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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Safety of Olaparib in Patients with Advanced Solid Tumours and Renal Impairment

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Abstract

Background Olaparib, a potent oral poly(ADP-ribose) polymerase inhibitor, is partially renally cleared. We investigated the pharmacokinetics and safety of olaparib in patients with mild or moderate renal impairment to provide dosing recommendations.

Methods This phase I open-label study assessed the pharmacokinetics, safety and tolerability of single-dose, oral 300-mg olaparib tablets in adults (aged 18–75 years) with solid tumours. Patients had normal renal function, or mild or moderate renal impairment (estimated creatinine clearance ≥81, 51–80 or 31–50 mL/min, respectively). Blood was collected for 96 h, and urine samples collected for 24 h post-dose. Patients could continue taking olaparib 300 mg twice daily for a long-term safety assessment.

Results Overall, 44 patients received one or more doses of olaparib and 38 were included in the pharmacokinetic assessment. Patients with mild renal impairment had an area under the curve geometric least-squares mean ratio of 1.24 (90% confidence interval 1.06–1.47) and a geometric least-squares mean maximum plasma concentration ratio of 1.15 (90% confidence interval 1.04–1.27) vs. those with normal renal function. In patients with moderate renal impairment, the geometric least-squares mean ratio for the area under the curve was 1.44 (90% confidence interval 1.10–1.89) and for the maximum plasma concentration was 1.26 (90% confidence interval 1.06–1.48) vs. those with normal renal function. No new safety signals were detected in patients with mild or moderate renal impairment.

Conclusions In patients with mild renal impairment, the small increase in exposure to olaparib was not considered clinically relevant. In patients with moderate renal impairment, exposure to olaparib increased by 44%; thus, these patients should be carefully monitored and the tablet dose should be adjusted to 200 mg twice daily.

Clinical Trials Registration NCT01894256.

Key Points

In patients with mild renal impairment, the small increase in exposure to olaparib is not considered clinically relevant, and the safety profile is consistent with that observed in patients with normal renal function.

No new safety signals were detected in patients with moderate renal impairment; however, exposure to olaparib increased by 44% in these patients; thus, these patients should be carefully monitored and the tablet dose should be adjusted from 300 to 200 mg twice daily.

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1 Introduction

Olaparib (Lynparza™) is a potent oral poly(ADP-ribose) polymerase inhibitor [1]. The initially approved dose of olaparib in ovarian cancer was 400 mg twice daily (bid) administered as a capsule formulation [2, 3], which resulted in patients taking 8 × 50 mg capsules bid. An alternative tablet formulation was developed to reduce the pill burden. Administration of 300 mg of olaparib as tablets (2 × 150 mg bid) has similar, or exceeds, the exposure of the 400-mg capsule formulation [4], which led to the tablet formulation being assessed in phase III studies. The tablet formulation of olaparib has received approval in Europe and USA for the treatment of patients with ovarian cancer and in USA for the treatment of BRCA-mutated

human epidermal growth factor receptor–2-negative metastatic breast cancer [5, 6].

Olaparib and its metabolites are eliminated via both renal and hepatic routes, with approximately 44% of the dose being eliminated in urine (approximately 15% of which was unchanged olaparib) and 42% in faeces [7]. Patients with cancer experience varying degrees of renal impairment, as a result of common risk factors (such as increased age), disease-related renal complications and nephrotoxic effects of cancer treatment [8].

The aims of this two-part study (D0816C00006; NCT01894256) were (1) to evaluate the olaparib tablet formulation pharmacokinetic profile after a single oral dose of 300 mg in patients with advanced solid tumours and mild or moderate renal impairment (Part A) and (2) to investigate olaparib tolerability following single (Part A) and multiple bid (Part B) dosing compared with patients with normal renal function. This study also supported label dose recommendations for the olaparib tablet formulation in patients with renal impairment.

2 Methods

2.1 Study Design

This was a phase I, two-part, interventional, comparative open-label pharmacokinetic study (NCT01894256). It was performed at 13 sites in five European countries (Belgium, Denmark, France, the Netherlands and UK). Part A of the study investigated the pharmacokinetics (PK) of a single 300-mg dose of olaparib in patients with mild or moderate renal impairment, compared with patients with normal renal function.

Part B sought to provide additional safety data, by allowing patients to continue taking olaparib 300 mg bid for long-term safety assessment. In this part of the study, no further pharmacokinetic analyses were collected. Patients were evaluated for safety in terms of adverse events (AEs), vital signs, electrocardiogram, laboratory data and physical examination. Although efficacy was not assessed in this study, Part B also allowed patients with clinical benefit to continue.

2.2 Patients

Adult patients (aged 18–75 years) were included in the study if they had: a body mass index (BMI) between 18 and 30 kg/m^2 to limit any potential confounding factors in pharmacokinetic comparisons across the renal impairment groups, such as co-morbidities associated with an extreme BMI (although pharmacokinetic modelling has reported that BMI has no effect on the PK of olaparib) [9]; a histologically or cytologically confirmed malignant solid tumour, disease refractory or resistant to standard therapy, or for which no suitable effective standard therapy exists; normal liver and bone marrow function measured within 28 days prior to olaparib administration; Eastern Cooperative Oncology Group performance status ≤ 2; a life expectancy of at least 12 weeks; evidence of non-childbearing status for women of childbearing potential, or postmenopausal status.

Three patient cohorts were included: one cohort of normal renal function (defined as a creatinine clearance ≥ 81 mL/min); and two cohorts of stable renal impairment (mild: creatinine clearance 51–80 mL/min or moderate: 31–50 mL/min). Serum creatinine clearance was calculated according to the Cockcroft–Gault equation. The classification for renal insufficiency was based upon the Committee for Medicinal Products for Human Use guidance, in operation for the period from 1 December, 2004 to 1 July, 2016 (CHMP/EWP/225/02). Since the approval of the protocol of this study, new renal impairment criteria have been released (EMA/CHMP/83874/2014) defining normal renal function as a creatinine clearance of ≥ 90 mL/min, mild as 60–89 mL/min and moderate as 30–59 mL/min.

The main exclusion criteria included renal transplant or end-stage renal disease, gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of olaparib, systemic chemotherapy or radiotherapy within 2 weeks prior to the start of study treatment (or more based on the characteristics of the agents used), the use of inhibitors or inducers of cytochrome P450 3A4, and for Part A only, drugs that can affect creatinine clearance within 7 days of olaparib dosing.

Where possible, patients in each of the three groups were matched for age and BMI, and were selected to ensure an overall similar proportion of male and female individuals. Patients with normal renal function and mild renal impairment were recruited before those with moderate renal impairment; at least 3 months of safety information from a minimum of three patients with mild renal impairment were to be reviewed prior to recruiting patients into the moderate renal impairment cohort.

2.3 Study Drug Administration

In Part A of the study, patients received a single oral dose of an olaparib 300-mg tablet formulation; while in Part B, patients received olaparib 300 mg bid (tablet formulation), which was continued for the duration of the patient's participation.

2.4 Outcomes

In Part A of the study, the primary outcome variables included: maximum plasma concentration (C_{max}), time to C_{max}, area under the plasma concentration–time curve from zero to the last measurable time point, area under the plasma concentration–time curve from zero extrapolated to infinity (AUC), apparent plasma clearance following oral administration (*CL/F*), terminal half-life, apparent volume of distribution following oral administration (V_z/F), renal clearance, percentage of the dose excreted unchanged (FE%) in the urine and amount of olaparib excreted. Secondary outcomes included safety and tolerability of single and multiple doses of olaparib. Exploratory outcomes were plasma protein binding at 1 h after dosing, used to calculate free C_{max} (C_{max} of unbound olaparib), free AUC (AUC of unbound olaparib) and unbound *CL/F* (*CL/F* of unbound olaparib).

For pharmacokinetic measurements, venous blood samples were collected pre-dose, and at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 h post-dose. All urine voided between 0–12 and 12–24 h post-dose was collected.

In Parts A and B of the study, safety profiles were assessed in terms of AEs (encoded per the *Medical Dictionary for Regulatory Activities*, Version 18.0), vital signs (including blood pressure and pulse rate), electrocardiogram, laboratory data (clinical chemistry, haematology and urinalysis) and physical examination. Adverse events were graded by the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

2.5 Statistical Analysis

No formal sample size calculations were performed. However, based on an estimate of a between-patient standard deviation for the log of AUC of 0.531 from a previous study of patients receiving olaparib tablet monotherapy (300 mg), 12 evaluable patients per group were determined to provide approximately 80% power of observing a one-sided 95% confidence limit for the ratio of geometric means of AUC less than 1.7 (to rule out a 70% increase), in patients with mild or moderate renal impairment compared with those with normal renal function. Therefore, a total of 36 evaluable patients (12 per cohort) was considered adequate to provide reasonable precision around the estimate of the magnitude of the effects of renal impairment on olaparib exposure. This is in line with European Medicines Agency (EMA) recommendations, which state six to eight subjects per group is sufficient to describe the relationship between renal function and drug clearance [10].

Log_e-transformed AUC and C_{max} were analysed using linear regression, fitting measured creatinine clearance and age as continuous explanatory variables. The slope parameter, representing the rate of change in log_e-transformed AUC and C_{max} per unit change in measured creatinine clearance (when age was held constant), and corresponding standard error were used to provide point estimates and two-sided 90% confidence intervals (CIs) for the ratio of olaparib exposures in patients with moderate and mild renal impairment compared with patients with normal renal function. Creatinine clearance values of 31, 51 and 81 mL/min were used in these calculations to represent the moderate renal impairment, mild renal impairment and normal renal function groups, respectively.

Pharmacokinetic data were summarised using descriptive statistics and parameters calculated using Phoenix™ WinNonlin (Certara USA, Inc., Princeton, NJ, USA). In Part A, the pharmacokinetic analysis set consisted of all patients who received the olaparib dose and had full pharmacokinetic sampling up to 96 h post-dose; in Parts A and B, the safety analysis population consisted of all patients who received at least one dose of olaparib and for whom any post-dose data were available.

3 Results

3.1 Part A

3.1.1 Patient Population

In total, 56 patients were screened, of whom 12 did not fulfil all of the eligibility criteria. The remaining 44 patients were assigned to treatment and received at least one dose of olaparib (15 patients each with normal renal function or mild renal impairment and 14 patients with moderate renal impairment). The first patient was enrolled on 20 November, 2013, and the last patient completed Part A of the study on 27 March, 2015. Patients in the normal renal function and mild renal impairment groups were recruited prior to patients with moderate renal impairment. Demographic and baseline characteristics were generally balanced between groups; however, age increased slightly with decreasing renal function (Table 1).

3.1.2 Protocol Deviations

One patient each from the normal renal function group and mild renal impairment group were excluded because of incomplete pharmacokinetic profiles. Four additional patients were excluded from the pharmacokinetic analysis: two patients in the normal renal function group (one history of gastric surgery; one taking disallowed concomitant medications); one patient in the moderate renal impairment group (previous gastric resection) and one patient in the mild renal impairment group (not taking stable concomitant medication and use of multiple

Table 1 Baseline characteristics of patients enrolled in the renal impairment study

	Normal renal function ($n=15$)	Mild renal impairment ($n=15$)	Moderate renal impairment ($n=14$)
Median age (range), year	55 (40–72)	63 (50–75)	68 (32–76)
Female, *n* (%)	10 (66.7)	8 (53.3)	7 (50.0)
Race, *n* (%)			
White	15 (100)	14 (93.3)	14 (100)
Asian	0	1 (6.7)	0
Mean CrCL (SD), mL/min	108.7 (22.0)	60.1 (8.1)	41.7 (5.8)
Primary tumour location, *n* (%)			
Breast	3 (20)	1 (6.7)	0
Bladder	1 (6.7)	1 (6.7)	1 (7.1)
Colorectal[a]	3 (20.0)	1 (6.7)	1 (7.1)
Lung	2 (13.3)	1 (6.7)	0
Prostate	0	2 (13.3)	0
Renal	0	2 (13.3)	3 (21.4)
Ovary[b]	3 (20.0)	6 (40.0)	5 (35.7)
Other[c]	3 (20.0)	1 (6.7)	4 (28.6)
Overall disease classification, *n* (%)			
Metastatic	12 (80.0)	13 (86.7)	11 (78.6)
Locally advanced	0	0	2 (14.3)
Both metastatic and locally advanced	3 (20.0)	2 (13.3)	1 (7.1)
ECOG performance status, *n* (%)			
0 (normal activity)	9 (60.0)	3 (20.0)	5 (35.7)
1 (restricted activity)	6 (40.0)	12 (80.0)	9 (64.3)

CrCL creatinine clearance, *ECOG* Eastern Cooperative Oncology Group, *SD* standard deviation

[a]Included colorectal, colon and rectal

[b]Included ovarian and peritoneal

[c]Other included oesophagus, head and neck (including nasopharynx, larynx and trachea), mesothelioma, pancreas, testicular, anal, squamous histology of unknown primary and adenocarcinoma of unknown primary (all $n=1$)

homeopathic products). Additional protocol deviations were reported in 14 patients (normal renal function $n=4$; mild renal impairment $n=4$; moderate renal impairment $n=6$); however, these deviations were not considered to have an impact on the pharmacokinetic analyses.

3.1.3 Pharmacokinetics

The geometric mean plasma concentration–time profile for each renal status group is shown in Fig. 1. There was no detected relationship between creatinine clearance and the degree of protein binding (Fig. 2); therefore, total plasma PK was reflective of the free drug.

Olaparib renal clearance and, to a lesser extent, *CL*/*F* declined with decreasing renal function, as did the proportion of olaparib dose excreted unchanged in the urine (FE%) (Fig. 3, Table 2). A reduced volume of distribution and terminal half-life was found in patients with mild (131.2 L, 17.5 h) and moderate (125.7 L, 16.1 h) renal impairment, compared with patients with normal renal function (283.4 L, 24.3 h) (Table 2). The percentage of olaparib dose (FE%) was 16% in patients with normal renal function, and 12% and 8% for patients with mild and moderate renal impairment, respectively (Table 2).

Single-dose olaparib led to peak plasma exposures after around 2 h across all patient groups (Fig. 1; see Table 2 for plasma and urine pharmacokinetic parameters). In patients with mild renal impairment, total plasma exposure was higher compared with patients with normal renal function; geometric least-squares mean (GLSmean) AUC was 24% higher (GLSmean ratio 1.24; 90% CI 1.06–1.47) and GLSmean C_{max} was increased by 15% (GLSmean ratio 1.15; 90% CI 1.04–1.27) compared with patients with normal renal function (Fig. 4). In patients with moderate renal impairment, GLSmean AUC was 44% higher (GLSmean ratio 1.44; 90% CI 1.10–1.89) and GLSmean C_{max} was

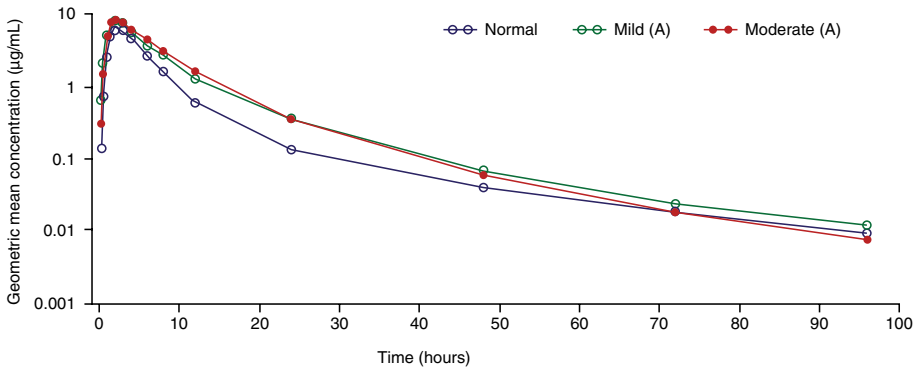

Fig. 1 Geometric mean plasma concentration of olaparib (single-dose tablet formulation, 300 mg) over time in patients with mild and moderate renal function and normal renal function (log scale) evaluated during Part A of the study

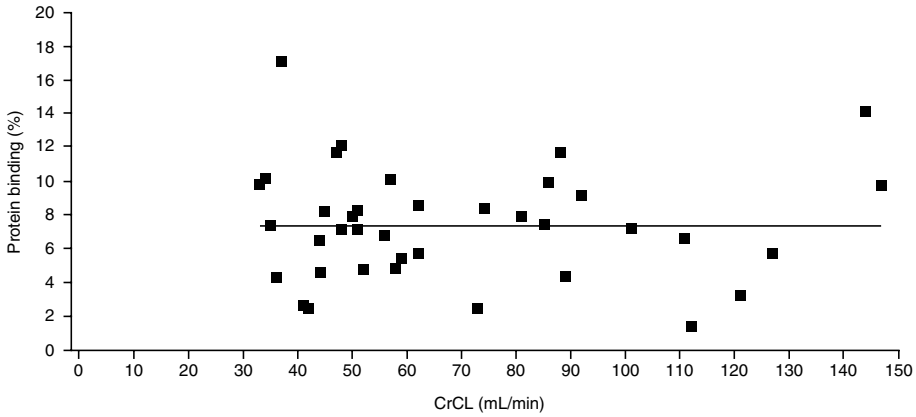

Fig. 2 Olaparib plasma protein binding (% free) in patients with impaired renal function evaluated during Part A of the study. Squares represent individual patients, and the straight line represented the fitted linear regression model of protein binding against creatinine clearance (CrCL)

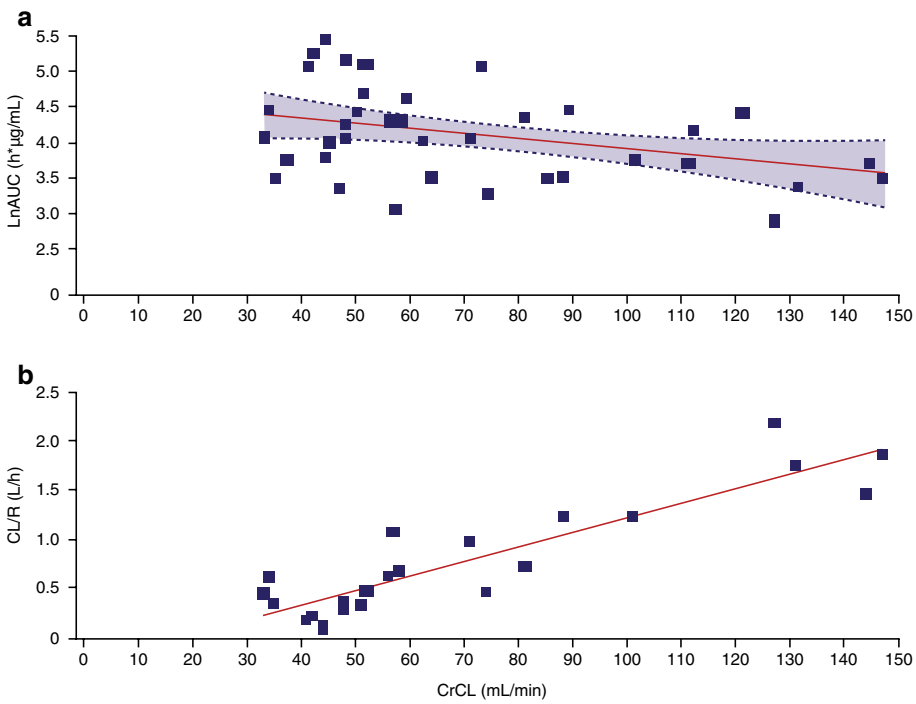

Fig. 3 Scatter plot shows a correlation between **a** renal function [creatinine clearance (CrCL)] and area under the plasma concentration–time curve from zero to infinity (AUC) [$r^2 = 0.197$] evaluated during Part A of the study. **b** A stronger relationship ($r^2 = 0.811$) can be seen for renal function (CrCL) and renal clearance (CL/R) evaluated during Part A of the study. Squares represent individual patients, the red line represents the fitted linear regression model of the natural logarithm of AUC (LnAUC) against CrCL and age, and the shaded areas represent 90% confidence intervals

Table 2 Plasma and urine pharmacokinetic parameters of a single 300-mg dose of olaparib in patients with renal impairment compared with patients with normal renal function evaluated during Part A of the study

	Normal renal function ($n=12$)	Mild renal impairment ($n=13$)	Moderate renal impairment ($n=13$)
C_{max}, µg/mL	7.2 (31.0)	9.1 (40.6)	10.0 (44.2)
t_{max}, h	2.0 (1.1–3.0)	1.6 (1.0–3.0)	2.0 (1.0–3.0)
AUC, µg·h/mL	43.7 (50.1)	70.6 (75.6)	76.4 (78.2)
$t_{½}$, h	24.3 (9.7)	17.5 (8.0)	16.1 (9.4)
CL/F, L/h	7.6 (3.6)	5.3 (3.9)	4.8 (2.9)
V_Z/F, L	283.4 (62.8)	131.2 (90.7)	125.7 (133.0)
CL/R, L/h	1.5 (0.5)	0.6 (0.3)	0.3 (0.2)
FE, %	15.8 (2.7)	12.4 (5.7)	8.1 (4.0)
Amount of olaparib excreted, mg	15.8 (2.7)	12.4 (5.7)	8.1 (4.0)

C_{max} and AUC values are geometric mean (geometric coefficient of variation, %), *CL/F*, $t_{½}$, FE% and amount of olaparib excreted values are arithmetic mean (SD); V_Z/F values are arithmetic mean (percentage coefficient of variation %]), t_{max} is represented as median (range)

AUC area under the plasma concentration–time curve from zero to infinity, *CL/F* apparent plasma clearance, *CL/R* renal clearance, C_{max} maximum plasma concentration, *FE* percentage of the dose excreted unchanged in urine, *SD* standard deviation, $t_{½}$ terminal half-life, t_{max} time to reach maximum plasma concentration, V_Z/F apparent volume of distribution

increased by 26% (GLSmean ratio 1.26; 90% CI 1.06, 1.48) compared with patients with normal renal function (Fig. 4).

3.1.4 Additional Analysis Based on the Updated European Medicines Agency Guidance (EMA/CHMP/83874/2014) on Categories of Renal Impairment

During the conduct of the study, new guidance for categorising renal impairment was issued by the EMA [11]. The updates included the measurement of renal capacity using absolute glomerular filtration rate with normal renal elimination capacity, mildly decreased renal elimination capacity and moderately decreased renal elimination capacity defined as a glomerular filtration rate of ≥ 90, 60–89 and 30–59 mL/min, respectively. According to the new EMA guidance, there were eight patients with normal renal function, nine patients with mild renal impairment and 21 patients with moderate renal impairment. The GLSmean ratios were 1.15 (90% CI 1.04–1.27) and 1.24 (90% CI 1.06–1.47) for C_{max} and AUC, respectively, in the mild renal impairment group, compared with patients with normal renal function. The GLSmean ratios were 1.31 (90% CI 1.07–1.61) and 1.55 (90% CI 1.12–2.15) for C_{max} and AUC, respectively, in the moderate renal impairment group, compared with patients with normal renal function. The updated categorisation does not change the dose modification guidance resulting from the study.

3.1.5 Safety and Tolerability

In total, 29 patients (65.9%) reported 59 AEs. Eleven patients (25.0%) had 14 AEs that were considered causally related to a single dose of olaparib and the incidence was similar between the three groups.

Nausea was the most commonly reported AE and occurred in three patients (20.0%) in the normal renal function group, and in two patients (13.3%) in the mild renal impairment group. Other AEs that occurred in at least two patients (> 10%) are summarised below. Cough occurred in two patients (13.3%) in the normal renal function group. Abdominal pain and vomiting each occurred in two patients (13.3%) in the mild renal impairment group, while anaemia and constipation each occurred in two patients (14.3%) in the moderate renal impairment group. There was one AE of CTCAE grade 3 in the normal renal function group (hyponatraemia) and one serious AE of asthenia (grade 2) in the mild renal impairment group (both events considered not related to olaparib).

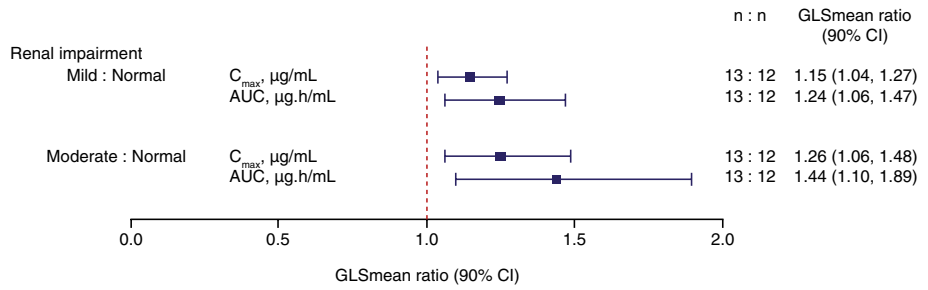

Fig. 4 Summary of geometric least-squares mean (GLSmean) ratios and 90% confidence intervals (CIs) for maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve from zero to infinity (AUC) of olaparib in patients with mild or moderate renal impairment, compared with patients with normal renal function evaluated during Part A of the study

3.2 Part B

3.2.1 Patients

In total, 43 patients (15 in the normal renal function group and 14 in each of the mild and moderate renal impairment groups) entered Part B of the study and continued treatment until disease progression/lack of therapeutic response [40 (93.0%)]. Other causes of treatment discontinuation were death [due to disease progression, two (4.7%)] and patient decision [one (2.3%)]. The first patient entered Part B of the study on 9 December, 2013, and the last patient completed Part B of the study on 11 February, 2016. The mean (range) actual treatment duration was 134.2 (29–381) and 158.5 (18–627) days for patients with normal renal function and mild renal impairment, but was markedly lower in patients with moderate renal impairment [60.8 (4–247) days].

3.2.2 Safety and Tolerability

Dose interruptions occurred in four patients (26.7%) in the normal renal function group; six patients (42.9%) in the mild renal impairment group and seven patients (50.0%) in the moderate renal impairment group.

Two of four patients had a dose interruption because of an AE in the normal renal function group, four of six in the mild renal impairment group and five of seven in the moderate renal impairment group. Other reasons for dose interruptions were that patients forgot to take the dose ($n=7$) and other reasons (such as patient choice or for radiotherapy; $n=6$). Three patients required dose reductions (two in the mild renal impairment group and one in the moderate renal impairment group); all three patients required only one dose reduction, which was because of AEs.

Adverse events in Part B are detailed in Table 3. Thirty-six patients had AEs reported by the investigator to be related to olaparib, with nausea (60%, 50% and 57% of patients in the normal renal function group and mild and moderate renal impairment groups, respectively), fatigue (53%, 57% and 57%), decreased appetite (20%, 36% and 36%) and anaemia (20%, 36% and 36%) being commonly reported. In addition to decreased appetite and anaemia, urinary tract infections (7%, 0% and 21% of patients in the normal renal function group and mild and moderate renal impairment groups, respectively) and decreased weight (0%, 7% and 21%) were reported more frequently in the moderate renal impairment group compared with those with normal renal function or mild renal impairment. Thirty-one grade ≥ 3 AEs occurred in 16 patients (Table 3); seven of these were assessed by the investigator to be related to olaparib. Grade ≥ 3 AEs of urinary tract infection and asthenia were reported in two patients (14%) in the moderate renal impairment group compared with no patients with normal renal function or mild renal impairment. Nine patients had a total of 16 serious AEs, of which five were considered by the investigator to be related to olaparib [three events of anaemia (one each in the normal renal function, mild and moderate renal impairment groups), one event each of thrombocytopenia and neutropenia (both in the same patient in the mild renal impairment group)]. Two deaths were reported, both owing to the progression of their cancer under investigation. No AEs resulted in permanent discontinuation of olaparib treatment. Clinical laboratory investigations showed that seven patients had a haemoglobin decrease to CTCAE grade ≥ 3: one patient in the normal renal function group, three patients in the mild renal impairment group and three patients in the moderate renal impairment group (all of which were classified as AEs of anaemia).

4 Discussion

Renal clearance is an important route of elimination of olaparib, with approximately 44% of the dose eliminated through this route (15% of which is unchanged olaparib) and 42% through faeces [7]. Following a single 300-mg dose of olaparib (tablet formulation), patients with normal renal function excreted 16% of the dose, vs. only 12% and 8% in patients with mild and moderate renal impairment, respectively, suggesting a direct relationship between renal function and renal clearance of olaparib. Renal impairment did not affect the extent of olaparib plasma protein binding, thus total plasma exposure reflected the free drug. Olaparib plasma clearance also declined in a linear manner with decreasing creatinine clearance, with the reduction in clearance reflected by an increase in systemic exposure to olaparib. Patients with mild renal impairment had a 24% increase in exposure (AUC), which was not considered clinically relevant. The increase in exposure (AUC) was more marked (44%) in patients with moderate renal impairment. As a result of the updating of the EMA guidance for the evaluation of the PK of medicinal products in patients with decreased renal function (EMA/CHMP/83874/2014), a post-hoc analysis was performed. Overall, the analyses performed according to the new criteria did not impact on the dosing recommendations derived from the original analysis. Based on the potential for increased exposure (AUC) in patients with moderate renal impairment, these patients should be carefully monitored, particularly for haematological toxicities [12], and the tablet dose should be adjusted to 200 mg bid (2 × 100 mg).

In our study, the apparent volume of distribution and terminal half-life of olaparib decreased with decreasing renal function. While this finding is unexpected, it might be owing to limitations in characterising the terminal elimination phase using the pharmacokinetic blood sampling scheme.

Table 3 Summary of adverse events (AEs) during the long-term safety assessment of olaparib in Part B of the study

	Normal renal function ($n=15$)	Mild renal impairment ($n=14$)	Moderate renal impairment ($n=14$)
Any AE, *n* (%)	15 (100)	14 (100)	14 (100)
Any AE causally related, *n* (%)	12 (80.0)	12 (85.7)	12 (85.7)
Any SAE, *n* (%)	3 (20.0)	3 (21.4)	3 (21.4)
Anaemia	1 (6.7)	1 (7.1)	1 (7.1)
Neutropenia	0	1 (7.1)	0
Thrombocytopenia	0	1 (7.1)	0
Ileus	0	1 (7.1)	0
Non-cardiac chest pain	0	0	1 (7.1)
Infection	0	0	1 (7.1)
Urinary tract infection	0	0	2 (14.3)
Urosepsis	0	1 (7.1)	0
Hyponatraemia	0	1 (7.1)	0
Intervertebral disc degeneration	0	1 (7.1)	0
Confusional state	1 (6.7)	0	0
Pleural effusion	1 (6.7)	0	0
Any AE of CTCAE grade ≥ 3, *n* (%)	3 (20.0)	6 (42.9)	7 (50.0)
Anaemia	2 (13.3)	3 (21.4)	4 (28.6)
Neutropenia	0	1 (1.71)	0
Thrombocytopenia	0	2 (14.3)	0
Asthenia	0	0	2 (14.3)
Fatigue	1 (6.7)	0	1 (7.1)
Oedema peripheral	0	1 (7.1)	0
Clostridium difficile infection	0	0	1 (7.1)
Infection	0	0	1 (7.1)
Urinary tract infection	0	0	2 (14.3)
Urosepsis	0	1 (7.1)	0
Hyperglycaemia	0	0	1 (7.1)
Hyperkalaemia	0	0	1 (7.1)
Hyponatraemia	0	1 (7.1)	1 (7.1)
Cancer pain	2 (13.3)	0	0
Tumour thrombosis	0	0	1 (7.1)
Confusional state	1 (6.7)	0	0

Patients with multiple AEs are counted once for each preferred term

CTCAE Common Terminology Criteria for Adverse Events, *SAE* serious adverse event

No new safety signals for olaparib in these patients with mild or moderate renal impairment were identified in this study compared with those reported previously following treatment with olaparib tablets [13, 14]. In Part B, continuous dosing with olaparib 300 mg bid (tablet formulation) showed an acceptable tolerability profile in patients with mild or moderate renal impairment with an AE profile similar to that previously observed for olaparib.

Although no increase in AEs was evident in patients with moderate renal impairment, despite the 44% increase in exposure, there is a theoretical risk of increased toxicity, particularly haematological toxicity. The recommended dose reduction in patients with moderate renal impairment will provide exposure to olaparib that is comparable to the 300-mg bid dose given to patients with normal renal function, for which a large clinical safety database is available.

Population pharmacokinetic–pharmacodynamic analyses of olaparib in a patient population showed a significant exposure–safety relationship with the haemoglobin level, where increased exposure to olaparib was associated with a reduction in the haemoglobin level [12]. Population pharmacokinetic–pharmacodynamic simulations have suggested that for patients with an AUC > 100 μg h/mL, a clinically significant decrease in haemoglobin may occur, particularly in patients with low baseline haemoglobin. This study has demonstrated that some patients with moderate renal

impairment had very high exposure to olaparib (five patients had an AUC > 100 µg h/mL) compared with the mean exposure to olaparib for patients with normal renal function (43.7 µg h/mL) [12]. Patients with very high exposure to olaparib may experience reduced haemoglobin levels and therefore a risk of developing anaemia.

There is no requirement, from an efficacy perspective, to over-expose patients to olaparib. Population pharmacokinetic–pharmacodynamic analyses of 410 patients with ovarian cancer with normal renal function or mild renal impairment evaluated the efficacy (progression-free survival) of olaparib tablets at 300 mg bid and 200 mg bid. The exposure–progression-free survival, Cox proportional hazards model indicated that the 300-mg bid tablet dose was statistically superior to the 200-mg bid tablet dose, although the difference was numerically small [12].

Based on the potential for increased exposure (AUC) in patients with moderate renal impairment, these patients should be carefully monitored, particularly for haematological toxicities, and the tablet dose should be adjusted to 200 mg bid (2 × 100 mg). A dose reduction to 200 mg bid in patients with moderate renal impairment will provide exposure to olaparib that is comparable to the 300-mg bid dose given to patients with normal renal function.

A limitation of this study is that patients with moderate renal impairment tended to be older than those with normal function, but as age has been observed to have no impact on the PK of olaparib [9], this was considered unlikely to affect study findings. In addition, the mild and moderate renal impairment cohorts in our study were evenly distributed across sex, whereas olaparib studies have been conducted in predominantly female patients with ovarian and breast cancer; however, to date, no sex effect has been observed on the PK of olaparib [9]. Finally, the ECOG performance status of patients has been reported to affect the overall clearance of olaparib; patients with an ECOG performance status score of 1 and 2 were estimated to exhibit decreased olaparib clearance by 24.0% and 58.5%, respectively, when compared with patients with an ECOG performance status score of 0 [9]. In the current study, there were some slight variations in the number of patients who had an ECOG performance status of 0 and 1 between the groups, and this may have therefore affected the overall olaparib clearance.

5 Conclusions

In our study, patients with mild renal impairment receiving olaparib tablets had a small increase in olaparib exposure, which was not considered clinically relevant. The safety profile was also consistent with that observed in patients with normal renal function. No new safety signals were detected in patients with moderate renal impairment; however, exposure (AUC) to olaparib was increased by 44%. To address this, patients with moderate renal impairment should be closely monitored, particularly for haematological toxicities, and should receive a dose reduction from 300 mg bid (2 × 150 mg tablets) to 200 mg bid (2 × 100 mg tablets). Olaparib is not recommended in patients with severe renal impairment or end-stage renal disease because safety and PK have not been studied in these patients.

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Compliance with Ethical Standards

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Conflict of interest Christian Rolfo has received research grants from OncoDNA and consulting fees/honorarium from Mylan, and has participated in speaker bureaus for MSD, Novartis and Guardant Health. Judith de Vos-Geelen, Nicolas Isambert, L. Rhoda Molife, Peter Grundtvig-Sørensen, Karin Leunen, Ruth Plummer, Luc Dirix and Alain Ravaud have no conflicts of interest that are directly relevant to the content of this article. Jan H.M. Schellens is employed by and holds stock in Modra Pharmaceuticals, has a patent with oral taxanes and has a consultancy with Debiopharm. Morten Mau-Sørensen has received a research grant from AstraZeneca. Jacques De Grève has received a research grant from AstraZeneca, has attended advisory boards for AstraZeneca and is a board member of the AstraZeneca Foundation in Belgium. Guy Jerusalem has received research grants from Roche and Novartis, and consulting fees/honorarium from Novartis, Celgene, Roche, Amgen, Pfizer, Bristol-Myers Squibb, Lilly, Puma Biotech, AstraZeneca, Daiichi Sankyo and AbbVie. Maria Learoyd and Anitra Fielding are employees of, and hold stock in AstraZeneca. Wendy Bannister is a contractor for AstraZeneca.

Ethics 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 was obtained from all individual participants included in the study.

Data accessibility Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data sharing policy

described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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