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Phase I study of olaparib in combination with liposomal doxorubicin in patients with advanced solid tumours

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Background: Olaparib, an oral PARP inhibitor, has shown antitumour activity as monotherapy in patients with germline *BRCA1/2* (gBRCA)-mutated breast and ovarian cancer. This study evaluated olaparib capsules in combination with liposomal doxorubicin (PLD) in patients with advanced solid tumours (NCT00819221).

Methods: Patients received 28-day cycles of olaparib, continuously (days 1–28) or intermittently (days 1–7), plus PLD (40 mg m^{-2}, day 1); seven olaparib dose cohorts (50–400 mg bid) were explored to determine the recommended dose. Assessments included safety, pharmacokinetics, pharmacodynamics and preliminary efficacy (objective response rate (ORR)).

Results: Of 44 patients treated (ovarian, $n=28$; breast, $n=13$; other/unknown, $n=3$), two experienced dose-limiting toxicities (grade 3 stomatitis and fatal pneumonia/pneumonitis (200 mg per 28-day cycle); grade 4 thrombocytopenia (400 mg per 7-day cycle)). The maximum tolerated dose was not reached using continuous olaparib 400 mg bid plus PLD. Grade $\geqslant 3$ and serious AEs were reported for 27 (61%) and 12 (27%) patients, respectively. No major pharmacokinetic interference was observed between olaparib and PLD. The ORR was 33% ($n=14$ out of 42; complete response, $n=3$). A total of 13 responders had ovarian cancer: 10 were platinum-sensitive, 11 had a gBRCA mutation.

Conclusions: Continuous/intermittent olaparib (up to 400 mg bid) combined with PLD (40 mg m^{-2}) was generally tolerated and showed evidence of antitumour activity in ovarian cancer.

Poly(ADP-ribose) polymerases (PARPs), which repair single-strand DNA breaks through the base-excision repair (BER) pathway, have emerged as important targets for cancer therapies in patients with an homologous recombination repair deficiency (HRD), because PARP inhibition leads to the formation of double-stranded DNA breaks that cannot be accurately repaired in tumours with an HRD, such as a *BRCA1/2* mutation; this concept is known as synthetic lethality. In preclinical studies, PARP inhibitors have demonstrated efficacy in tumours with *BRCA1/2* mutations (Moynahan *et al*, 1999, 2001; Bryant *et al*, 2005; Farmer *et al*, 2005).

Olaparib is a potent oral PARP inhibitor that has demonstrated efficacy as monotherapy in trials involving ovarian and breast cancer patients with germline *BRCA1/2* (gBRCA) mutations and/or sensitivity to platinum-based therapies (Fong *et al*, 2009; Audeh *et al*, 2010; Fong *et al*, 2010; Tutt *et al*, 2010; Gelmon *et al*, 2011;

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Kaye *et al*, 2012; Ledermann *et al*, 2012). The maximum tolerated dose (MTD) of olaparib monotherapy (capsule formulation) was identified as 400 mg twice daily (bid) (Fong *et al*, 2009). In Phase II trials in patients with recurrent ovarian cancer and gBRCA mutations, olaparib 400 mg bid monotherapy led to response rates of 31–33% (Audeh *et al*, 2010; Kaye *et al*, 2012). Furthermore, olaparib monotherapy demonstrated activity in high-grade serous or poorly differentiated ovarian cancer patients with and without gBRCA mutations (objective response rate (ORR): 41% and 24%, respectively) (Gelmon *et al*, 2011). In a randomized Phase II study targeting patients highly enriched for HRDs, olaparib maintenance treatment significantly improved progression-free survival (PFS) in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer compared with placebo (hazard ratio = 0.35; 95% CI, 0.25–0.49; $P < 0.00001$; median PFS 8.4 *vs* 4.8 months, respectively) (Ledermann *et al*, 2012).

Monotherapy studies have shown that olaparib is relatively well tolerated; the most common adverse events (AEs) being nausea, fatigue, vomiting and anaemia (Fong *et al*, 2009; Audeh *et al*, 2010; Fong *et al*, 2010; Tutt *et al*, 2010; Gelmon *et al*, 2011; Kaye *et al*, 2012; Ledermann *et al*, 2012). Combination studies with standard chemotherapeutic agents in patients with advanced solid tumours (ASTs) have resulted in sub-therapeutic recommended doses (RD) because of haematologic toxicities (Giaccone *et al*, 2010; Khan *et al*, 2011; Samol *et al*, 2012).

Pegylated liposomal doxorubicin (PLD) is an approved treatment for ovarian cancer patients failing platinum and taxane chemotherapies (Gordon *et al*, 2001; Rose, 2005), and has shown efficacy in a Phase II trial of ovarian cancer patients with gBRCA mutations (Kaye *et al*, 2012) and a Phase III trial in recurrent ovarian cancer patients (Gordon *et al*, 2001). In practice, the placement of PLD in the treatment algorithm varies between countries, with use in the second-line setting for patients with platinum-sensitive epithelial ovarian cancer in combination with carboplatin or trabectedin according to the duration of the platinum-free interval since last chemotherapy cycle. However, other second-line options exist and other regimens, such as carboplatin, gemcitabine and bevacizumab, may be applied (Aghajanian *et al*, 2012). The combination of PARP inhibition with PLD may provide a synergistic effect in patients with advanced ovarian cancer, especially those with HRDs, because of the decreased ability to repair chemotherapy-induced DNA damage. Preclinical studies with PARP inhibitors have shown potentiation of the cytotoxic effects of chemotherapeutic agents (Drew and Plummer, 2009). In particular, PARP inhibition has been shown to sensitise human hepatocellular carcinoma cell lines to doxorubicin treatment in a dose-dependent manner (Muñoz-Gámez *et al*, 2011). In another study, performed in HeLa cells, the combination of a PARP inhibitor with doxorubicin treatment led to a 50% increase in doxorubicin-mediated cell death compared with doxorubicin treatment alone (Magan *et al*, 2012). The toxicity profile of PLD appears to be distinct from that of olaparib, with the most common AEs associated with PLD being palmar–plantar erythrodysesthesia syndrome (PPES), stomatitis and nausea (Kaye *et al*, 2012). PARP inhibition should be sustained throughout the DNA damage and repair processes but, when combining PARP inhibitors with chemotherapy, prolonged inhibition may be unnecessary provided that a critical inhibitory level is maintained during DNA repair. Consequently, intermittent olaparib treatment schedules may show comparable activity, but better tolerability, *vs* continuous regimens and represent an interesting option for combination studies.

The aim of this study was to determine the optimal treatment schedule and RD of oral olaparib capsules when administered bid for either 1 week (intermittent) or 4 weeks (continuous), in combination with PLD, in patients with ASTs.

MATERIALS AND METHODS

Patients. Eligible patients were aged $\geqslant 18$ years with histologically/cytologically confirmed metastatic cancer; adequate bone marrow, hepatic and renal functions; ECOG performance status $\leqslant 2$; and $\leqslant 3$ before chemotherapy regimens for advanced disease. gBRCA mutation status was obtained retrospectively for patients in whom gBRCA testing had been performed before study entry. Exclusion criteria included active treatment or high-dose radiotherapy within the last 28 days, prior cumulative dosing ($> 300\ \mathrm{mg\,m^{-2}}$) of doxorubicin equivalent, anthracycline resistance and persistent Common Terminology Criteria (CTC) grade $\geqslant 2$ toxicities caused by prior therapy. Please see the Supplementary File for further details. All patients provided written informed consent.

Study design. This Phase I, open-label, multicentre dose-finding study (NCT00819221) was designed to evaluate the safety/tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of olaparib capsules in combination with PLD ($40\ \mathrm{mg\,m^{-2}}$ every 28 days) in patients with ASTs. Olaparib was administered for either 7 days (intermittent schedule) or 28 days (continuous schedule) per 28-day treatment cycle. Up to seven olaparib dose levels were to be explored; the dose schedule for the initial cohort (cohort 0) was 50 mg once daily on day 1, followed by 50 mg bid for 7 days. Further patient cohorts were: 100, 200 and 400 mg bid for 7 days (per treatment cycle), and 100, 200 and 400 mg bid for 28 days (per treatment cycle). The MTD was determined as the dose for the cohort in which $\geqslant 2$ out of 6 patients experienced a dose-limiting toxicity (DLT). The two cohorts below the MTD would be expanded to $\leqslant 12$ patients each (expansion phase) to confirm the RD. The study was based on a standard $3 + 3$ design, with three patients recruited initially to a cohort (starting with cohort 0); if no DLTs were observed, recruitment to the next dose level commenced. If one patient experienced a DLT, the cohort would be expanded to six patients. The intermittent schedule for each dose level would be tested initially; if tolerable, the continuous schedule for that dose level would be assessed in a separate cohort concomitantly with 7-day dosing at the next dose level. This concerted escalation of dose, and dosing duration, was designed to increase patient accrual and potentially shorten the study duration, while preserving patient safety (Sessa *et al*, 2007). In the event of toxicity, a maximum of two-dose reductions were allowed provided the olaparib dose was $\geqslant 50$ mg bid. After two cycles, patients who had not met a withdrawal criterion (voluntary discontinuation, severe non-compliance, disease progression, AE or safety concern) could continue receiving combination therapy for $\leqslant 6$ cycles or switch to olaparib monotherapy (according to efficacy).

The study was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice and the AstraZeneca policy on Bioethics (AstraZeneca, 2011).

End points and assessments. The primary objective was to determine the RD of twice-daily olaparib combined with PLD, based on the incidence of DLTs. Secondary objectives were to determine the PK of olaparib alone and in combination with PLD, and to evaluate two different schedules of olaparib administration. Exploratory objectives included an evaluation of preliminary efficacy of olaparib plus PLD; an assessment of antitumour activity in patient subgroups with ovarian and breast cancer; and an assessment of the effects of the combination on DNA repair by evaluating phosphorylation of histone H2AX (γH2AX) in peripheral blood mononuclear cells (PBMCs) as a biomarker of double-strand DNA breaks.

Toxicity was graded using NCI-CTCAE v3.0. DLTs included the following events occurring during the first treatment cycle and

considered, by the investigator, to be related to combination treatment: grade 4 neutropenia lasting >5 days, grade 4 thrombocytopenia, grade ⩾3 febrile neutropenia, grade ⩾3 nausea and/or vomiting (despite maximal anti-emetic therapy) or any other CTCAE grade ⩾3 non-haematologic toxicity. Preliminary efficacy was determined by assessing objective responses based on Response Evaluation Criteria In Solid Tumors (RECIST; v1.0) (Therasse *et al*, 2000) as determined by the study site investigators. Efficacy was analysed by tumour type and gBRCA mutation status. Additional analyses of ovarian cancer patients were performed by subdividing patients into platinum-sensitive (patients who experienced a progression-free interval of ⩾6 months following discontinuation of the last platinum-containing chemotherapy) and platinum-resistant subgroups. Analyses by gBRCA mutation status and platinum sensitivity were not prespecified in the study design and were performed retrospectively.

Blood samples (4 ml) were collected according to limited (escalation phase) or full (expansion phase) sampling schedules and analysed to determine plasma concentrations of olaparib and PLD (Supplementary Figure 1). Plasma concentrations were used to derive PK parameters following intermittent and continuous dosing. Olaparib concentrations were determined by solid-phase extraction and LC–MS/MS chromatography. Total doxorubicin was measured by a high-performance liquid chromatography (HPLC)/fluorescence method following liposome dispersion with Triton-X and on-line plasma extraction. PK data were analysed by non-compartmental methods.

For the determination of γH2AX, PBMCs were isolated from venous blood samples (8 ml) obtained on days 1, 8, 15 and 28 of cycle 1 (Supplementary Figure 1); fixed, and stained for intracellular γH2AX. Cytofluorimetric detection was performed with an anti-phospho-H2AX (Ser139) antibody (Cell Signaling Technology, Beverly, MA, USA). Further analyses were performed to correlate γH2AX data with preliminary evidence of antitumour activity.

Statistical analyses. No formal statistical analysis of safety/tolerability was planned. A Student's *t*-test for paired data (two tailed) was applied to PK data and a Wilcoxon signed-rank test was performed for PD data to determine statistically significant differences.

RESULTS

Patient disposition. All 44 patients enroled from January 2009–December 2010 were treated and evaluable for safety (Table 1). Two patients receiving continuous olaparib 400 mg bid are ongoing. Two patients receiving continuous olaparib (100 and 200 mg, respectively) did not complete a 28-day treatment cycle, owing to tumour-related intestinal obstruction and tumour-related ileus, so were not evaluable for DLT or efficacy evaluations. Pre-existing gBRCA mutation status data only were collected following a protocol amendment; therefore, gBRCA status was unknown for 45% of patients in this study. Patient characteristics were generally balanced across each cohort.

MTD, RD and DLTs. All seven cohorts were assessed because DLTs were not experienced by ⩾2 patients in any cohort. The MTD of olaparib with PLD could not be determined and the olaparib 400 mg cohorts were expanded. Two DLTs were experienced: grade 3 stomatitis plus fatal pneumonia/pneumonitis and dyspnoea in a patient receiving continuous 200 mg and grade 4 thrombocytopenia, leading to treatment discontinuation, in a patient receiving intermittent 400 mg.

Safety and tolerability. Thirty-nine patients (89%) completed the planned 2 cycles of combination therapy and 14 patients (32%) completed ⩾6 cycles. The most common reason for patient withdrawal was malignant disease progression ($n=31$; 76%). Three patients had dose reductions; all from 400 to 200 mg bid (continuous dosing) because of AEs (oesophagitis, thrombocytopenia, anaemia). The reductions occurred at cycles 2, 7 and 9.

Across all cohorts, the most common treatment-related AEs (any grade) were stomatitis and nausea (Table 2). The overall incidence of CTCAE grade ⩾3 events was 61%, with the most common being decreased neutrophil count. Serious AEs were experienced by 12 patients (27%), although only five patients had treatment-related serious AEs (pneumonitis ($n=2$); pneumonia/pneumonitis and dyspnoea ($n=1$); thrombocytopenia ($n=1$); oesophagitis ($n=1$)). Except for the patient who experienced oesophagitis, all patients with treatment-related serious AEs discontinued owing to these events; a further three patients withdrew because of non-serious treatment-related AEs (stomatitis ($n=1$); dysphagia, erythema and PPES ($n=1$); asthenia and vomiting ($n=1$)), accounting for seven patients in total.

Five patients died during the study. One ovarian cancer patient in the olaparib 200 mg 28-day cohort presented with cancer-related ileus during the first cycle that was not attributed to study treatment. One patient with breast and metastatic lung cancer (200 mg 28-day cohort) discontinued study treatment on day 26 of the first treatment cycle owing to stomatitis; nine days later, the patient experienced severe dyspnoea and pneumonia and later died due to right lung pneumonia (leading to bilateral pneumonitis) and dyspnoea, all of which were considered possibly related to study treatment. One patient with small-cell lung cancer (100 mg 28-day cohort) discontinued treatment on day 22 of the third treatment cycle, having had several AEs including pulmonary fibrosis; 10 days after the discontinuation of study treatment, the patient experienced severe pneumonitis and later died from treatment-related pneumonitis. The remaining two patients (100 mg 28-day and 200 mg 7-day cohorts) died following a general worsening of their condition. Both patients with treatment-related deaths had previous/ongoing medical conditions (one had asthma treated with steroids, infection, suppurating bronchopneumonia; the other had mediastinal radiotherapy, medical history of chronic interstitial lung disease, thromboses, infection) that potentially contributed to pneumonitis.

Clinically significant haematological abnormalities reported as AEs included alterations in neutrophil count ($n=13$) and haemoglobin ($n=4$). Grade ⩾3 haematologic alterations were observed in neutrophils ($n=9$; 20%), platelets ($n=3$; 7%), haemoglobin ($n=2$; 5%) and white blood cells ($n=2$; 5%).

Pharmacokinetics. The maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve ($AUC_{0-10\,h}$) of olaparib increased with dose when given alone (day 1) and in the presence of PLD; olaparib exposure tended to be higher in the presence of PLD (Table 3; Supplementary Figure 2). Following a single dose, olaparib was absorbed rapidly with a mean time to maximum observed concentration (T_{max}) of 2.1 h. The minimum plasma concentrations (C_{min}) of olaparib were maintained during 28 days of treatment (400 mg bid: day 8, $3.6 \pm 2.2\,\mu g\,ml^{-1}$; day 28, $3.9 \pm 2.6\,\mu g\,ml^{-1}$) indicating that PLD did not interfere with steady-state olaparib plasma concentrations. PLD parameters were generally similar when olaparib was administered for 7 or 28 days; a statistically significant increase in $AUC_{0\text{-}inf}$ and a corresponding decrease in total body clearance (CL_{TB}) were observed in patients receiving continuous olaparib 400 mg bid (day 1–28) compared with short-term administration (day 1–7).

Efficacy. The ORR in the overall population was 33% (14 out of 42). Overall, three evaluable patients (7%) achieved a complete response (CR) and 11 (26%) achieved a partial response (PR) (Table 4). Thirteen responders had ovarian cancer; the ORR in this subgroup was 50% (13 out of 26). In the ovarian subgroup, the response rate in platinum-resistant and platinum-sensitive

Table 1. Patient characteristics

	Olaparib dose cohort, *n*[c] (%)							
	50 mg bid 7 day (*n* = 3)	100 mg bid 7 day (*n* = 3)	100 mg bid 28 day (*n* = 4)	200 mg bid 7 day (*n* = 3)	200 mg bid 28 day (*n* = 7)	400 mg bid 7 day (*n* = 12)	400 mg bid 28 day (*n* = 12)	Total (*n* = 44)
Characteristic								
Median age (range), years	48.0 (46–54)	63.0 (53–71)	62.5 (49–74)	66.0 (59–68)	55.0 (32–63)	55.0 (37–71)	52.0 (31–64)	55.5 (31–74)
Sex								
Female	3 (100)	3 (100)	4 (100)	2 (67)	7 (100)	11 (92)	12 (100)	42 (95)
ECOG status								
0	3 (100)	3 (100)	3 (75)	2 (67)	3 (43)	8 (67)	12 (100)	34 (77)
1	–	–	1 (25)	1 (33)	4 (57)	4 (33)	–	10 (23)
Prior chemotherapy[a]								
Yes	3 (100)	3 (100)	3 (75)	3 (100)	2 (29)	11 (92)	10 (83)	35 (80)
No	–	–	1 (25)	–	5 (71)	1 (8)	2 (17)	9 (20)
Primary tumour site								
Ovarian	3 (100)	2 (67)	2 (50)	2 (67)	3 (43)	8 (67)	8 (67)	28 (64)
Breast	–	1 (33)	1 (25)	–	4 (57)	3 (25)	4 (33)	13 (30)
SCLC	–	–	1 (25)	–	–	–	–	1 (2)
Prostate/colon	–	–	–	–	–	1 (8)	–	1 (2)
Unknown	–	–	–	1 (33)	–	–	–	1 (2)
Evaluable patients								
DLT	3 (100)	3 (100)	3 (75)	3 (100)	6 (86)	12 (100)	12 (100)	42 (95)
Safety	3 (100)	3 (100)	4 (100)	3 (100)	7 (100)	12 (100)	12 (100)	44 (100)
Efficacy	3 (100)	3 (100)	3 (75)	3 (100)	6 (86)	12 (100)	12 (100)	42 (95)
gBRCA mutation status								
BRCA1 and/or *BRCA2* positive	3 (100)	2 (67)	1 (25)	1 (33)	2 (29)	5 (42)	9 (75)	23 (52)
Negative	–	–	–	–	–	1 (8)	–	1 (2)
Unknown	–	1 (33)	3 (75)	2 (67)	5 (71)	6 (50)	3 (25)	20 (45)
Platinum sensitivity status[b]								
Sensitive	3 (100)	–	–	–	3 (100)	5 (63)	4 (50)	15 (54)
Resistant	–	2 (100)	2 (100)	2 (100)	–	3 (38)	4 (50)	13 (46)

Abbreviations: DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group ;gBRCA = germline BRCA; SCLC = small-cell lung cancer.
[a]For advanced disease.
[b]Ovarian patients only.
[c]Number of patients.

patients was 25% and 71%, respectively (Table 5). Eleven (61%) gBRCA-mutated patients in the ovarian subgroup achieved a response. Of the two additional patients in the ovarian subgroup who experienced a response, one patient with no gBRCA mutation had a CR and one patient with unknown gBRCA status had a PR; both were platinum-sensitive. The remaining response (PR) was in a gBRCA-mutated patient with breast cancer.

Pharmacodynamics. Cytofluorimetric determination of γH2AX phosphorylation level was performed in 41 out of 44 (93%) patients receiving intermittent or continuous olaparib. For both regimens, downregulation of phospho-γH2AX was particularly evident in ovarian patients on days 8 and 15 during the first treatment cycle. Decreases were statistically significant for patients with platinum-resistant ovarian cancer on day 8 ($P = 0.046$), and for patients receiving intermittent olaparib treatment, and was independent of the olaparib dose. However, in platinum-sensitive ovarian patients, the phospho-γH2AX level was stable throughout 28 days of treatment (Figure 1). A rebound of phospho-γH2AX levels occurred between days 15 and 28 in the platinum-resistant ovarian subgroup; this effect was most noticeable in patients with PR or stable disease (Supplementary Figure 3) and in those receiving intermittent dosing (data not shown). A trend towards higher basal phospho-γH2AX levels was observed in the platinum-resistant subgroup compared with the platinum-sensitive subgroup (Supplementary Figure 4). This study only measured phospho-H2AX in surrogate tissue. PBMCs, as tumour samples were not available. The measured levels of phospho-H2AX may therefore not reflect any DNA damage in the tumour target lesions induced by the combination of olaparib and doxorubicin treatment.

Table 2. Summary of common treatment-related AEs[a] and CTC grade ⩾3 AEs

	Olaparib dose cohort							
	50 mg bid 7 day (*n* = 3)	100 mg bid 7 day (*n* = 3)	100 mg bid 28 day (*n* = 4)	200 mg bid 7 day (*n* = 3)	200 mg bid 28 day (*n* = 7)	400 mg bid 7 day (*n* = 12)	400 mg bid 28 day (*n* = 12)	Total (*n* = 44), *n* (%)
Adverse event								
Stomatitis	**3**[b]	**3**	**2**	**2**	**5**	**6**	**11**	**32 (73)**
	–	2[c]	–	–	1	2	2	7 (16)
Nausea	**3**	**2**	**2**	**2**	**3**	**8**	**8**	**28 (64)**
	–	1	–	–	–	4	–	5 (11)
Asthenia	**2**	**1**	**2**	**2**	**2**	**6**	**6**	**21 (48)**
	–	–	–	–	–	1	–	1 (2)
Anorexia	**–**	**–**	**1**	**–**	**3**	**4**	**4**	**12 (27)**
	–	–	1	–	1	–	–	2 (5)
Vomiting	**–**	**1**	**–**	**–**	**3**	**6**	**3**	**13 (30)**
	–	–	–	–	–	1	–	1 (2)
Decreased neutrophil count	**2**	**3**	**2**	**1**	**1**	**2**	**2**	**13 (30)**
	2	3	1	–	1	1	1	9 (20)
PPES	**–**	**–**	**–**	**1**	**2**	**4**	**4**	**11 (25)**
	–	–	–	–	–	–	1	1 (2)

Abbreviations: AEs = adverse events; CTC = Common Terminology Criteria; PPES = palmar–plantar erythrodysesthesia syndrome.
[a]AEs experienced by ⩾25% patients overall.
[b]Values in bold denote the number of patients (*n*, (%)) with AEs.
[c]Values in non bold denote the number of patients (*n*, (%)) with grade ⩾3 AEs.

DISCUSSION

This study evaluated olaparib (intermittent and continuous dosing up to 400 mg bid) in combination with the optimal dose of PLD (40 mg m^{-2} every 28 days) in patients with ASTs. Although the MTD was not reached, our results suggest that continuous dosing with olaparib capsules, at the recommended monotherapy dose of 400 mg bid, combined with PLD (40 mg m^{-2}) could be considered for Phase II trials of longer duration.

The AEs reported were consistent with known events associated with olaparib and PLD when given as monotherapy (Gordon *et al*, 2001; Fong *et al*, 2009; Audeh *et al*, 2010; Fong *et al*, 2010; Tutt *et al*, 2010; Gelmon *et al*, 2011; Kaye *et al*, 2012; Ledermann *et al*, 2012), and the combination was generally tolerated up to the highest doses administered. Two DLTs were reported in patients from separate cohorts (continuous 200 mg; intermittent 400 mg); the MTD was not reached, as the protocol did not permit exploration of olaparib doses above continuous 400 mg bid. The maximum dose permitted in this trial was olaparib 400 mg bid because this dose was determined as the MTD in a previous trial (Fong *et al*, 2009). The PLD 40 mg m^{-2} dose investigated in this trial is a commonly used single-agent dose in clinical practice (Julius *et al*, 2013), despite being lower than the FDA-approved dose for patients with breast and ovarian cancer (50 mg m^{-2}). In addition, this study used the capsule formulation of olaparib, whereas ongoing Phase III studies in ovarian and breast cancer use the tablet formulation of olaparib. It has been shown that exposure with tablet doses ⩾300 mg bid matched or exceeded that of the 400 mg bid capsule, and olaparib 300 mg bid is the recommended tablet dose for Phase III studies (Mateo *et al*, 2013).

The tolerability profile observed in this study compares favourably to that seen in studies of PLD monotherapy and in combination with carboplatin. The Phase III CALYPSO study compared PLD (30 mg m^{-2}) plus carboplatin (AUC5) every 4 weeks with paclitaxel plus carboplatin in 976 patients with platinum-sensitive ovarian cancer. PLD plus carboplatin treatment was associated with severe non-haematological toxicity in 28.4% of patients and Grade 3 − 4 neutropenia in 35.2% of patients. Grade ⩾2 fatigue, nausea and hand-foot syndrome occurred in 36.9%, 35.2% and 12% of patients, respectively (Pujade-Lauraine *et al*, 2010). Treatment with single-agent PLD (mainly 50 mg m^{-2} every 4 weeks) is associated with fewer events of neutropenia, anaemia, thrombocytopenia, and gastrointestinal toxicity, but increased cutaneous toxicity compared with other monotherapies (Gibson *et al*, 2013). Compared with other second-line regimens seen in the clinic, olaparib and PLD combination therapy was associated with fewer grade ⩾3 AEs than carboplatin, gemcitabine and bevacizumab as determined in the OCEANS study (Aghajanian *et al*, 2012), and carboplatin plus paclitaxel regimens (Pignata *et al*, 2014).

In the current trial, three patients experienced serious AEs of pneumonitis, resulting in death in two patients. The three events occurred in different patient cohorts (100 mg 28-day cohort, 200 mg 28-day cohort and 400 mg 7-day cohort) and were all considered to be related to study treatment by the investigator. Of the two patients who died because of lung toxicities, both had a history of medical conditions that may have contributed to the observed pneumonitis. The third patient had no known risk factors associated with lung toxicity, but developed grade 3 pneumonitis after receiving five cycles of therapy and, following withdrawal of treatment, made a full recovery. Although previous lung conditions may have contributed to both fatal cases of pneumonitis, we cannot exclude the role of olaparib in the observed events. A previous case of presumed treatment-related pneumonitis leading to treatment discontinuation was seen in a Phase I trial of combination olaparib, gemcitabine and cisplatin (Rajan *et al*, 2012); however, cases of pneumonia have also been seen in previous trials of PLD (Numico *et al*, 2002; Berenson *et al*, 2012).

The combination of olaparib with platinum-based chemotherapies has previously been associated with increased myelosuppression;

Table 3. Pharmacokinetic parameters of olaparib alone (day 1), olaparib in the presence of PLD (day 2), and PLD 1-h infusion by olaparib administration schedule (mean ± s.d.)

		Pharmacokinetic parameters of olaparib	
Olaparib (mg bid)	***n***	**$AUC_{0-10\,h}$ ($\mu g \times h\,ml^{-1}$)**	**C_{max} ($\mu g\,ml^{-1}$)**
50			
Day 1 alone	3	8.7 ± 5.8	1.8 ± 1.1
Day 2 + PLD		—	1.4 ± 0.7
100			
Day 1 alone	3	6.8 ± 2.7	1.7 ± 0.8
Day 2 + PLD		9.4 ± 3.0	2.2 ± 1.0
200			
Day 1 alone	2	29.5 (12.2, 46.9)	5.6 (3.3, 7.9)
Day 2 + PLD	3	46.2 ± 52.0	5.2 ± 2.8
400			
Day 1 alone	11	25.9 ± 9.0	5.1 ± 1.7
Day 2 + PLD		35.2 ± 17.1[a]	6.6 ± 2.0[a]

		Pharmacokinetic parameters of PLD					
Olaparib (mg bid)	***n***	**$AUC_{0-24\,h}$($\mu M \times h$)**	**$AUC_{0\text{-}inf}$($\mu M \times h$)**	**C_{max}(μM)**	**$T_{½}$(h)**	**CL_{TB}(l)**	**V_{ss}(l)**
50							
Q7	3	732 ± 42	4359 ± 998	36.3 ± 0.8	77 ± 7	17 ± 4	1.5 ± 0.1
100							
Q7	3	623 (574–672)	4885 (4232–5537)	38.9 ± 16.4	83 ± 24	15 ± 3	1.6 ± 0.6
Q28	3	566 ± 50	4129	30.0 ± 0.5	82 ± 13	22 ± 5	2.0 ± 0.02
200							
Q7	2	624 (609–639)	3846 (3823–3868)	33.9 (34.2–33.6)	67 (69–65)	18 (18–18)	1.6 (1.7–1.5)
Q28	3	658 ± 46	3968 ± 44	36.2 ± 3.1	74 ± 10	17 ± 1	1.5 ± 0.3
400							
Q7	11	562 ± 108	3319 ± 707[b]	30.6 ± 4.3	72 ± 12	23 ± 6[c]	2.0 ± 0.3
Q28	12	609 ± 104	4209 ± 928[b]	33.5 ± 5.2	77 ± 13	18 ± 4[c]	1.7 ± 0.4

Abbreviations: AUC = area under the plasma concentration–time curve; C_{max} = maximum concentration; CL_{TB} = total body clearance; PLD = pegylated liposomal doxorubicin; Q7 = 7-day dosing of olaparib; Q28 = 28-day dosing of olaparib; $T_{½}$, = half-life; V_{ss} = distribution volume at steady state.
[a] $P < 0.01$ by Student's *t*-test for paired data.
[b] $P = 0.0276$.
[c] $P = 0.0233$ by Student's *t*-test for unpaired data.

in a Phase I study, 5 out of 23 (22%) patients with ASTs receiving olaparib plus cisplatin and gemcitabine experienced haematological DLTs (Giaccone *et al*, 2010). Although, in the present study, 30% of patients experienced alterations in neutrophil count, the events appeared not to be dose related, there were no neutropenia-associated DLTs and the overall tolerability profile of olaparib plus PLD appeared more favourable than that observed in most previous olaparib combination studies (Giaccone *et al*, 2010; Khan *et al*, 2011; Balmaña *et al*, 2012; Samol *et al*, 2012). A Phase I study of olaparib plus weekly paclitaxel showed higher-than-expected rates of neutropenia despite prophylactic administration of granulocyte colony-stimulating factor (Dent *et al*, 2013).

PK interference between olaparib and PLD was minor and unlikely to have clinical relevance. C_{max} and $AUC_{0-10\,h}$ of olaparib in the presence of PLD increased with increasing doses, suggesting lack of acute interference on the absorption and distribution of olaparib (Supplementary Figure 2). A trend towards increased olaparib $AUC_{0-10\,h}$ and C_{max} on day 2 was observed and was statistically significant with the 400 mg dose; this is probably the result of drug accumulation between the doses. The PK parameters of PLD were similar, regardless of whether olaparib was administered for 7 or 28 days (Table 3). Differences in $AUC_{0\text{-}inf}$ and CL_{TB} for PLD after olaparib 400 mg administration for 28 days compared with 7 days were probably related to inter-patient variability and not considered clinically significant.

Preliminary evidence of antitumour activity was observed in ovarian cancer patients; although the ovarian subgroup in this study was relatively small, the 50% ORR is higher than that reported previously for Phase II trials that assessed olaparib monotherapy (400 mg bid) in recurrent ovarian cancer patients with gBRCA mutations (31–41%) (Audeh *et al*, 2010; Gelmon *et al*, 2011; Kaye *et al*, 2012). The ORR was also higher than reported in

Table 4. Best objective response for the overall population and for those patients with ovarian cancer

	Olaparib dose cohort							
Overall population	**50 mg bid 7 day (n = 3)**	**100 mg bid 7 day (n = 3)**	**100 mg bid 28 day (n = 4)**	**200 mg bid 7 day (n = 3)**	**200 mg bid 28 day (n = 7)**	**400 mg bid 7 day (n = 12)**	**400 mg bid 28 day (n = 12)**	**Total (n = 42)**
Ovarian cancer patients	(n = 3)	(n = 2)	(n = 2)	(n = 2)	(n = 3)	(n = 8)	(n = 8)	(n = 26)
Best objective response [a], (%)								
Complete response	**1** 1	**0** 0	**0** 0	**0** 0	**0** 0	**1** 1	**1** 1	**3 (7)** 3 (12)
Partial response	**1** 1	**1** 1	**0** 0	**1** 1	**1** 1	**2** 2	**5** 4	**11 (26)** 10 (38)
Stable disease	**1** 1	**1** 0	**1** 0	**1** 1	**2** 1	**5** 4	**2** 1	**13 (31)** 8 (31)
Progressive disease	**0** 0	**1** 1	**2** 1	**1** 0	**2** 0	**3** 1	**4** 2	**13 (31)** 5 (19)
Not evaluable/unknown	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**2 (5)**

[a]RECIST version 1.0.

Table 5. Ovarian cancer patients with a complete or partial objective response by germline BRCA (gBRCA) status and platinum sensitivity

	gBRCA mutation status			
Platinum sensitivity	**gBRCAm (n = 18)**	**gBRCAwt (n = 1)**	**Unknown (n = 7)**	**Total (n = 26)**
Platinum sensitive (n = 14)	8/12	1/1	1/1	10/14 (71%)
Platinum resistant (n = 12)	3/6	0/0	0/6	3/12 (25%)
Total (n = 26)	11/18 (61%)	1/1 (100%)	1/7 (14%)	13/26 (50%)

Abbreviations: gBRCA = germline BRCA; gBRCAm = gBRCA mutated; gBRCAwt = gBRCA wild type (no mutation).

randomized trials of single-agent PLD (18–20%) (Gordon *et al*, 2001; Kaye *et al*, 2012). As a result, the combination of olaparib (400 mg bid) and PLD (40 mg m^{-2}) may offer an advantage over either agent alone, particularly since both drugs were combined at their full recommended monotherapy dosages. The ORR in patients with ovarian cancer is within the range achieved by other potential second-line regimens seen in the clinic (Monk *et al*, 2010; Pujade-Lauraine *et al*, 2010; Aghajanian *et al*, 2012). Responses were achieved by 25% of platinum-resistant and 71% of platinum-sensitive ovarian patients. Consistent with previous olaparib trials (Fong *et al*, 2010; Gelmon *et al*, 2011), the ORR was higher in platinum-sensitive patients with a gBRCA mutation (67%); however, responses were also seen in platinum-sensitive ovarian patients with wild type or unknown gBRCA mutation status (100%). The ORR in platinum-resistant patients with a gBRCA mutation (50%) was in line with that observed in a recent Phase II trial (Gelmon *et al*, 2011). Consistent with findings by Gelmon *et al* (2011), few objective responses were observed in the subgroup of evaluable patients with breast cancer (8%), although only 3 out of 13 were known to have a gBRCA mutation. Although a formal comparison of intermittent and continuous olaparib administration schedules was not performed, antitumour activity was observed with both schedules (7 out of 21 and 7 out of 23 patients, respectively), and both appeared similar in terms of tolerability.

Phosphorylation of γH2AX is associated with cytotoxic agents and has been used widely as a marker of DNA damage (Sedelnikova and Bonner, 2006; Bonner *et al*, 2008; Fong *et al*, 2009; Redon *et al*, 2010). We studied γH2AX in isolated, fixed PBMCs to determine the effects on DNA repair. In contrast to results reported by Fong *et al* (2009), downregulation of phospho-γH2AX was observed with both continuous and intermittent olaparib regimens during the first treatment cycle. This effect was independent of olaparib dose and most noticeable in platinum-resistant ovarian patients, who presented with higher baseline levels of this marker. Although the decrease in phospho-γH2AX levels was unexpected, peak levels have previously been shown to occur within 6–7 h of treatment with PARP inhibitors (Fong *et al*, 2009; Kummar *et al*, 2011, 2012), whereas our observations were not conducted until days 8, 15 and 28. As the phosphorylation of γH2AX is a dynamic phenomenon, we studied the late phase of this event (Supplementary Figure 4). Our aim was to assess changes in γH2AX phosphorylation during chronic treatment with olaparib plus PLD combination; therefore, we selected time points from day 8 onwards so that olaparib had reached a steady-state plasma concentration. In accordance with the results reported by Fong *et al* (2009), which were unavailable when our study was initiated, we cannot exclude the possibility that, in our study, peak levels of γH2AX phosphorylation may have occurred before day 8. Phosphorylation of γH2AX may be a useful marker for future studies provided that samples are collected at early time points ($\leqslant$6 h post treatment).

In conclusion, our data suggest that continuous olaparib 400 mg bid (capsule formulation) in combination with PLD 40 mg m^{-2} would be suitable for assessment in Phase II studies in patients with ovarian cancer. However, it should be noted that, following

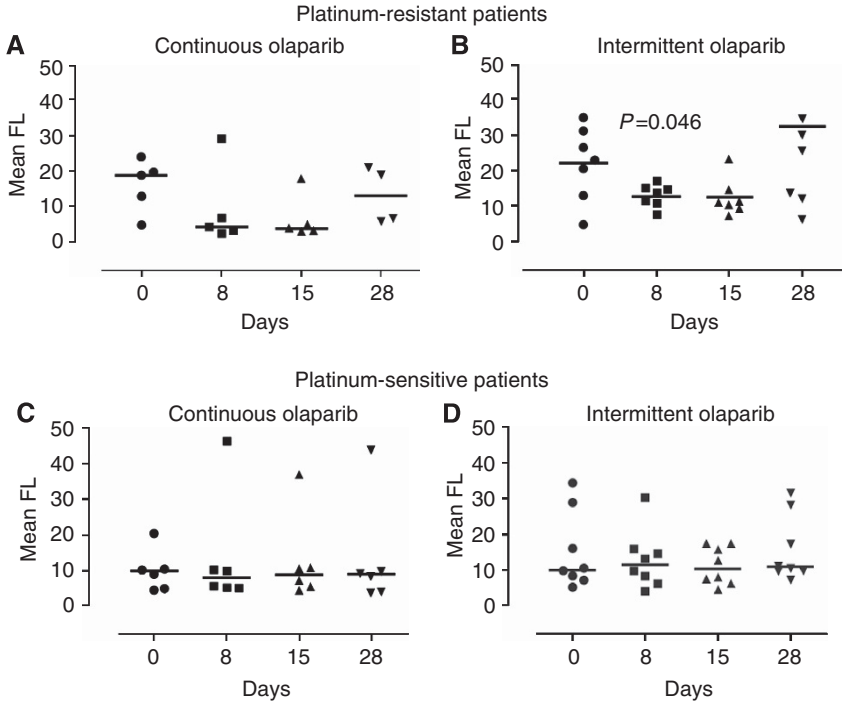

Figure 1. Analysis of γH2AX phosphorylation in ovarian cancer patients. Both treatment regimens are shown: continuous olaparib dosing, days 1–28 in platinum-resistant (**A**) and platinum-sensitive (**C**) patients, and intermittent olaparib dosing, days 2 8, in platinum-resistant (**B**) and platinum-sensitive (**D**) patients. A Wilcoxon signed-rank test was performed ($P=0.046$; statistical significance was defined as $P<0.05$). Median values are indicated.

recent results from a Phase I study, the recommended monotherapy dose for the olaparib tablet formulation is 300 mg bid (continuous dosing). The encouraging efficacy results seen in ovarian cancer patients were not limited by gBRCA mutation status or sensitivity to platinum therapy, and the tolerability profiles appeared distinct, suggesting that the combination of olaparib with PLD should be explored further.

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CONFLICT OF INTEREST

Advisory/consulting roles have been held by RVM for Amgen, GlaxoSmithKline, Novartis, Merck Sharp & Dohme and Bristol-Myers Squibb; by CS and RC for AstraZeneca; and by LG for Roche, Genentech, GlaxoSmithKline, Novartis, Pfizer, Boehringer Ingelheim, Celgene and Tahio Pharmaceutical. No potential conflict of interest were disclosed by the other authors.

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