation*] and itraconazole is an inhibitor of this transporter system as well as of CYP3A4 mediated metabolism.[18] Given, these findings, it is recommended that potent CYP3A4 enzyme inhibitors (eg, itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritinovir, lopinavir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) and moderate CYP3A inhibitors (eg, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) should be avoided during olaparib treatment.

In Study 8, CYP3A4 was induced by administration of rifampin 600 mg/day for 9 days before dosing with a single 300 mg olaparib dose (2 x 150 mg tablets). Exposure to

rifampin 600 mg was of a similar magnitude to that reported in other controlled clinical PK studies using a similar dosing regimen where significant drug–drug interactions have been demonstrated.[19–21] CYP3A4 enzyme induction by rifampin was shown in all patients by a consistent increase in the endogenous biomarker 4β-hydroxycholesterol. Co-administration of olaparib with rifampin significantly reduced olaparib mean plasma AUC by approximately 87%. There was also a significant decrease of 71% in the C_{max} of olaparib. The treatment ratio and 90% CI for AUC and C_{max} were <0.5 (ie, greater than halving of the exposure), indicating a statistically significant interaction between olaparib and rifampin.

As with Study 7, given the lack of any apparent change in elimination $t_{½}$ of olaparib, the changes in olaparib exposure may reflect a change in the extent of drug absorption, in this case a decrease in drug absorption possibly transporter protein-mediated (P-glycoprotein). It is, therefore, recommended that potent CYP3A4 enzyme inducers (eg, phenytoin, rifampin, carbamazepine, St John's Wort) and moderate CYP3A inducers (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided during olaparib treatment.

Across both studies, the number and type of AEs reported were in line with what would be expected for this patient population and the known safety profile for olaparib.[7,22–25] The majority of AEs reported were of mild or moderate severity. Olaparib showed an acceptable tolerability profile, and no new safety findings were observed. Phase III trials of olaparib tablet formulation in patients with ovarian, breast, pancreatic, and gastric cancers are ongoing.[26–32]

Conclusions

In these Phase I studies, exposure to olaparib as assessed by AUC and C_{max} was increased when a single 100 mg dose was given in combination with the CYP3A4 inhibitor, itraconazole. Conversely, olaparib exposure was decreased when a single 300 mg dose was given in combination with the CYP3A4 inducer, rifampin. Based on these findings, it is recommended that potent and moderate CYP3A4 enzyme inhibitors and inducers should be avoided during olaparib treatment. No clinically relevant safety signals were observed when a single dose of olaparib was administered in combination with itraconazole or rifampin. The safety data for olaparib tablets were consistent with the known safety profile of this drug.

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Conflict of interest statement

GJ has acted in a consulting/advisory role, received travel/accommodation expenses, honoraria or research funding from Celgene, GlaxoSmithKline, MSD Oncology, Novartis and Roche/Genentech; CR has participated in a Speakers' Bureau or received research funding from Novartis and Sanofi Aventis; LRM has received research funding from

AstraZeneca; RK has received honoraria, acted in a consulting/advisory role or received travel/accommodation expenses from AstraZeneca and Clovis Oncology with regard to PARP inhibitor development; HS, AF, KS and WB are employees of, and own stock or other ownership interests in AstraZeneca. RP has acted in a consulting/advisory role, received travel/accommodation expenses, honoraria or research funding from AstraZeneca, Biomarin, BMS, Clovis Oncology, GlaxoSmithKline, MSD Oncology, Roche/Genentech, Tesaro and Vertex; LD, HV, SR, KL, DN, JDV-G, MM-S, PS, and CVH declare no conflict of interest.

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