An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib

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ABSTRACT

Purpose: Olaparib is poorly soluble and requires advanced drug delivery technologies to achieve adequate bioavailability. Using a capsule (CAP) formulation, 16 CAP/day are required to deliver the approved dose of 400 mg BD; a tablet (TAB) formulation was developed to reduce pill burden. This clinical trial evaluated the optimal dose and administration schedule of the TAB formulation.

Experimental design: The study sequentially enrolled cohorts into two stages; stage 1, the pharmacokinetic properties of the TAB and CAP formulation were compared in patients with advanced solid tumors; stage 2, dose-escalation (TAB) with expansion cohorts at doses/schedules of interest was performed in patients with solid tumors, focusing on germline *BRCA1/2* mutation carriers with breast and ovarian cancers.

Results: Olaparib 200 mg TAB resulted in similar $C_{max,ss}$ but lower AUC_{ss} and $C_{min,ss}$ than the approved CAP dose. Following multiple dosing, steady-state exposure with TAB doses ≥300 mg matched or exceeded that of 400 mg CAP. After dose-escalation, while 400 mg BD was the TAB MTD based on hematological toxicity during the DLT observation period, 65% of patients eventually required dose reduction to 300 mg. Preliminary data on tumor shrinkage was similar between the 300 and 400 mg TAB, and 400 mg CAP cohorts. Alternative schedules of TAB, including intermittent administration, did not significantly improve tolerability.

Conclusions: The two formulations are not bioequivalent. Olaparib 300 mg BD was the recommended monotherapy dose of olaparib TAB for investigation in Phase III clinical trials, simplifying drug administration from 16 capsules to four tablets per day.

Word count: 249 (max 250)

STATEMENT OF TRANSLATIONAL RELEVANCE

An alternative tablet (TAB) formulation of the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib with improved bioavailability has been developed to facilitate olaparib administration to patients. Prior clinical trials using the original capsule (CAP) formulation of olaparib reported a direct association between dose and antitumor activity in germline *BRCA* mutation carriers. Therefore, it is critical to evaluate drug administration strategies; this adaptive study was performed to select the optimal dose of olaparib TAB formulation to use in randomized studies in ovarian cancer, assessing PK, tolerability and antitumor activity. Additionally, the study explored the potential for alternative schedules of olaparib TAB administration to assess the impact on tolerability. Our multi-stage trial showed that patients' exposure following tablet doses ≥300 mg BD matched or exceeded that of the approved olaparib 400 mg BD CAP dose; 300 mg BD TAB was better tolerated than higher doses, without apparently compromising antitumor activity of the agent.

Word count: 150 (120–150 words)

INTRODUCTION

Poly-(ADP-ribose) polymerases (PARPs) are a family of enzymes with a key role in detecting DNA damage and triggering the activation of DNA repair pathways. Two seminal publications laid down the foundation for the clinical development of PARP inhibitors in cancer medicine: silencing of PARP-1 with siRNA was shown to result in selective killing of *BRCA*1/2-deficient cell lines, and selective antitumor activity in *BRCA2*-deficient preclinical models was demonstrated (1, 2). These findings presented clinicians with an opportunity to exploit the biological concept of synthetic lethality in anticancer treatments, as individuals carrying *BRCA* mutations (*BRCA*m) account for 15% of cases of high-grade serous ovarian carcinoma (3, 4) and 10–20% of cases of triple-negative breast cancer (5, 6) (defined as estrogen receptor-, progesterone receptor-, and HER2-negative tumors).

A proof-of-concept clinical trial of olaparib (Lynparza™), a potent oral inhibitor of PARP1 and PARP2, comprising a dose-escalation and expansion phase (enriched for *BRCA1/2*m carriers), established 400 mg capsule [CAP] formulation twice daily (BD) as the maximum tolerated CAP dose (7). Drug exposure was shown to increase proportionally with doses up to 100 mg BD, with a less marked increase above this threshold. In parallel, a plateau on pharmacodynamic (PD) effects was observed at doses over 60 mg BD. However, data from further non-randomized clinical trials in *BRCA*m carriers with breast and ovarian cancer suggested a dose-response relationship, supporting the use of the maximum tolerated dose (MTD) of olaparib over a minimal biologically effective dose (8-10).

Subsequent Phase II studies of olaparib confirmed a greater selective and sustained antitumor response in patients with germline *BRCA*m (g*BRCA*m) high-grade serous epithelial ovarian cancer (8, 10), breast and other tumor types (9, 11). Antitumor activity of olaparib has also been observed in sporadic cancers (12). The term ‘BRCAness’ is used to refer to those tumors with BRCA-like genomic or post-transcriptional aberrations, raising the likelihood of a wider application of PARP inhibitors (13-15) beyond tumors associated with *BRCA*m. In a randomized Phase II study in patients with platinum sensitive recurrent ovarian cancer, olaparib improved progression-free survival (PFS) when given as maintenance therapy in patients responding to platinum-based chemotherapy (16, 17). This study led to marketing authorization of olaparib CAP in 2014 by the

European Medicines Agency as maintenance therapy for adult patients with platinum-sensitive relapsed *BRCA*m high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who have demonstrated a response to platinum-based chemotherapy. In parallel, the US Food and Drug Administration approved olaparib CAP as the first monotherapy for patients with g*BRCA*m advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy. Phase III trials to define the role of olaparib in ovarian cancer are ongoing. In order to receive the 400 mg BD CAP dose, patients are required to take 8 x 50 mg large size 0 capsules twice daily. To improve the dosing constraints of the CAP formulation, a melt-extrusion tablet (TAB) formulation with improved bioavailability has been developed.

We report the results of an open-label, multicenter, multi-stage Phase I trial comparing the pharmacokinetics (PK) of the two formulations of olaparib and evaluate the tolerability of different doses and alternative scheduling of the TAB formulation in g*BRCA*m carriers in order to aid selection of an optimal dosing strategy.

PATIENTS AND METHODS

STUDY DESIGN

This was a Phase I study conducted in two sequential stages (Stages 1 and 2; Figure 1; ClinicalTrials.gov NCT00777582, AstraZeneca code D0810C00024 [Study 24]). Stage 1 was a randomized, 2-period crossover design to determine the comparative bioavailability of the two formulations (Bioavailability assessment; patients could then enter a continued supply phase [CSP; Cohorts 1–3]) followed by a dose-expansion phase (Groups 1–2) to validate PK modeling and determine steady-state PK. Stage 2 determined the MTD and optimum schedule of the tablet formulation (using dose-expansion and dose-escalation, Groups 1–5.2; dose-expansion, randomized TAB/CAP comparison, Group 6; dose-expansion, randomized TAB alternative dosing schedules, Group 8).

The institutional review boards/independent ethics committees of the ten investigational sites approved the protocol. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca policy on bioethics (18).

Stage 1 Bioavailability assessment: Stage 1 was an open-label, randomized, two-period crossover phase in patients with advanced solid tumors to study olaparib PK. Patients were randomized to two treatment periods of olaparib CAP and TAB, separated by a washout period of 6–14 days to study the PK profile of olaparib at different dose levels of the two formulations (Figure 1). On completion of this Bioavailability assessment, patients could enter a CSP, where they received olaparib 400 mg BD CAP until disease progression, unacceptable toxicity or withdrawal of consent. Based on an estimate of intra-subject variability following CAP dosing, a sample size of six patients for each dose level was expected to produce a 90% confidence interval (CI) of 1.61–2.49 for the comparative bioavailability assessment. PK modeling and simulation of data from this part of the study was performed to select a TAB dose which would be expected to have comparable steady state C_{max} and AUC to the 400 mg BD CAP dose.

Once the TAB dose was determined, a dose-expansion phase was initiated to validate PK modeling for the selected TAB and 400 mg BD CAP (Group 1). A

second group of six patients (Group 2) were randomly assigned to one of two treatment sequences: selected TAB dose BD days 1–8 followed by 400 mg BD CAP days 9–15 or vice versa. After day 15, all patients received 200 mg BD TAB until treatment discontinuation.

The primary objectives of Stage 1 were to: determine the comparative bioavailability of the TAB and CAP formulations and to compare safety and tolerability of the two formulations (Group 1). Secondary objectives were to: generate single-dose PK data and information on dose linearity of the TAB formulation; describe the preliminary efficacy of the TAB and CAP formulations (Group 1); and compare the steady-state exposure achieved with olaparib 200 mg BD TAB and 400 mg BD CAP (Group 2).

Stage 2 Dose-schedule optimization: Data from Stage 1 indicated that higher TAB doses should be explored. The protocol was therefore amended to include a second stage with a rolling dose-escalation design (Groups 3–5.2). The MTD was defined as the maximum dose that did not result in DLTs in ≥33% of patients.

Following completion of dose-escalation, a randomized safety and efficacy comparison between the selected TAB dose levels and the original CAP regimen was conducted in patients with confirmed g*BRCA1/2*m breast or ovarian cancer (Group 6).

To further assess tolerability and scheduling of the higher total daily doses, the protocol was amended to recruit patients with *gBRCA*m ovarian cancer in a further randomized group using alternative schedules of TAB (Group 8). Patients were randomized 1:1:1:1 to Schedule A: 200 mg three times daily (TID); Schedule B: 250 mg TID, 2 weeks on, 1 week off; Schedule C: 400 mg BD 1 week on, 1 week off; or Schedule D: 400 mg once daily (QD).

Primary objectives of Stage 2 were to: determine the safety and tolerability profile of doses higher than 200 mg BD TAB (Groups 3–5.2); compare the safety of higher TAB doses with 400 mg CAP dose in patients with *gBRCA1/2*m breast or ovarian cancer (Group 6); and determine the safety and tolerability of alternative TAB schedules in patients with *gBRCA1/2*m breast or ovarian cancer (Group 8). Secondary objectives were to: determine single-dose and steady-state exposures

with higher doses and selected schedules of TAB (Groups 3–5, and 8); compare single and steady-state exposures of TAB with 400 mg CAP; and describe efficacy in patients treated with TAB or CAP (Groups 6 and 8).

PATIENTS

Key patient eligibility criteria were: age ≥18 years; advanced solid tumors for which no effective treatment was available; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; adequate bone marrow (hemoglobin ≥9.0 g/dL, platelet count ≥100x10^9/L, white blood cells >3x10^9/L), renal (serum creatinine ≤1.5x ULN), and hepatic (total bilirubin ≤1.5x upper limit of normal [ULN]; aspartate transaminase [AST]/alanine transaminase [ALT] ≤2.5x ULN, unless liver metastases were present, in which case ≤5x ULN) function; a full list of eligibility criteria is available in Supplemental Table 1. After protocol amendments, Group 8 required ECOG PS 0–1 and baseline hemoglobin ≥10 g/L, independent of blood transfusion, within 4 weeks of randomization.

Groups 1 and 6 exclusively recruited patients with *gBRCA1/2*m breast or ovarian cancer. Group 8 was limited to *gBRCA1/2*m patients with ovarian, primary peritoneal or fallopian tube cancer. Patients in these groups were required to have at least one measurable lesion.

Supplemental Table 1. Patient inclusion and exclusion criteria

Patients had to fulfill the following criteria for inclusion into the study:	The following were regarded as a criteria for exclusion from the study:
>18 years of age and have a life expectancy ≥16 weeks	Major surgery within 2 weeks of starting the study and patients must have recovered from any effects of any major surgery
Histologically confirmed malignant advanced solid tumour, which was refractory to standard therapies (except Group 8 patients who were not platinum refractory) or for which no suitable effective standard therapy existed. If a diagnosis based on a histological sample was not available, a diagnosis based on cytology was allowed for those tumour entities in which this method was a generally accepted alternative	Patients who received any chemotherapy, radiotherapy (except for palliative reasons), or any other anti-cancer therapy within 4 weeks from the last dose prior to study randomization (or a longer period depending on the defined characteristics of the agents used). Patients were allowed to continue the use of bisphosphonates for bone metastases, and corticosteroids provided the dose was stable before and during the study and these must have been started at least 4 weeks prior to the beginning of study treatment. Patients were allowed to continue on hormone replacement therapy and on Luteinizing Hormone-Releasing Hormone (LHRH)
ECOG Performance status 0–1 (Group 8 only), ECOG performance status 0–2 (all other groups)	Patients with symptomatic uncontrolled brain metastases
Patients must have had adequate organ and bone marrow function measured within 7 days prior to administration of study treatment as defined below: • Hemoglobin ≥10.0 g/dL and no blood transfusions in the 4 weeks prior to randomization (Group 8 only) ≥9.0 g/dL (all other groups) • Absolute neutrophil count (ANC) ≥1.5x10^9/L • No dysplastic features on peripheral blood smear (Group 8 only) • White blood cells (WBC) >3x10^9/L • Platelet count ≥100x10^9/L • Total bilirubin ≤1.5 x institutional upper limit of normal (ULN) • Aspartate transaminase (AST [SGOT])/Alanine transaminase (ALT [SGPT]) ≤2.5 x ULN unless liver metastases were present in which it must have been ≤5 x ULN • Serum creatinine ≤1.5 x ULN	Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection
	Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication
	Pregnant or breastfeeding women
	Immunocompromised patients, eg, patients who were known to be serologically positive for human immunodeficiency virus (HIV) and were receiving antiviral therapy
	Patients with known hepatic disease
	Persistent toxicities (CTCAE Grade 2 or greater) caused by previous cancer therapy (excluding alopecia)

Female patients must have had evidence of non-childbearing status: negative urine or serum pregnancy test within 7 days of study treatment for women of childbearing potential, or postmenopausal status	Treatment with any investigational product during the previous 14 days (or a longer period depending on the defined characteristics of the agents used)
Patients must have had solid tumors originating from the ovary or breast with a confirmed genetic BRCA1/2 mutation (Group 8 gBRCA ovarian [including primary peritoneal and fallopian tube] cancer patients only). The mutation must have been confirmed as a loss of function mutation ie, a known deleterious or suspected deleterious mutation (Groups 1, 6, 7 and 8)	Patients who were at the time of the study experiencing seizures or who were at the time of the study being treated with only anti-epileptics for seizures (use of antiepileptic drugs to control pain was allowed in patients not suffering from seizures) unless drug was excluded due to CYP3A4 induction
Patients must have had at least one lesion, not previously irradiated, that could be accurately measured as ≥10 mm in the longest diameter with spiral computed tomography (CT) scan or as ≥20 mm with conventional techniques (conventional CT or magnetic resonance imaging [MRI]) and which was suitable for accurate repeated measurements (Groups 1, 6, 7 and 8)	Patients who received the following classes of inhibitors of CYP3A4 (azole antifungals, macrolide antibiotics, protease inhibitors)
	Group 8 only: • Patients with myelodysplastic syndrome/acute myeloid leukemia • Patients who were platinum refractory • Patients who had previously received a PARP inhibitor

STUDY ENDPOINTS AND ASSESSMENTS

Study assessments included medical review, physical examination, vital signs and clinical laboratory tests. Assessments were performed weekly during the first 4 weeks and 4-weekly thereafter. All adverse events (AEs) were graded according to Common Toxicity Criteria for Adverse Events (CTCAE) v3.0. During TAB dose-escalation, DLT was defined as any of the following AEs occurring in the first 28 days of treatment and judged by the investigators to be related to olaparib: grade (G) 4 neutropenia lasting more than 5 days or associated with fever; G4 thrombocytopenia; G≥2 cardiac or neurologic toxicity; any AE that delayed the start of course 2 within 14 days of the planned date, or other G3–4 events, with the exception of fatigue, nausea and vomiting, diarrhea, myalgia or arthralgia, unless appropriate prophylactic or therapeutic measures have been administered. Guidelines for management of common toxicities were implemented at investigational sites, including uniform rules for dose modifications. Radiological assessments were performed every 8 weeks according to Response Criteria in Solid Tumors (RECIST) v1.0. Tumor shrinkage, objective response rate (ORR) and response rate in ovarian cancer were based on CA-125 (GCIG) and RECIST (19, 20).

PHARMACOKINETICS AND MODELLING ANALYSIS

Blood samples were collected at pre-specified times during Stage 1 and 2 of the study. Primary outcome variables to determine the comparative bioavailability of the TAB and CAP formulations were single-dose maximum plasma concentrations (C_{max}), area under the plasma concentration-time curve (AUC) and AUC to time (AUC_{0-t}). Single-dose PK parameters of time to maximum plasma concentration (t_{max}), oral clearance (CL/F), terminal half-life ($t_{½}$) and volume of distribution (V_{area}/F) were also determined. Multiple-dose PK parameters for Groups 1, 2 and 3–8, of the dose-escalation phase and randomized tablet formulations included assessment of AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$.

PK parameters for the comparative Bioavailability phase and Group 2 CAP/TAB crossover phase were generated using standard non-compartmental analysis. In addition, the PK data from the Bioavailability assessment cohorts were utilized to build a population PK model for olaparib by fitting a two-compartment model with first-order absorption, first-order elimination and a lag time to the data. The

population parameter and inter-individual variability estimates obtained from this model were used to predict the TAB dose which would be expected to deliver steady state plasma exposures within the range of those previously observed following dosing of the 400 mg BD CAP dose by simulating multiple-dose PK parameters ($C_{max,ss}$ and AUC_{ss}) following administration of the TAB formulation at doses of 1–250 mg BD for a 10,000 patient population. The steady-state C_{max} and AUC_{0-12} values obtained were compared with previously determined ranges of values following 400 mg BD CAP dosing, and the percentage of patients for whom values fell within these ranges was determined for each TAB dose. The TAB dose that was chosen for Groups 1 and 2 was a dose predicted to provide a $C_{max,ss}$ and AUC_{ss} that would be expected to be within the 400 mg CAP range for these parameters in 95% of patients dosed. In Stage 2 of the study (Groups 1 and 3–8), $C_{max,ss}$, $C_{min,ss}$ and AUC_{ss} at different doses and schedules of administration of the TAB formulation were determined following sparse PK sampling data which were analyzed using the same population PK model.

PHARMACODYNAMICS

Samples for assessment of PARP inhibition in peripheral blood mononuclear cells (PBMC) were collected from patients participating in Stage 1 of the study, in each of the single-dose treatment period at pre-dose and 3, 10 and 24 hours post-dose. Results of the PD analysis are provided in Supplemental Table 2.

Supplemental Table 2. Mean percentage inhibition of PARP-1 from baseline (± standard error) in peripheral blood mononuclear cell (PBMC) samples following administration of single oral doses of the tablet or capsule formulation (n=6 per cohort; Stage 1).

Time after dose (hrs)	Tablet formulation			Capsule formulation		
	25 mg dose	50 mg dose	250 mg dose	50 mg dose	100 mg dose	400 mg dose
3	49.4 ± 43.5	58.2 ± 22.0	22.4 ± 43.0	42.8 ± 282	66.9 ± 167	50.5 ± 274
10	69.9 ± 31.0	74.9 ± 55.0	89.4 ± 63.0	66.9 ± 331	55.7 ± 47.0	83.7 ± 28.0
24	39.0 ± 45.0	41.5 ± 174	46.2 ± 215	16.7 ± 402	83.6 ± 100	54.4 ± 256

Median PARP inhibition relative to baseline ranged 22–67% three hours after dosing, with maximum levels 10 hours post-dose.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the extent of exposure, AEs, DLTs

and percentage inhibition of PARP in PBMC. Single-dose PK, linearity, and comparative bioavailability of both formulations were assessed in patients enrolled in Stage 1.

Plasma concentration data, PK and PD parameters were summarized descriptively by dose level and formulation administered. Within each cohort, comparative bioavailability and 90% CIs were estimated using an analysis of variance with factors for patient, formulation and period.

A planned comparison of the preliminary data on antitumor activity in patients with ovarian cancer in Groups 1, 6 and 8 was conducted, based on an analysis of covariance (ANCOVA) of the percentage change in tumor size after 8 and 16 weeks of treatment, using comparator data from all ovarian patients receiving the CAP formulation. The ANCOVA models were adjusted for baseline tumor size, and additionally for Group 8, prior platinum chemotherapy status (with categories for resistant, sensitive and no prior platinum use/unknown) (21), number of prior chemotherapy regimens (discrete variable) and peritoneal involvement at baseline (as a dichotomous variable); the latter two variables were identified as possible prognostic factors based on exploratory analysis of data from the olaparib clinical program. At each time point (8 and 16 weeks), the least squares mean (LSM) difference in percentage change in tumor size is presented along with corresponding 2-sided 80% and 95% CIs, and 2-sided p-values. The statistical analysis was performed to determine whether the anti-tumor activity of a given TAB dose was considered non-inferior to the 400 mg BD CAP formation. Non-inferiority was defined as ruling out that a given TAB dose was not more than 20% worse than the 400 mg BD CAP in terms of average percentage change in tumor size. This difference was considered important, based on similar differences being observed in other Phase II studies comparing 100 mg and 400 mg CAP-based doses (8, 9). Therefore, ruling out a difference of 20% (based on a 1-sided 80% upper confidence limit of <20%) was used as a definition of similarity.

RESULTS

Patient characteristics

Between 2008–12, a total of 210 patients (87% female) were enrolled in the study, and 196 received treatment with olaparib. Twenty-seven patients were enrolled in Stage 1 and 183 in Stage 2, including 31 in dose-escalation. Patient characteristics are detailed in Table 1. All patients had metastatic or locally-advanced non-resectable disease at enrollment.

Table 1. Patient demographics and baseline characteristics

	Stage 1						Stage 2											
	Bioavailability assessment/CSP			Dose expansion			Dose expansion, dose-escalation					Dose expansion, randomized TAB/CAP comparison			Dose expansion, randomized TAB alternative dosing schedules			
	Cohort 1	Cohort 2	Cohort 3	Group 1		Group 2	Group 3	Group 4	Group 5	Group 5.1	Group 5.2	Group 6			Group 8			
	Single dose: 50 mg CAP, 25 mg TAB CSP: 400 mg BD CAP	Single dose: 100 mg CAP, 50 mg TAB CSP: 400 mg BD CAP	Single dose: 400 mg CAP, 250 mg TAB CSP: 400 mg BD CAP	200 mg BD TAB	400 mg BD CAP	200 mg TAB and 400 mg CAP – crossover[a]	250 mg BD TAB	300 mg BD TAB	350 mg BD TAB	400 mg BD TAB	450 mg BD TAB	300 mg BD TAB	400 mg BD TAB	400 mg BD CAP	200 mg TID TAB cont	250 mg TID TAB inter (2 weeks on, 1 week off)	400 mg BD TAB inter (1 week on, 1 week off)	400 mg OD TAB cont
Patients enrolled, n	6	6	6	13	11	9	6	6	6	7	6	66			16	15	16	15
Patients treated, n	6	6	6	13	11	9	6	6	6	6	6	18	17	18	16	15	16	15
Age (years), mean (SD)	61.2 (9.2)	57 (11.4)	53.8 (12.5)	59.1 (8.8)	50.9 (9.8)	58.3 (10.5)	53.2 (17)	56 (10)	49.3 (5.1)	53.4 (8.9)	57.5 (7.9)	55.8 (10.4)	54.2 (11)	52.5 (10.6)	55.6 (10.4)	53.1 (9.2)	54.5 (9.8)	54.5 (10.4)
Sex, n (%)																		
Female	4 (67)	2 (33)	3 (50)	13 (100)	10 (91)	8 (89)	6 (100)	5 (83)	6 (100)	5 (71)	6 (100)	18 (100)	17 (100)	18 (100)	16 (100)	15 (100)	16 (100)	15 (100)
Male	2 (33)	4 (67)	3 (50)	0	1 (9)	1 (11)	0	1 (17)	0	2 (29)	0	0	0	0	0	0	0	0
ECOG performance status, n (%)																		
0	3 (50)	5 (83)	4 (67)	8 (61)	5 (45)	4 (44)	5 (83)	4 (67)	4 (67)	3 (43)	5 (83)	9 (50)	3 (18)	11 (61)	11 (69)	7 (47)	9 (56)	11 (73)
1	3 (50)	1 (17)	2 (33)	4 (31)	6 (55)	5 (56)	1 (17)	1 (17)	2 (33)	3 (43)	1 (17)	7 (39)	12 (70)	7 (39)	5 (31)	8 (53)	7 (44)	4 (27)
2	0	0	0	1 (8)	0	0	0	1 (17)	0	1 (14)	0	2 (11)	2 (12)	0	0	0	0	0
Primary tumor location, n (%)																		
Ovarian[b]	1 (17)	2 (33)	2 (33)	9 (69)[e]	7 (64)	2 (22)	3 (50)	1 (17)	4 (67)	2 (29)	4 (67)	13 (72)	12 (71)	13 (72)	16 (100)	15 (100)	16 (100)	15 (100)
Breast	0	0	1 (17)	4 (31)	4 (36)	3 (33)	2 (33)	3 (50)	2 (33)	3 (43)	2 (33)	5 (28)	5 (29)	5 (28)	0	0	0	0
Colorectal	3 (50)	1 (17)	0	0	0	3 (33)	0	0	0	0	0	0	0	0	0	0	0	0
Pancreas	0	0	0	0	0	1 (11)	0	0	0	0	0	0	0	0	0	0	0	0
Lung	1 (17)	1 (17)	1 (17)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Prostate	0	1 (17)	0	0	0	0	0	1 (17)	0	0	0	0	0	0	0	0	0	0
Other	1 (17)	1 (17)	2 (33)	0	0	0	1 (17)	1 (17)	0	2 (29)	0	0	0	0	0	0	0	0
Prior chemotherapy regimes, n (%)																		
0	0	2 (33)	1 (17)	0	0	0	0	1 (17)	0	1 (14)	0	0	0	1 (6)	0	0	0	0
1	2 (33)	1 (17)	2 (33)	0	2 (18)	0	1 (17)	0	0	1 (14)	2 (33)	1 (6)	2 (12)	3 (17)	2 (13)	1 (7)	1 (6)	2 (13)
2	0	2 (33)	0	2 (15)	3 (27)	3 (33)	2 (33)	1 (17)	2 (33)	3 (43)	0	2 (11)	1 (6)	4 (22)	2 (13)	1 (7)	2 (13.5)	5 (33)
3	0	0	2 (33)	2 (15)	3 (27)	1 (11)	2 (33)	1 (17)	0	1 (14)	2 (33)	3 (17)	8 (47)	3 (17)	5 (31)	6 (40)	3 (19)	4 (27)
4	0	0	0	2 (15)	0	2 (22)	0	0	3 (50)	1 (14)	0	5 (28)	1 (6)	5 (28)	5 (31)	3 (20)	5 (31)	2 (13)
≥5	4 (67)	1 (17)	1 (17)	7 (54)	3 (27)	3 (33)	1 (17)	3 (50)	1 (17)	0	2 (33)	7 (39)	3 (18)	2 (11)	2 (13)	4 (27)	5 (31)	2 (13)
Median	5	2	2	6	3	4	3	4	4	2	3	4	3	3	3	3	4	3
BRCA mutation status, n (%)	NC	NC	NC			NC	NC	NC	NC	NC	NC							
BRCA1/2m				13 (100)	10 (91)							18 (100)	17 (100)	18 (100)	16 (100)	15 (100)	16 (100)	15 (100)
Negative				0	0							0	0	0	0	0	0	0
Unknown				0	1 (9)							0	0	0	0	0	0	0
Baseline hemoglobin CTCAE grade,[c] n (%)	CSP (400 mg BD CAP)																	
0	9 (53)			7 (58)	4 (57)		5 (83)	4 (57)	4 (67)	3 (50)	3 (50)	6 (33)	8 (47)	12 (67)	11 (69)	11 (73)	13 (81)	10 (67)

1 2	8 (47) 0	5 (42) 0	3 (43) 0		1 (17) 0	3 (43) 0	2 (33) 0	3 (50) 0	3 (50) 0	10 (56) 2 (11)	6 (35) 3 (18)	6 (33) 0	5 (31) 0	4 (27) 0	3 (19) 0	5 (33) 0
Patient demographic and baseline characteristic for ovarian cancer patients included in efficacy analyses																
Ovarian cancer patients only		8 (62)[e]	7 (64)							13 (72)	12 (71)	13 (72)	16 (100)	15 (100)	16 (100)	15 (100)
Platinum-sensitivity,[d] n (%) Sensitive Resistant No prior plat Unknown		NC	NC							3 (23) 7 (54) 1 (8) 2 (15)	6 (50) 5 (42) 0 1 (8)	7 (54) 6 (46) 0 0	6 (38) 10 (63) 0 0	4 (27) 11 (73) 0 0	5 (31) 11 (69) 0 0	9 (60) 6 (40) 0 0
BRCA mutation status, n (%) BRCA1/2m Negative Unknown		8 (100) 0 0	7 (100) 0 0							13 (100) 0 0	12 (100) 0 0	13 (100) 0 0	16 (100) 0 0	15 (100) 0 0	16 (100) 0 0	15 (100) 0 0

PKP, pharmacokinetic phase; CSP, continued supply phase; (%), percentage of patients treated with olaparib; NC, data not collected

[a]used to directly compare steady state CAP and TAB PK; [b]includes patients with primary peritoneal or fallopian tube tumor; [c]patients with a baseline value and at least one on-treatment value; percentages have been calculated using the number of patients at baseline; [d]assessed by the investigator; [e]one patient was mistratified as having a primary tumor location of breast cancer, when this should have been stratified as ovarian cancer. This patients was excluded from the ovarian cancer subset as this was based on randomization stratification data but included as ovarian in summaries of primary tumor location

Stage 1: Ovarian, breast and colorectal cancers were the most common tumor types treated (Table 1). Median time on treatment was 87 days for patients in the PKP/CSP (cohorts 1–3).

Stage 2: Patients in the dose-escalation (Groups 3–5.2; n=31) and expansion phase of Stage 2 (Groups 6 and 8; n=115) had ovarian (n=114) or breast (n=27) cancer, with the exception of five patients (n=1 each; metastatic castration-resistant prostate cancer, gastric cancer, leiomyosarcoma of the uterus, renal cell carcinoma, esophageal-gastric junction carcinoma). Sixty-two *gBRCA1/2*m patients with ovarian, primary peritoneal or fallopian tube cancer were randomized to receive the four alternative schedules of olaparib administration (Group 8). Patients in Groups 6 and 8 had a confirmed g*BRCA1/2*m; g*BRCA*m status for patients in Groups 1, 6 and 8 can be found in Supplemental Table 3.

Overall, 137 patients with serous (all grades) ovarian carcinoma, including primary peritoneal and fallopian tube adenocarcinoma, received olaparib. Platinum sensitivity status was available for patients in the randomized treatment Groups 6 and 8, of which 40/100 patients (40%) had platinum-sensitive disease, assessed by the investigator, at study entry. The median number of prior lines of chemotherapy ranged from 2 to 6 across cohorts.

Supplemental Table 3. Germline BRCA mutation status of patients in dose expansion Groups 1, 6 and 8.

Treatment group	Primary tumor location	BCRA mutation type		
		BRCA1	BRCA2	BRCA1 and BRCA2
Group 1				
200 mg TAB (n=13)	Ovary[a] (n=8)	4	2	2
	Breast (n=5)	2	1	2
400 mg CAP (n=11)	Ovary (n=7)	3	1	3
	Breast (n=4)[b]	0	3	0
Group 6				
300 mg TAB (n=18)	Ovary (n=13)	10	3	0
	Breast (n=5)	2	3	0
400 mg TAB (n=17)	Ovary (n=12)	9	3	0
	Breast (n=5)	3	2	0
400 mg CAP (n=18)	Ovary (n=13)	9	4	0
	Breast (n=5)	4	1	0
Group 8				
200 mg TID TAB cont (n=16)	Ovary (n=16)	11	3	2
250 mg TID TAB inter (n=15)	Ovary (n=15)	12	3	0
400 mg BD TAB inter (n=16)	Ovary (n=16)	13	3	0
400 mg OD TAB cont (n=15)	Ovary (n=15)	9	6	0

Cont = continuous dosing schedule; Inter = intermittent dosing schedule; CAP = capsule formulation; TAB = tablet formulation. [a]One patient was mistratified as having a primary tumour location of breast cancer, when this should have been stratified as ovarian cancer. This patients was excluded from the ovarian cancer subset as this was based on randomization stratification data but included as ovarian in summaries of primary tumor location; [b]*BRCA*m data missing for one patient with breast cancer receiving 400 mg CAP

Bioavailability assessment

Following PK analysis for single oral doses of 25 and 50 mg TAB in cohorts 1 and 2, a dose of 250 mg was selected for cohort 3, assuming that dose proportionality would occur at TAB doses >50 mg and expected exposures would not exceed those previously achieved following ≤600 mg of the CAP formulation (7).

In all three cohorts (1, 2 and 3; Table 2A, Figure 2), absorption was rapid, with maximum concentrations typically observed 0.5–2 hours after dosing for TAB (compared with 1–3 hours for CAP [50, 100 and 400 mg doses]). Following this peak, the plasma concentration time profiles at all dose levels declined biphasically with a terminal half-life ($t_{½}$) of between approximately 5–9 hours and no change in $t_{½}$ with increasing dose. The overall mean $t_{½}$ for TAB was 6.97 hours (standard deviation [SD] 1.06 hours). The mean (SD) apparent plasma clearance (CL/F) and volume of distribution was 5.42 (2.60) L/h and 54.9 (30.1) L, respectively. Exposure increased approximately dose proportionally, with geometric mean (gmean) C_{max} increasing 1.9- and 7.5-fold, and gmean AUC increasing 1.6- and 12.2-fold, respectively, for a 2- and 10-fold increase in dose.

The relative bioavailability of TAB doses compared with CAP was higher based on $C_{max,}$ however, AUC values were similar at the two lower TAB doses (Table 2A). Exposure following CAP dosing increased less than proportionally at doses >100 mg, and both C_{max} and AUC values were higher with the 250 mg TAB than with the comparative CAP dose (400 mg). Based on geometric LSM (glsmean) C_{max} and AUC ratios and 90% CI from the 18 patients in these three cohorts, the TAB and CAP formulations cannot be considered bioequivalent. Further PK modeling and simulation of data predicted that a TAB dose of 200 mg BD would deliver steady-state C_{max} and $AUC_{0–12}$ values within the range observed for patients receiving 400 mg BD of the CAP formulation. To validate these modeling results, six additional patients received 200 mg TAB and 400 mg CAP in a crossover design. Although gmean $C_{max,ss}$ was similar (8.02 and 8.10 µg/mL for 200 mg TAB and 400 mg CAP, respectively), gmean AUC_{ss} was ~20% lower (38.4 vs 48.5 µg.h/mL) and gmean $C_{min,ss}$ ~50% lower (0.68 vs 1.38 µg/mL) following 200 mg TAB. Bioavailability assessments are summarized in Table 2A.
Further assessment of steady-state PK was conducted during Stage 2; the 300 and 400 mg TAB BD dosing schedules in the expansion cohorts delivered gmean

$C_{max,ss}$, $C_{min,ss}$ and $AUC_{0–12,ss}$ which exceeded those achieved following the 400 mg BD CAP dose (Table 2B).

Table 2A. Pharmacokinetic parameters and relative bioavailability for olaparib following single dosing of CAP and TAB formulations in Cohorts 1 to 3 and following multiple doses of CAP 200 mg and TAB 200 mg in the pharmacokinetic comparison phase of Group 2.

	Olaparib dose and formulation groups					
	Cohort 1		**Cohort 2**		**Cohort 3**	
PK parameter	**25 mg TAB**	**50 mg CAP**	**50 mg TAB**	**100 mg CAP**	**250 mg TAB**	**400 mg CAP**
C_{max} (µg/ml), geometric mean (CV%)	1.17 (48)	1.82 (26)	2.22 (36)	2.90 (23)	8.81 (23)	5.67 (47)
t_{max} (h), median (range)	1.0 (0.5–3.0)	1.5 (1.0–3.0)	0.5 (0.5–2.0)	1.25 (1.0–2.0)	1.25 (1.0–4.0)	1.25 (1.0–8.0)
AUC (µg.h/ml), geometric mean (CV%)	5.15 (69)	10.0 (45)	8.34 (42)	16.9 (32)	63.0 (37)	57.9 (78)
Half-life (h), arithmetic mean (SD)	7.27 (0.79)	7.87 (1.71)	7.47 (1.01)	8.44 (2.94)	6.17 (0.88)	11.9 (4.82)
CL/F (l/h), arithmetic mean (SD)	5.65 (3.29)	5.38 (2.37)	6.42 (2.60)	6.18 (2.08)	4.19 (1.64)	8.64 (7.11)
V_{area}/F (l), mean (SD)	59.3 (36.3)	60.6 (31.3)	69.2 (31.2)	81.1 (49.8)	36.2 (10.7)	167 (196)
Relative bioavailability	25 mg TAB vs 50 mg CAP		50 mg TAB vs 100 mg CAP		250 mg TAB vs 400 mg CAP	
*C_{max} (95% CI)	1.29 (1.10–1.52)		1.53 (1.11–2.11)		2.49 (1.87–3.31)	
*AUC ratio (95% CI)	1.03 (0.85–1.24)		0.99 (0.69–1.42)		1.74 (1.36–2.23)	

	PK comparison phase of Group 2, 200 mg TAB and 400 mg CAP - crossover		
PK parameter	200 mg TAB	400 mg CAP	Ratio TAB:CAP
$C_{max,ss}$ (µg/ml), geometric mean (CV%)	8.02 (38)	8.10 (35)	0.991
AUC_{ss} (µg.h/ml), geometric mean (CV%)	38.36 (46)	48.48 (52)	0.791
$C_{min,ss}$ (µg/ml), geometric mean (CV%)	0.68 (86)	1.38 (101)	0.540

*C_{max} and AUC values were normalized for administered dose

Table 2B. Steady state pharmacokinetic parameters (Day 29) for olaparib following multiple dosing with the tablet and capsule during the efficacy expansion phase of Groups 1 and 6.

	Olaparib capsule and tablet dose during the dose expansion phase				
	Dose expansion 1 (Group 1)		Dose expansion 2 (Group 6)		
	200 mg BD TAB	**400 mg BD CAP**	**300 mg BD TAB**	**400 mg BD TAB**	**400 mg BD CAP**
Day 29*	(n=11)	(n=10)	(n=17)	(n=10)	(n=17)
$C_{max, ss}$ (µg/ml)	6.88 (4.01–10.4)	5.71 (2.38–10.9)	9.37 (2.28–14.7)	12.0 (8.45–16.9)	6.36 (3.88–13.3)
$C_{min, ss}$ (µg/ml)	1.00 (0.28–3.10)	1.86 (0.53–6.67)	1.84 (0.34–3.83)	2.01 (0.76–3.61)	1.04 (0.23–8.49)
$AUC_{0–12ss}$ (µg.h/ml)	36.1 (16.0–69.0)	43.1 (18.1–98.6)	58.4 (23.1–96.0)	72.8 (44.8–106)	41.5 (18.7–147)

*Only subjects remaining on the starting dose at Day 29 were included in the summary statistics. All data expressed as Gmean (CV [%]); CV, co-efficient of variation

SAFETY AND TOLERABILITY

Table 3 lists the median exposure to olaparib, the most commonly reported AEs and ≥G3 AEs for the dose-escalation and dose-expansion cohorts. Supplemental Table 4 summarizes hemoglobin toxicity for Groups 6 and 8.

During dose-escalation of TAB, the 450 mg BD dose level was deemed non-tolerable; G3 anemia occurred in 3/6 patients (50%), G3 thrombocytopenia in 1/6 patients (17%) and G3 neutropenia in 1/6 patients (17%); overall 5/6 patients (83%) required a dose reduction due to drug-related AEs. The 400 mg BD TAB dose was defined as the MTD for additional expansion cohorts.

Nausea and vomiting were the most commonly reported AEs in the dose-expansion and dose-escalation phases (reported in 84% [nausea] and 80% [vomiting] of patients in Groups 1, 3–6). The incidence of G3–4 anemia and thrombocytopenia was higher in the 400 mg BD group compared with the 300 mg BD group (30% vs 22%, and 18% vs 0%, respectively).

In 18 patients randomized to the approved 400 mg BD CAP regimen (Group 6), anemia was reported for 6/18 patients (33%; including four cases of ≥G3 anemia [22%]; G1–2 nausea occurred in 15/18 cases [83%] and vomiting in 5/18 patients [28%], including one G3 [5.6%]).

Eight patients in the dose-expansion required permanent discontinuation of olaparib due to an AE across dose levels. There were a total of seven deaths, all of which were related to the disease under investigation; three of these deaths had an intercurrent SAE (n=1 patient each; pneumocystis carinii pneumonia; intra-abdominal hemorrhage; small intestinal obstruction). The AE of pneumocystis carinii pneumonia was thought to be secondary to bone pancytopenia and was considered by the investigator to be related to olaparib.

When considering all patients who received 300 or 400 mg BD TAB (during dose-escalation and randomized expansion phases), 7/24 (29.2%) and 14/23 (61%) patients required at least one dose reduction due to AEs (mainly due to gastrointestinal toxicities, fatigue and anemia), respectively. Six patients who started at 400 mg TAB BD required ≥2 dose de-escalations; dose reductions

were more common during the first two cycles of therapy compared with other doses and CAP. Supplemental Table 5 summarizes drug interruptions and dose reductions for Groups 6 and 8. Median time on treatment for ovarian cancer patients receiving 400 mg TAB BD was 212 days, although the median duration of time that patients received the cohort starting dose of 400 mg TAB BD before requiring a dose modification was only 51 days.

Intermittent dosing (Group 8) did not affect patient adherence to treatment, and the mean compliance was between 94.6% and 97.4% across the schedules. For the alternative-scheduling cohorts (Group 8) the inclusion criteria were amended to restrict enrollment for patients with higher baseline hemoglobin (Supplemental Table 1), resulting in a lower incidence of anemia overall (12 cases, 19.4%) in comparison with the patients in the previous expansion cohorts (Groups 1 and 6; 22/64, 34.4%). Three and two cases of G3 anemia were observed in the intermittent and continuous dosing groups (3/31, 9.6%; 2/31, 6.4%), respectively.

The most common AEs observed in Group 8 were nausea and vomiting (reported in 82% and 68% of patients, respectively); all grade and ≥G3 AEs are summarized in Table 3. Intermittent administration of 400 mg BD led to G3 vomiting in 18.8% of cases (3/16 patients) while only one case was reported in each of the other dose schedules (6–7%). Moreover, the 400 mg BD intermittent dose level had the highest number of patients requiring dose reductions (6/16; 37.5%) due to AEs, compared with a range of 6.7–18.8% patients in the other dose schedules.

Table 3. Summary of actual treatment exposure and number (%) of patients who had at least one AE of any grade (≥ 20% incidence in any treatment group) and AEs of grade ≥3 (occurring in more than one patient) in the dose-expansion phase for Groups 1 (200 mg TAB and 400 mg CAP) and 6 and dose-escalation Groups 3, 4, 5, 5.1, 5.2 or for Group 8 (expansion phase, alternative dosing schedules) patients who had at least one AE of any grade (occurring in more than 3 patients in any treatment group) and AEs of grade ≥3 (occurring in more than one patient)

	Group 1				Group 3		Group 4		Group 5		Group 5.1		Group 5.2		Group 6					
	200 mg BD TAB		400 mg BD CAP		250 mg BD TAB		300 mg BD TAB		350 mg BD TAB		400 mg BD TAB		450 mg BD TAB		300 mg BD TAB		400 mg BD TAB		400 mg BD CAP	
	n=13		n=11		n=6		n=6		n=6		n=6		n=6		n=18		n=17		n=18	
Actual olaparib treatment exposure, days, median (range)	114 (0–844)		193 (34–416)		249.5 (22–551)		326.5 (50–491)		115.5 (8–380)		110.5 (44–196)		207 (57–240)		135 (53–281)		166 (17–281)		178 (62–277)	
AE, n (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE	13 (100)	5 (39)	10 (91)	2 (18)	6 (100)	1 (17)	6 (100)	4 (67)	6 (100)	2 (33)	6 (100)	5 (83)	6 (100)	4 (67)	18 (100)	11 (61)	17 (100)	10 (59)	18 (100)	7 (40)
Blood and lymphatic system disorders																				
Anemia	1 (8)	0	0	0	1 (17)	0	2 (33)	2 (33)	1 (17)	1 (17)	2 (33)	1 (17)	3 (50)	3 (50)	7 (39)	4 (22)	9 (53)	5 (30)	6 (33)	4 (22)
Neutropenia	0	0	0	0	0	0	1 (17)	0	0	0	1 (17)	1 (17)	1 (17)	1 (17)	3 (17)	2 (11)	1 (6)	0	2 (11)	1 (6)
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0	1 (17)	1 (17)	1 (6)	0	3 (18)	3 (18)	0	0
Gastrointestinal disorders																				
Abdominal pain	1 (8)	1 (8)	1 (9)	0	0	0	1 (17)	0	2 (33)	0	1 (17)	1 (17)	1 (17)	0	2 (11)	2 (11)	2 (12)	0	0	0
Constipation	7 (54)	0	1 (9)	0	3 (50)	0	1 (17)	0	1 (17)	0	3 (50)	0	2 (33)	0	4 (22)	0	1 (6)	0	2 (11)	0
Diarrhea	4 (31)	0	3 (27)	1 (9)	4 (67)	0	4 (68)	0	2 (33)	0	1 (17)	0	3 (50)	0	9 (50)	2 (11)	4 (24)	0	2 (11)	0
Dyspepsia	1 (8)	0	2 (18)	0	3 (50)	0	2 (33)	0	0	0	0	0	3 (50)	0	1 (6)	0	2 (12)	0	3 (17)	0
Nausea	10 (77)	1 (8)	7 (64)	1 (9)	5 (83)	0	5 (83)	0	5 (83)	0	6 (100)	0	5 (83)	0	13 (72)	0	15 (88)	2 (12)	15 (83)	0
Stomatitis	0	0	0	0	0	0	0	0	2 (33)	0	1 (17)	0	2 (33)	0	0	0	1 (6)	0	1 (6)	0
Vomiting	5 (39)	1 (8)	3 (27)	1 (9)	2 (33)	0	4 (67)	0	1 (17)	0	1 (17)	0	0	0	8 (44)	0	6 (35)	0	5 (28)	1 (6)

General disorders																			
Alopecia	0	0	1 (9)	0	0	0	0	0	1 (17)	0	0	0	2 (33)	0	1 (6)	0	1 (6)	0	1 (6)	0
Edema peripheral	1 (8)	0	1 (9)	1 (9)	1 (17)	0	0	0	2 (33)	0	1 (17)	0	2 (33)	0	4 (22)	0	1 (6)	0	1 (6)	0
Fatigue	9 (69)	5 (39)	5 (45)	1 (9)	5 (83)	0	6 (100)	0	3 (50)	0	5 (83)	2 (33)	4 (67)	0	13 (72)	3 (17)	14 (82)	2 (12)	9 (50)	0
Non-cardiac chest pain	1 (8)	1 (8)	0	0	0	0	2 (33)	0	0	0	0	0	0	0	1 (6)	0	2 (12)	0	0	0
Pyrexia	0	0	0	0	0	0	1 (17)	0	0	0	0	0	0	0	0	0	6 (35)	0	0	0
Infections																				
Lower respiratory tract infection	0	0	1 (9)	0	1 (17)	0	2 (33)	0	0	0	1 (17)	0	1 (17)	0	2 (11)	0	3 (18)	0	2 (11)	0
Urinary tract infection	2 (15)	0	1 (9)	0	1 (17)	0	0	0	0	0	1 (17)	0	0	0	7 (39)	0	3 (18)	0	2 (11)	0
Metabolism and nutritional disorders																				
Decreased appetite	7 (54)	1 (8)	3 (27)	0	2 (33)	0	2 (33)	0	1 (17)	0	3 (50)	0	1 (17)	0	9 (50)	0	5 (29)	0	8 (44)	0
Musculoskeletal disorders																				
Arthralgia	2 (15)	0	2 (18)	0	0	0	3 (50)	0	0	0	1 (17)	0	1 (17)	0	2 (11)	0	1 (6)	0	2 (11)	0
Back pain	5 (39)	1 (8)	3 (27)	0	1 (17)	0	1 (17)	0	0	0	0	0	1 (17)	0	3 (17)	0	4 (24)	0	2 (11)	0
Musculoskeletal chest pain	3 (23)	0	0	0	0	0	0	0	1 (17)	0	0	0	1 (17)	0	0	0	1 (6)	0	1 (6)	0
Musculoskeletal pain	0	0	1 (9)	0	0	0	1 (17)	0	0	0	0	0	2 (33)	0	2 (11)	0	3 (18)	1 (6)	0	0
Pain in extremity	2 (15)	0	1 (9)	0	0	0	1 (17)	0	0	0	2 (33)	0	0	0	0	0	1 (6)	0	1 (6)	0
Nervous system disorders																				
Dizziness	1 (8)	0	1 (9)	0	0	0	1 (17)	0	0	0	2 (33)	0	0	0	2 (11)	0	1 (6)	0	0	0
Dysgeusia	0	0	0	0	1 (17)	0	2 (33)	0	0	0	0	0	1 (17)	0	6 (33)	0	3 (18)	0	2 (11)	0
Headache	1 (8)	0	0	0	1 (17)	0	1 (17)	0	1 (17)	0	2 (33)	0	3 (50)	0	2 (11)	0	1 (6)	0	2 (11)	0
Paresthesia	1 (8)	0	1 (9)	0	0	0	0	0	1 (17)	0	0	0	2 (33)	0	0	0	0	0	1 (6)	0
Renal and urinary disorders																				
Pollakiuria	0	0	0	0	0	0	2 (33)	0	0	0	0	0	0	0	1 (6)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders																				

Cough	5 (39)	0	1 (9)	0	2 (33)	0	1 (17)	0	1 (17)	0	1 (17)	0	0	0	3 (17)	0	2 (12)	0	2 (11)	0
Dyspnoea	2 (15)	1 (8)	2 (18)	1 (9)	0	0	1 (17)	0	0	0	1 (17)	0	1 (17)	1 (17)	5 (28)	0	4 (24)	1 (6)	4 (22)	0
Dyspnea exertional	1 (8)	0	0	0	0	0	0	0	0	0	1 (17)	0	2 (33)	0	2 (11)	0	1 (6)	0	1 (6)	0

	Olaparib randomized tablet formulation for Group 8							
	200 mg TID TAB cont		**250 mg TID TAB inter (2 weeks on, 1 week off**		**400 mg BD TAB inter (1 week on, 1 week off)**		**400 mg OD TAB cont**	
	n=16		**n=15**		**n=16**		**n=16**	
Actual olaparib treatment exposure, median (range)	164 (4–390)		221 (5–413)		271 (58–366)		211 (26–463)	
AE, n (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE	15 (94)	6 (38)	15 (100)	7 (47)	16 (100)	6 (38)	14 (93)	5 (33)
Blood and lymphatic system disorders								
Anemia	3 (19)	1 (6)	5 (33)	3 (20)	1 (6)	0	3 (20)	1 (7)
Thrombocytopenia	0	0	2 (13)	2 (13)	0	0	0	0
Gastrointestinal disorders								
Abdominal pain	3 (19)	0	4 (27)	1 (7)	6 (38)	1 (6)	3 (20)	2 (13)
Constipation	2 (13)	0	6 (40)	0	6 (38)	0	7 (47)	0
Diarrhea	2 (13)	1 (6)	2 (13)	0	9 (56)	1 (6)	3 (20)	0
Nausea	13 (81)	0	12 (80)	1 (7)	13 (81)	2 (13)	10 (67)	0
Small intestinal obstruction	0	0	1 (7)	0	0	0	2 (13)	2 (13)
Vomiting	8 (50)	1 (6)	10 (67)	1 (7)	12 (75)	3 (19)	6 (40)	1 (7)

General disorders								
Fatigue	8 (50)	2 (13)	8 (53)	0	10 (63)	1 (6)	10 (67)	0
Gamma-glutamyltransferase increased	0	0	0	0	0	0	2 (13)	2 (13)
Infections								
Urinary tract infection	0	0	0	0	2 (13)	0	4 (27)	0
Metabolism and nutritional disorders								
Decreased appetite	4 (25)	1 (6)	6 (40)	0	5 (31)	0	5 (33)	0
Musculoskeletal disorders								
Arthralgia	2 (13)	0	0	0	4 (25)	0	3 (20)	0
Nervous system disorders								
Dysgeusia	5 (31)	0	2 (13)	0	4 (25)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	1 (6)	0	1 (7)	0	3 (19)	0	4 (27)	0
Dyspnoea	0	0	2 (13)	0	4 (25)	0	1 (7)	0

Supplemental Table 4. Summary of hematological toxicity – hemoglobin (g/l), neutrophils (109/l) and platelets (109/l) maximum overall CTCAE grade change during treatment for Groups 6 and 8

Group/treatment	Baseline CTCAE grade* Total	Patients at baseline with one on-treatment measurement, n (%)†	Patients with maximum overall CTCAE grade during treatment, n (%)‡		
			Grade ≤2	Grade 3	Grade 4
Group 6					
300 mg BD TAB	**Hemoglobin**				
	0	6 (33.3)	5 (27.7)	1 (5.6)	0
	1	10 (55.6)	8 (44.4)	1 (5.6)	1 (5.6)
	2	2 (11.1)	1 (5.6)	0	1 (5.6)
	Total	18 (100)	14 (77.7)	2 (11.1)	2 (11.1)
400 mg BD TAB	**Hemoglobin**				
	0	8 (47.1)	4 (23.5)	2 (11.8)	2 (11.8)
	1	6 (35.3)	5 (29.4)	1 (5.9)	0
	2	3 (17.6)	2 (11.8)	1 (5.9)	0
	Total	17 (100)	11 (64.7)	4 (23.5)	2 (11.8)
400 mg BD CAP	**Hemoglobin**				
	0	12 (66.7)	11 (61.1)	1 (5.6)	0
	1	6 (33.3)	5 (27.7)	1 (5.6)	0
	Total	18 (100)	16 (88.8)	2 (11.1)	0
Group 8					
200 mg TID TAB Cont	**Hemoglobin**				
	0	11 (68.8)	10 (90.9)	1 (6.3)	0
	1	5 (31.3)	5 (31.3)	0	0
	Total	16 (100)	15 (93.7)	1 (6.3)	0
250 mg TID TAB Inter	**Hemoglobin**				
	0	11 (73.3)	11 (73.3)	0	0
	1	4 (26.7)	3 (20.0)	1 (6.7)	0
	Total	15 (100)	14 (93.3)	1 (6.7)	0
400 mg BD TAB inter	**Hemoglobin**				
	0	13 (81.3)	13 (81.3)	0	0
	1	3 (18.8)	3 (18.8)	0	0
	Total	16 (100)	16 (100)	0	0
400 mg TID TAB Cont	**Hemoglobin**				
	0	10 (66.7)	10 (66.7)	0	0
	1	5 (33.3)	5 (33.3)	0	0
	Total	15 (100)	15 (100)	0	0

*Baseline was defined as the last result obtained prior to the start of olaparib.

†Patients with a baseline value and at least one on-treatment value; percentages have been calculated using the number of patients at baseline.
‡Derived from lab assessments between the start of treatment and 30 days following the date of last dose of olaparib.
Cont = continuous dosing schedule; Inter = intermittent dosing schedule; CAP = capsule formulation; TAB = tablet formulation

Supplemental Table 5. Summary of number (%) of patients with interruptions and dose reductions of olaparib due to adverse events for Groups 6 and 8

		Number of patients with an interruption					Number of patients with a dose reduction					Total number of patients with a dose interruption and/or reduction				
	n	Total	1	2	≥3	AE	Total	1	2	≥3	AE	Total	1	2	≥3	AE
Group 6																
300 mg BD TAB	18	8 (44.4)	3 (16.7)	2 (11.1)	3 (16.7)	7 (38.9)	4 (22.2)	3 (16.7)	0	1 (5.6)	4 (22.2)	9 (50.0)	2 (11.1)	3 (16.7)	4 (22.2)	8 (44.4)
400 mg BD TAB	17	10 (58.8)	5 (29.4)	4 (23.5)	1 (5.9)	10 (58.8)	11 (64.7)	7 (41.2)	2 (11.8)	2 (11.8)	11 (64.7)	13 (76.5)	4 (23.5)	2 (11.8)	7 (41.2)	13 (76.5)
400 mg BD CAP	18	6 (33.3)	3 (16.7)	2 (11.1)	1 (5.6)	3 (16.7)	3 (16.7)	3 (16.7)	0	0	3 (16.7)	8 (44.4)	4 (22.2)	3 (16.7)	1 (5.6)	6 (33.3)
Group 8																
200 mg TID TAB cont	16	13 (81.3)	2 (12.5)	4 (25.0)	7 (43.8)	7 (43.8)	4 (25.0)	3 (18.8)	1 (6.3)	0	3 (18.8)	13 (81.3)	2 (12.5)	2 (12.5)	9 (56.3)	7 (43.8)
250 mg TID TAB inter	15	11 (73.3)	1 (6.7)	2 (13.3)	8 (53.3)	7 (46.7)	2 (13.3)	2 (13.3)	0	0	1 (6.7)	11 (73.3)	1 (6.7)	2 (13.3)	8 (53.3)	7 (46.7)
400 mg BD TAB inter	16	16 (100)	6 (37.5)	3 (18.8)	7 (44.0)	8 (50.0)	6 (37.5)	5 (31.3)	0	1 (6.3)	6 (37.5)	16 (100)	4 (25.0)	5 (31.3)	7 (43.8)	8 (50.0)
400 mg OD TAB cont	15	7 (46.7)	3 (20.0)	2 (13.3)	2 (13.3)	5 (33.3)	2 (13.3)	1 (6.7)	0	1 (6.3)	2 (13.3)	7 (46.7)	3 (20.0)	2 (13.3)	2 (13.3)	5 (33.3)

*Received planned starting dose in the CSP
†Received planned starting dose in the CSEP.
Interruptions and reductions are only summarized for the CSP phase/continuous dose phase of the CSEP.
Cont = continuous dosing schedule; Inter = intermittent dosing schedule

ANTITUMOR ACTIVITY IN g*BRCA*m CARRIERS AND SEROUS OVARIAN CARCINOMA [Note to Prof Friedlander: I have not included high-grade in this title as we do not have data to confirm which grade of serous cancer patients had]

A total of 53 g*BRCA*m carriers with serous ovarian carcinoma were enrolled at the different expansion cohorts (Groups 1 and 6) of the study at either 200 mg BD TAB (n=8), 300 mg BD TAB (n=13), 400 mg BD TAB (n=12), 400 mg BD CAP (n=20). Data on platinum sensitivity were available for patients in Group 6 (Table 1).

The radiological ORR in g*BRCA*m carriers with serous ovarian carcinoma was 30% (16/53, 95% CI 18.3%, 44.3%) across cohorts, although it appeared higher for patients receiving 300 mg TAB BD (5/13, 38%, 95% CI 13.9%, 68.4%) and 400 mg TAB BD (5/12, 42%, 95% CI 15.2%, 72.3%). The RR based on either a RECIST response and/or CA-125 was 40% (21/53, 95% CI 26.5%, 54.0%).

Supplemental Tables 6 and 7 compare the antitumor activity in patients with ovarian cancer treated at different dose levels or schedules, based on the ANCOVA of the percentage change in tumor size after 8 and 16 weeks of treatment. The one-sided upper limit of the 80% CI was below the pre-specified criteria of 20% compared with the original formulation (400 mg BD CAPS) for both groups at 300 mg BD TAB (LSmean change in tumor size at week 8: 1.8%, 1-sided 80% UCL 12.1) and 400 mg BD TAB (LSmean change in tumor size at week 8: –10.5%, 1-sided 80% UCL 0) indicating similar efficacy. However, the 200 mg BD CAP dose failed to meet the criteria to be considered similar to 400 mg BD CAPS (difference in LSmeans at week 8: 8.6%, 1-sided 80% UCL 21.1). Consistent results were obtained after 16 weeks of therapy (Supplemental Tables 6, 7 and Supplemental Figure 1).

Comparison of change in tumor size for patients receiving 400 mg BD CAP with the patients participating in the alternative-scheduling cohorts (Group 8) shows that only 200 mg TID continuous and 400 mg BD intermittent dose schedules fulfilled the predefined criteria to be considered non-inferior to 400 mg BD CAP (Supplemental Table 7, Supplemental Figure 1).

Supplemental Table 6. Analysis of percentage change in tumor size at Week 8 and Week 16 – dose expansion Group 1 and Group 6 – patients with ovarian cancer

	Group 1		Group 6		
	200 mg BD TAB (n=8)	**400 mg BD CAP (n=7)**	**300 mg BD TAB (n=13)**	**400 mg BD CAP (n=13)**	**400 mg BD TAB (n=12)**
Week 8					
Unadjusted mean*	–3.7%	–12.4%	–16.8%	–17.0%	–28.7%
LS mean†	–3.7%	–12.4%	–16.1%	–17.9%	–28.4%
Treatment effect†					
Difference in LS means	8.6%		1.8%		–10.5%
80% CI	–10.7, 28.0		–14.0, 17.6		–26.6, 5.6
95% CI	–22.5, 39.8		–22.8, 26.4		–35.5, 14.6
2-sided p-value	0.557		0.881		0.401
1-sided 80% UCL	21.1		12.1		0.0
Week 16					
Unadjusted mean*	–2.0%	–15.3%	–11.5%	–16.3%	–26.6%
LS mean†	–1.9%	–15.2%	–10.6%	–17.6%	–26.2%

Treatment effect[†]			
Difference in LS means	17.1%	7.0%	–8.6%
80% CI	–9.8, 44.1	–16.1, 30.0	–32.1, 14.9
95% CI	–26.2, 60.5	–28.9, 42.8	–45.1, 28.0
2-sided p-value	0.406	0.696	0.637
1-sided 80% UCL	34.5	22.0	6.8

*Imputed values at Week 8/Week 16 included; [†]Adjusted for baseline tumour size
CAP = capsule formulation; TAB = tablet formulation; LS = least squares; CI = confidence interval; UCL = upper confidence limit

Supplemental Table 7. Analysis of percentage change in tumor size at Week 8 and Week 16 – Randomized dose expansion Groups 1, 6 and Group 8 – patients with ovarian cancer

	Group 1 and 6	Group 8			
	400 mg BD CAP cont (n=20)	200 mg TID TAB cont (n=15)	250 mg TID TAB inter (2 weeks on, 1 week off (n=14)	400 mg BD TAB inter (1 week on, 1 week off) (n=16)	400 mg OD TAB cont (n=15)
Week 8					
Unadjusted mean	–15.4%	–17.8%	–5.1%	–15.8%	–9.0%
LS mean	–19.35%	–16.4%	–5.4%	–14.8%	–3.4%
Treatment effect versus 400 mg BD CAP*					
Difference in LS means		2.91%	13.9%	4.6%	15.9%
80% CI		–9.1, 14.9	1.2, 26.7	–7.6, 16.8	3.6, 28.3
95% CI		–15.6, 21.4	–5.7, 33.6	–14.1, 23.4	–3.1, 34.9
2-sided p-value		0.756	0.162	0.627	0.099
1-sided 80% UCL		10.8	22.3	12.6	24.0
Week 16					

Unadjusted mean	–15.9%	–12.8%	–7.2%	–14.4%	–11.3%
LS mean	–19.7%	–10.6%	–9.1%	–14.3%	–3.3%
Treatment effect versus 400 mg BD CAP*					
Difference in LS means		9.1%	10.6%	5.4%	16.4%
80% CI		–8.5, 26.7	–8.0, 29.2	–12.5, 23.2	–1.7, 34.4
95% CI		–18.0, 36.2	–18.1, 39.3	–22.1, 32.8	–11.4, 44.1
2-sided p-value		0.507	0.465	0.699	0.245
1-sided 80% UCL		20.6	22.8	17.0	28.2

*Data from the 400 mg BD capsule arm from ovarian cancer patients in Groups 1 and 6 have been combined to use as a comparator in analyses
Analysis for Group 8 was performed using an analysis of covariance with factors for treatment group, baseline sum of target lesions, prior platinum chemotherapy status, number of prior chemotherapy regimens and whether there was peritoneal involvement at baseline.
CAP = capsule formulation; TAB = tablet formulation; LS = least squares; CI = confidence interval; UCL = upper confidence limit

DISCUSSION

This adaptive trial was planned as a comparative bioavailability study with the objective of selecting optimal dosing of a TAB formulation of olaparib, in order to simplify drug administration for patients. Prior clinical trials using the original CAP formulation of olaparib reported a direct association between dose and antitumor activity in germline *BRCA* mutation carriers (8-10). To determine the most appropriate TAB dose, a comparison of olaparib TAB bioavailability, efficacy, and safety compared with the 400 mg CAP BD was required. This study determined that olaparib 300 mg BD TAB was defined as the recommended TAB monotherapy dose for further investigation in Phase III clinical trials of olaparib.

PK modeling using data obtained from the Bioavailability assessment of the study predicted that a 200 mg BD TAB dose would deliver multiple-dose exposure within the range of exposures previously seen following 400 mg BD CAP dose (7). However, the direct intra-subject comparison of steady-state exposure that could be made for the six patients treated at 200 mg, showed that although the gmean $C_{max,ss}$ achieved following these doses of the two formulations were similar, the gmean AUC_{ss} and gmean $C_{min,ss}$ were, approximately 20 and 50% lower following the TAB dose, respectively. Consequently, Stage 2 of the study was pursued to assess both tolerability and antitumor activity of higher doses of the TAB formulation.

The dose-escalation phase established 400 mg BD TAB as the MTD based on hematological toxicities at 450 mg BD. However, as there were small patient numbers in this phase, a randomized comparison between 300 mg BD TAB (lowest dose achieving similar drug exposure to the CAP recommended dose), 400 mg BD TAB (the defined TAB MTD) and the original 400 mg CAP regimen was performed to better determine the tolerability profiles. For patients who were receiving 400 mg BD TAB in the randomized dose-expansion phase, the number of AEs of anemia, gastrointestinal toxicities and patients requiring dose reductions, confirmed that olaparib 400 mg BD TAB was not optimally tolerated in this population of heavily pre-treated breast and ovarian cancer patients.

Although antitumor activity was not a primary objective of this study and there were limited numbers of patients in each dose subgroup, it is noteworthy that this

is one of the largest series of *gBRCA*m carriers receiving a single-agent PARP inhibitor. The overall response rate across the different cohorts was 30% in ovarian cancer patients with a confirmed *gBRCA*m; these data further support the confirmed the anticancer activity of olaparib in patients with a *gBRCA*m (11, 17). For ovarian cancer patients, the analysis of preliminary data on antitumor activity concluded that 300 mg BD TAB was similar to the approved dose of 400 mg BD CAP. Hence, 300 mg BD was selected as the recommended monotherapy dose for continuous administration of the tablet formulation for Phase III clinical trials of olaparib.

We also evaluated olaparib administered in different schedules, maintaining similar cumulative doses in a prospective expansion cohort based on the hypothesis that different patterns of drug exposure may help to alleviate common AEs of anemia, nausea or vomiting. Intermittent PARP inhibition has been investigated in several combinatory trials, mainly with cytotoxic chemotherapy (22-24), but this is, to our knowledge, the first series of patients prospectively enrolled to receive single-agent PARP inhibitors in different intermittent schedules. In these cohorts, intermittent scheduling did not improve GI tolerability; in fact, olaparib-related nausea, vomiting or diarrhea seemed to be better controlled by reducing the daily amount of drug administered. However, it must be noted that this cohort was conducted only in patients with advanced ovarian carcinoma, where serosal bowel involvement is a common cause of gastrointestinal symptoms. Therefore, conclusions may not be generalizable to other tumor types where PARP inhibitors are being developed. Additionally, preclinical data have indicated that continuous inhibition of PARP is required for maximum efficacy (unpublished data), further supporting continuous rather than intermittent dosing for olaparib monotherapy.

Administration of the total daily dose of 600 mg as a three times a day schedule (200 mg TID) whilst showing similar efficacy, was not considered to improve tolerability over 300 mg BID, with the additional patient inconvenience of three times daily dosing. This study still provides necessary evidence of the advantages and pitfalls of intermittent versus continuous schedules of administration, becoming a suitable source of information when designing dose-finding combinatorial trials of olaparib, under the premise that a chemo/radio-

sensitizing intention may require different dosing in combinations, than a single-agent treatment seeking for synthetic lethality; however, potential different toxicities from the agents in combination would have to be considered when designing such dosing schedules.

In conclusion, this multi-stage clinical trial evaluated different doses and schedules of administration of a tablet formulation of the PARP inhibitor olaparib to determine the recommended monotherapy TAB dose for the ongoing olaparib clinical development program. PK analysis showed that patients' exposure following tablet doses ≥300 mg BD matched or exceeded that of the approved 400 mg BD CAP (8 x 50 mg capsules, twice daily). A dose of 300 mg BD TAB was better tolerated than higher doses, without compromising antitumor activity. While intermittent administration of PARP inhibitors may potentially be effective in managing side effects, none of the intermittent dosing schedules explored improved both efficacy and tolerability when compared with 300 mg BD continuous dosing. Therefore, continuous dosing of olaparib tablets 300 mg BD (2 x 150 mg tablets, twice daily) is recommended for Phase III clinical trials of olaparib, simplifying drug administration from 16 capsules to four tablets per day.

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FIGURE LEGENDS

Figure 1. Study design

*Indicates groups where patients were required to have a confirmed BRCAm; †seven patients were enrolled into Group 5.1, six patients received treatment

Figure 2. Mean olaparib plasma concentration profile for (a) single oral dosing of the capsule formulation at doses of 50, 100 and 400 mg to patients with advanced solid tumors, (b) following single oral dosing of the tablet formulation at doses of 25, 50 and 250 mg to patients with advanced solid tumors and (c) following multiple dosing of the tablet (200 mg BD) and capsule (400 mg BD) to patients in Group 2. **[Note to Dr Dean: the n-numbers for each time point vary, therefore we are unable to include a 'total' n for each treatment group as requested. As there is no restriction of the number of 'parts' to a figure, part a and b will remain separate so they are clearer]**

Supplemental Figure 1. Waterfall plots of percentage change in target lesion size at 16 weeks (a) following multiple dosing of olaparib capsule 400 mg BD (Group 1 and 6), (b) following multiple dosing of the tablet 200 mg BD to patients in Group 1, (c) following multiple dosing of the tablet 300 mg BD to patients in Group 6, (d) following multiple dosing of the tablet 400 mg BD to patients in Group 6, (e) following continuous dosing of the tablet 200 mg TID to patients in Group 8, (f) following intermittent dosing of the tablet 250 mg TID to patients in Group 8, (g) following intermittent dosing of the tablet 400 mg TID to patients in Group 8 and (h) following continuous dosing of the tablet 400 mg OD to patients in Group 8