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# A Phase I Combination Study of Olaparib with Cisplatin and Gemcitabine in Adults with Solid Tumors

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## Abstract

**Purpose:** To determine the safety and tolerability of olaparib with cisplatin and gemcitabine, establish the maximum tolerated dose (MTD), and evaluate the pharmacodynamic and pharmacokinetic profile of the combination.

**Experimental Design:** We conducted a phase I study of olaparib with cisplatin and gemcitabine in patients with advanced solid tumors. Treatment at dose level 1 (DL1) consisted of olaparib 100 mg orally every 12 hours on days 1 to 4, gemcitabine 500 mg/m$^2$ on days 3 and 10, and cisplatin 60 mg/m$^2$ on day 3. PAR levels were measured in peripheral blood mononuclear cells (PBMC).

**Results:** Dose-limiting toxicities (DLT) in two of three patients at DL1 included thrombocytopenia and febrile neutropenia. The protocol was amended to enroll patients treated with $\leq$2 prior severely myelosuppressive chemotherapy regimens and treated with olaparib 100 mg once daily on days 1 to 4 (DL−1). No DLTs were seen in six patients at DL−1. Because of persistent thrombocytopenia and neutropenia following a return to DL1, patients received 100 mg olaparib every 12 hours on day 1 only. No hematologic DLTs were observed; nonhematologic DLTs included gastrointestinal bleed, syncope, and hypoxia. Of 21 patients evaluable for response, two had partial response. Olaparib inhibited PARP in PBMCs and tumor tissue, although PAR levels were less effectively inhibited when olaparib was used for a short duration.

**Conclusions:** Olaparib in combination with cisplatin and gemcitabine is associated with myelosuppression even at relatively low doses. Modified schedules of olaparib in chemotherapy naive patients will have to be explored with standard doses of chemotherapy. *Clin Cancer Res; 18(8); 2344–51. ©2012 AACR.*

## Introduction

Poly (adenosine diphosphate [ADP]-ribose) polymerases (PARPs) comprise a family of enzymes that play an integral role in DNA repair through the process of base excision (1, 2). PARP1, a ubiquitous nuclear enzyme is a key member of the PARP family. Decreased activity of PARP results in the accumulation of single-strand breaks in DNA, which eventually leads to DNA double-strand breaks. The inability of the cell to repair this damage by the homologous recombination double-strand DNA repair pathway can prove lethal. BRCA1 and BRCA2 are important members of the homologous recombination pathway. Hence, BRCA-deficient tumors are more susceptible to the effects of PARP inhibition.

Olaparib (4-[(3-{[4-cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one; AZD2281; KU-0059436) is a potent oral PARP inhibitor (3). A phase I study of olaparib in 60 patients, including 23 carriers of mutations in BRCA1 or BRCA2, showed significant clinical benefit in mutation carriers (4). As a single agent, olaparib has been well tolerated at doses up to 400 mg twice daily using a continuous schedule (4). Adverse events were generally mild and the incidence of myelosuppression was low. In a phase I study of olaparib and dacarbazine, the optimal dose of olaparib was determined to be 100 mg twice daily on days 1 to 7 of a 21-day cycle with dacarbazine administered at a dose of 600 mg/m$^2$ on day 1. The incidence of myelosuppression, especially neutropenia, was higher than what could be expected with single-agent dacarbazine (5).

Platinum agents form complex adducts that damage DNA and lead to cell death (6). This is counteracted by the DNA repair mechanisms of base excision repair (BER) and nucleotide excision repair. Because of the role of PARP in DNA repair, PARP inhibition has been shown to potentiate DNA damage induced by platinum agents as well as other inhibitors of DNA synthesis such as gemcitabine and overcome

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## Translational Relevance

The therapeutic strategy of PARP inhibition has been extensively evaluated in recent years and various PARP inhibitors including olaparib are being studied in different clinical trials. However, recently concluded studies have shown that combining cytotoxic chemotherapy with PARP inhibitors produces dose-limiting adverse events, especially significant myelosuppression.

We believe our study is the first to evaluate a combination of the PARP inhibitor olaparib with cisplatin and gemcitabine using two different schedules of administration of olaparib. We have shown that despite using lower-than-normal doses of cytotoxic chemotherapy and two different dosing schedules, the addition of olaparib causes significant myelosuppression. Our correlative studies reveal that multiple doses of olaparib are required for sustained inhibition of PARP.

Hence, novel schedules of administration need to be explored including intermittent dosing to result in adequate inhibition of the primary target and better tolerance when combined with chemotherapy.

acquired resistance to these agents (7, 8). We conducted a phase 1 study to evaluate the safety and tolerability of olaparib administered with cisplatin and gemcitabine, an active regimen in several solid tumors.

## Patients and Methods

### Patients

Eligibility criteria included histologically confirmed advanced solid tumors for which standard curative treatments do not exist; completion of chemotherapy, radiotherapy, or surgery $\geq$4 weeks before study enrollment; age >18 years; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2; life expectancy 3 months or more; adequate organ and bone marrow function; and signed informed consent. Exclusion criteria included uncontrolled intercurrent illness, unstable brain metastases, primary CNS malignancies, and known deleterious BRCA1 and BRCA2 mutations (protocol was later amended to delete this exclusion criterion).

The primary endpoints were to establish the safety and tolerability of olaparib in combination with cisplatin and gemcitabine, determine the maximum tolerated dose (MTD), and evaluate the effect of treatment in peripheral blood mononuclear cells (PBMC) and tumor biopsies. The secondary objective was to evaluate the pharmacokinetics of olaparib.

This trial was approved by the Institutional Review Board. All patients provided written informed consent.

### Study design

For this study (NCT00678132), cohorts of 3 to 6 patients were enrolled at each dose level. At DL1, olaparib was administered orally twice daily on days 1 to 4. Cisplatin was administered i.v. at 60 mg/m$^2$ over 1 hour on day 3 and gemcitabine at 500 mg/m$^2$ i.v. over 1 hour on days 3 (after cisplatin) and 10. Because of significant myelosuppression the protocol was amended to enroll patients treated with 2 or less prior severely myelosuppressive chemotherapy regimens and initiate treatment with olaparib at 100 mg once daily on days 1 to 4 (DL−1). Because of persistent myelotoxicity following a return to DL1, olaparib administration was amended to 100 mg twice daily on day 1 only. Cisplatin and gemcitabine were administered at the same dose on day 1 and day 1 and 8, respectively. Treatment was repeated every 3 weeks up to a maximum of 6 cycles, disease progression, or development of intolerable toxicity. Dose modifications were carried out in patients who developed severe toxicities based on predefined criteria.

The MTD was the dose level at which no more than 1 of up to 6 patients experienced dose-limiting toxicities (DLT) during the first cycle of treatment and the dose below that at which at least 2 of $\leq$6 patients experienced a DLT. The definition of DLTs and detailed study assessments are provided in the Supplementary Section. Toxicity assessment was according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

### Pharmacodynamic analysis

Pharmacodynamic studies included estimation of PAR by ELISA in PBMCs and tumor samples. Pre- and posttreatment tumor biopsies were conducted in 2 patients. The prestudy biopsy was conducted within 1 week of the start of treatment, and the posttreatment biopsy was conducted on day 4 of cycle 1, 24 hours $\pm$ 4 hours after first dose of cisplatin/gemcitabine. PBMC samples were obtained at the following time points: when olaparib was administered from days 1 through 4, prestudy before day 1, 6 hours postdose on days 2 to 4, and before the first dose of olaparib on day 1 of cycle 2; when olaparib was administered on day 1 only, predose on day 1, 6, 12, 24, and 48 hours after the first dose of olaparib on day 1, and before the first dose of olaparib on day 1 of cycle 2. Details of sample processing and analysis are presented in the Supplementary Section.

### Pharmacokinetic analysis

Serial plasma samples for olaparib were collected and analyzed over 3 days. Plasma samples for olaparib and gemcitabine were collected and analyzed at predose and 30 minutes after initiation of gemcitabine infusion and 0.5, 1, 2, 3, 5, and 8 hours after the end of the infusion on day 1. The same sampling schedule was repeated on day 8 for gemcitabine. Details of sample processing and bioanalysis are presented in the Supplementary Section.

Pharmacokinetic parameters were estimated using noncompartmental methods for rich sample sets and population pharmacokinetic methods for sparse data. A one-compartment model with first-order absorption ($k_a$) and elimination parameterized in apparent volume of distribution (V/F) and clearance (CL/F) was used to describe the drug concentrations. Parameters and additional metrics were estimated with WinNonlin Professional version 5.0



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(Pharsight Corporation) and MONOLIX software version 3.2 for use of the SAEM algorithm in population. Details on the population modeling are included in the Supplementary Section.

Statistical analysis for the pharmacokinetic parameters was conducted with S-Plus v8.0 (Insightful Corporation). The nonparametric Wilcoxon rank-sum test was used for nonpaired data and the Wilcoxon signed-rank test for paired data. All $P$ values were 2-tailed with $P < 0.05$ considered statistically significant. Pharmacokinetic evaluations were conducted in an exploratory manner without any formal adjustment for multiple comparisons.

## Results

Between May 2008 and November 2009, 23 patients were enrolled (Table 1).

**Table 1.** Patient characteristics

| Patient characteristic | N (%) |
|---|---|
| Patients enrolled | 23 |
| Gender | |
| Male | 14 (61) |
| Female | 9 (39) |
| Age, y | |
| Median | 52 |
| Range | 25–88 |
| ECOG performance status | |
| 0 | 2 (9) |
| 1 | 19 (83) |
| 2 | 2 (9) |
| Tumor type | |
| Non–small cell lung cancer | 8 (35) |
| Ovarian | 3 (13) |
| Pancreatic | 3 (13) |
| Esophageal | 2 (9) |
| Thymic carcinoma | 2 (9) |
| Others[a] | 5 (21) |

[a]Others include head and neck, adrenocortical, sarcoma, mesothelioma, and small-cell lung cancers.

### DLTs and MTD

Two of the first 3 patients enrolled at DL1 experienced DLTs. One patient developed grade IV thrombocytopenia on day 16, which resolved within 1 day. Another patient developed grade IV neutropenia on day 17 that resolved after 5 days, an infection on day 18 and grade IV thrombocytopenia on day 16 that resolved within 1 day.

The next 3 patients were treated at DL−1 (olaparib 100 mg once daily from days 1–4, cisplatin 50 mg/m$^2$ on day 3, and gemcitabine 400 mg/m$^2$ on days 3 and 10) and no DLTs were observed. Following this, the protocol was amended to include patients who had received no more than 2 prior severely myelosuppressive chemotherapy regimens and start treatment at DL−1. Three patients were treated and no DLTs were observed. Thereafter, 3 patients were enrolled and treated at the next higher dose level, that is, DL1. One of 3 patients developed a DLT: grade IV thrombocytopenia on day 15 that resolved within 2 days. Because of the development of a DLT in 1 of 3 patients, this cohort was expanded to 6 patients. Two of the next 3 patients developed DLTs: one patient developed grade IV neutropenia and grade IV thrombocytopenia on day 16, which resolved after 10 and 4 days, respectively. Another patient developed grade IV thrombocytopenia on day 16, which lasted for 4 days.

Because of persistent myelotoxicity, the protocol was further amended to administer olaparib at 100 mg orally twice daily for 1 day only along with cisplatin on day 1 and gemcitabine on days 1 and 8 at previously described doses. Three patients were treated at DL1: one developed a DLT consisting of an upper gastrointestinal bleed on day 10, due to a duodenal ulcer and no further treatment was given. Three more patients were treated at DL1 and no further DLTs were seen. Dose escalation was then conducted but only 2 patients were treated at DL2 (cisplatin increased from 60 to 75 mg/m$^2$; olaparib and gemcitabine doses unchanged) and both developed nonhematologic DLTs. One patient developed a grade III syncopal episode of unclear etiology on day 6. Another patient developed grade III hypoxia on day 7 and received no further treatment. A computed tomographic scan of the chest showed diffuse bronchiolitis and symptoms improved substantially after initiation of steroid therapy. Hence, we believe the patient might have experienced pneumonitis that was possibly related to treatment.

On the basis of these findings, the MTD was determined to be olaparib 100 mg once daily on day 1, cisplatin 60 mg/m$^2$ on day 1, and gemcitabine 500 mg/m$^2$ on days 1 and 8.

### Adverse event profile

Anemia and leukopenia were mainly grade I or II (52% and 61%, respectively) and neutropenia, lymphopenia, and thrombocytopenia were mainly grade III–IV (61%, 61%, and 57%, respectively). The degree of myelosuppression did not change even after enrolling patients who were less heavily pretreated and decreasing the duration of olaparib. Nonhematologic toxicity was generally mild (grade I and II; Tables 2 and 3).

### Pharmacodynamic studies

Analysis of PAR levels in PBMCs showed that olaparib was inhibiting its primary target, that is, PARP-1 (Fig. 1). However there were differences in the degree and duration of inhibition that were dependent on the number of doses of olaparib administered. In 10 of 15 patients who received olaparib for 4 days every 21 days, PBMC samples were available for measurement of PAR at baseline, end of olaparib administration on day 4, and before initiation of cycle 2 of treatment. In all cases, PAR levels at the end of olaparib administration were lower than at baseline. However, in 5 of 10 cases PAR levels had rebounded to levels greater than at baseline before initiation of cycle 2.



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**Table 2.** Hematologic adverse events, at least possibly related to therapy

| Adverse event | Original schema[a], DL1 (N = 3) | First amendment[b], DL−1 (N = 6) | First amendment, DL1 (N = 6) | Second amendment[c], DL1 (N = 6) | Second amendment, DL2 (N = 2) | Total, (N = 23) |
|---|---|---|---|---|---|---|
| Anemia | | | | | | |
| Grade I–II | 1 | 4 | 2 | 4 | 1 | 12 (52%) |
| Grade III–IV | 1 | 2 | 3 | 2 | 0 | 8 (35%) |
| Leucopenia | | | | | | |
| Grade I–II | 1 | 6 | 3 | 4 | 0 | 14 (61%) |
| Grade III–IV | 2 | 0 | 3 | 1 | 1 | 7 (30%) |
| Neutropenia | | | | | | |
| Grade I–II | 1 | 3 | 1 | 2 | 0 | 7 (30%) |
| Grade III–IV | 2 | 3 | 5 | 3 | 1 | 14 (61%) |
| Lymphopenia | | | | | | |
| Grade I–II | 1 | 2 | 2 | 2 | 0 | 7 (30%) |
| Grade III–IV | 1 | 4 | 4 | 3 | 2 | 14 (61%) |
| Thrombocytopenia | | | | | | |
| Grade I–II | 0 | 5 | 1 | 3 | 0 | 9 (39%) |
| Grade III–IV | 2 | 1 | 5 | 3 | 2 | 13 (57%) |

[a]Olaparib twice a day D1–D4, cisplatin D3, gemcitabine D3 and D10.
[b]Patients should not have received more than 2 prior severely myelosuppressive chemotherapy regimens; olaparib every day D1–D4, cisplatin D3, gemcitabine D3 and D10.
[c]Olaparib twice a day D1, cisplatin D1, gemcitabine D1 and D8.

Among patients who received olaparib for 1 day every 21 days, PBMC samples were available for measurement of PAR at baseline, 6-, 12-, 24-, and 48-hour postdosing and before commencement of cycle 2 in 5 of 8 patients. Although PAR inhibition was seen in all cases, the levels had started rebounding toward baseline within 36 hours of the last dose of olaparib and exceeded baseline value in 4 of 5 cases before commencement of cycle 2. Assessment of PAR levels in tumor samples was conducted in the first 2 patients enrolled on the study and showed significant inhibition of PAR on a repeat biopsy conducted on day 4 of treatment.

### Pharmacokinetics of olaparib

Pharmacokinetics of gemcitabine was as expected and not influenced by olaparib coadministration (see Supplementary Results). Following administration of two 50 mg olaparib tablets, oral absorption was relatively rapid with a mean $C_{max}$ of 2,399.8 ± 1,371.5 μg/L observed at 2 hours in 8 patients versus 2,932.8 ± 672.6 μg/L observed at 1 hour in 5 frequently sampled patients receiving a first dose of olaparib ($n = 13$). Comparatively, the mean $C_{max}$ of olaparib when coadministered with gemcitabine on day 1 in a separate cohort ($n = 8$) was 3,772.3 ± 1,366.7 μg/L at approximately 3.37 hours on average, a statistically significant increase in $C_{max}$ of 44.8% over monotherapy ($P = 0.047$, exact Wilcoxon rank-sum; Fig. 2). Similar intergroup comparisons of $AUC_{0-12hr}$ showed a greater (compared with $C_{max}$) increase in olaparib exposure (1.79-fold AUC increase over olaparib alone) when coadministered with gemcitabine (Fig. 3; $P = 0.0464$, Wilcoxon rank-sum, olaparib $n = 9$, olaparib + gemcitabine $n = 8$). Intrapatient comparisons were consistent with these results as the relative exposure of olaparib given with gemcitabine in the morning was greater in 6 of 7 evaluable patients than with olaparib alone given in the evening (Fig. 3), as the mean $AUC_{0-12h}$ for the first and second doses (adjusted for residual trough values) were 19.66 ± 6.4 and 16.97 ± 6.4 mg hr/L, respectively ($P = 0.0469$, exact Wilcoxon signed-rank test, $n = 7$ subjects with percentage of AUC extrapolated <35% of second dose AUC).

### Olaparib multiple dose pharmacokinetics

For the cohort of patients who received olaparib twice daily for 4 days, expected levels of accumulation (i.e., $C_{max\_nth}/C_{max\_1st}$ and $AUC_{ss}/AUC_{0-12hr}$) were observed on day 2 suggestive of linear pharmacokinetics (based on the dosing interval/half-life ratio). The mean observed accumulation on day 2 was 1.3-fold for twice daily dosing where all observed $T_{max}$ values were at 1 or 2 hours. The mean observed accumulation of olaparib on day 3 when given with gemcitabine was 1.51- and 1.61-fold for $C_{max}$ and $AUC_{0-12hr}$, respectively, which was approximately 20% to 30% higher than expected steady-state levels and significantly higher than the immediately preceding dose level ($P = 0.0195$ and 0.0273, exact Wilcoxon signed-rank test, $n = 9$) suggesting a potential impact on olaparib exposure in the presence of gemcitabine.

### Pairwise effect of gemcitabine on olaparib pharmacokinetics

The effect of gemcitabine on olaparib pharmacokinetics was observed in patients who received olaparib on day 1



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**Table 3.** Nonhematologic adverse events, at least possibly related to therapy

| Adverse event | Original schema[a], DL1 (N = 3) | First amendment[b], DL−1 (N = 6) | First amendment, DL1 (N = 6) | Second amendment[c], DL1 (N = 6) | Second amendment, DL2 (N = 2) |
|---|---|---|---|---|---|
| Hypoalbuminemia | | | | | |
| Grade I–II | 1 | 4 | 4 | 6 | 2 |
| Grade III–IV | 2 | 1 | 0 | 0 | 0 |
| Dyselectrolytemia | | | | | |
| Grade I–II | 1 | 5 | 2 | 4 | 0 |
| Grade III–IV | 2 | 0 | 3 | 2 | 2 |
| Azotemia | | | | | |
| Grade I–II | 0 | 3 | 1 | 3 | 2 |
| Grade III–IV | 0 | 0 | 0 | 0 | 0 |
| Transaminitis | | | | | |
| Grade I–II | 2 | 4 | 3 | 3 | 2 |
| Grade III–IV | 0 | 0 | 0 | 0 | 0 |
| Hyperbilirubinemia | | | | | |
| Grade I–II | 2 | 3 | 1 | 1 | 0 |
| Grade III–IV | 1 | 0 | 0 | 0 | 0 |
| Elevated Alkaline Phosphatase | | | | | |
| Grade I–II | 1 | 1 | 3 | 4 | 1 |
| Grade III–IV | 1 | 0 | 0 | 0 | 0 |
| Infection | | | | | |
| Grade I–II | 0 | 0 | 0 | 1 | 1 |
| Grade III–IV | 2 | 2 | 1 | 0 | 1 |
| Fatigue | | | | | |
| Grade I–II | 0 | 3 | 3 | 1 | 1 |
| Grade III–IV | 0 | 0 | 0 | 0 | 0 |
| Constipation | | | | | |
| Grade I–II | 1 | 0 | 1 | 4 | 0 |
| Grade III–IV | 0 | 0 | 0 | 0 | 0 |
| Nausea | | | | | |
| Grade I–II | 2 | 3 | 3 | 3 | 1 |
| Grade III–IV | 0 | 0 | 0 | 0 | 0 |
| Vomiting | | | | | |
| Grade I–II | 0 | 0 | 2 | 1 | 1 |
| Grade III–IV | 0 | 0 | 1 | 0 | 0 |
| Diarrhea | | | | | |
| Grade I–II | 2 | 1 | 0 | 0 | 0 |
| Grade III–IV | 0 | 0 | 1 | 0 | 0 |
| Hypoxia | | | | | |
| Grade I–II | 0 | 0 | 0 | 0 | 0 |
| Grade III–IV | 0 | 0 | 0 | 0 | 1 |
| Syncope | | | | | |
| Grade I–II | 0 | 0 | 0 | 0 | 0 |
| Grade III–IV | 0 | 0 | 0 | 0 | 1 |
| Dizziness | | | | | |
| Grade I–II | 0 | 0 | 0 | 0 | 1 |
| Grade III–IV | 0 | 0 | 0 | 1 | 0 |
| Gastrointestinal bleed | | | | | |
| Grade I–II | 0 | 0 | 0 | 0 | 0 |
| Grade III–IV | 0 | 0 | 0 | 1 | 0 |
| Elevated troponin I | | | | | |
| Grade I–II | 0 | 0 | 0 | 0 | 0 |
| Grade III–IV | 0 | 0 | 0 | 1 | 0 |

[a]Olaparib twice a day D1–D4, cisplatin D3, gemcitabine D3 and D10.

[b]Patients should not have received more than 2 prior severely myelosuppressive chemotherapy regimens; olaparib every day D1–D4, cisplatin D3, gemcitabine D3 and D10.

[c]Olaparib twice a day D1, cisplatin D1, gemcitabine D1 and D8.



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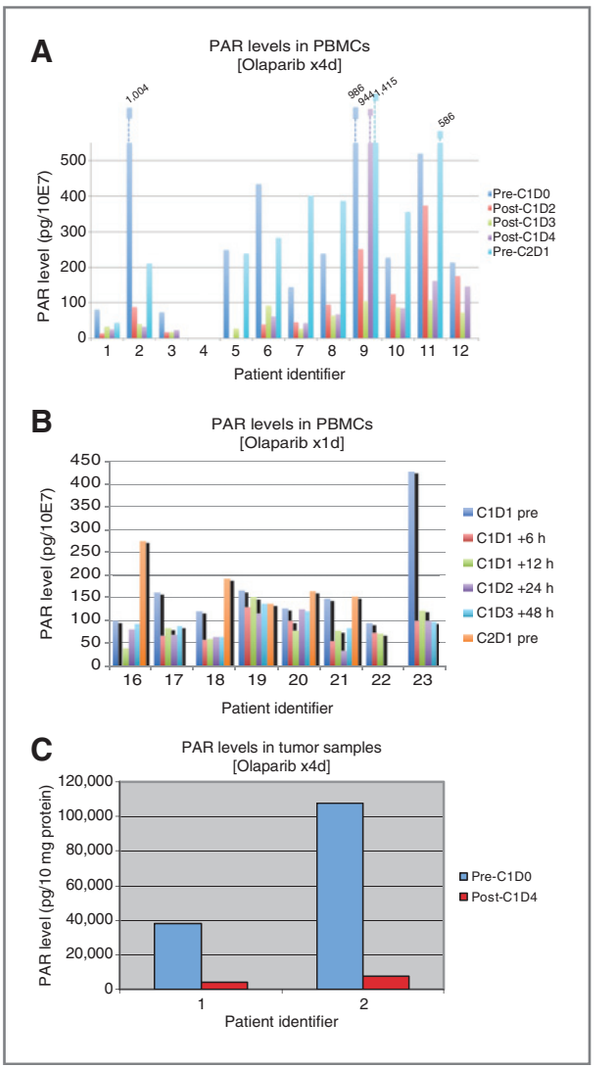


Figure 1. Effect of olaparib therapy on PAR levels. A, PAR levels in PBMCs after olaparib administration for 4 days (sample not tested for patients 3, 4, and 12 pre-C2D1 and patients 13 and 14 pre-C1D0 and post-C1D2). B, PAR levels in PBMCs after olaparib administration for 1 day (sample not tested for patient 17 pre-C2D1 and patient 22 at C1D2 + 24 hours and C1D3 + 48 hours). C, PAR levels in tumor samples after olaparib administration for 4 days.

only with gemcitabine compared with a second dose 12 hours later without gemcitabine. The mean $C_{max}$ values of olaparib during a second dose without gemcitabine was reduced in 6 of 8 patients by an average of 32% with a mean $C_{max}$ of 3,772.3 ± 1,366.7 μg/L versus 2,860.3 ± 1,087.2 μg/L ($n = 8$). The $C_{max}$ was approximately 50% lower than expected from accumulation of dose 1 trough plasma levels of 833 ± 561.7 μg/L. The second dose of olaparib displayed a prolonged elimination half-life in 6 of 8 patients with a mean of 5.46 ± 1.7 hours compared with the first dose mean of 4.07 ± 1.3 hours ($P = 0.016$, Wilcoxon signed-rank test, $n = 8$).

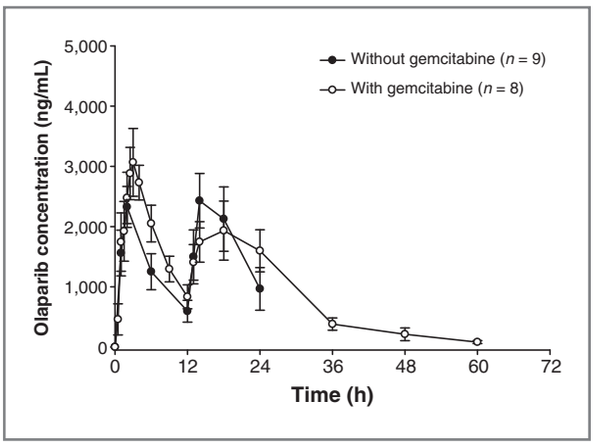


Figure 2. The mean plasma concentration versus time profile for olaparib with and without coadministration of 500 mg/m$^2$ gemcitabine.

### Antitumor activity

Twenty one patients were evaluable for response (treatment was discontinued because of development of presumed treatment-related pneumonitis in one patient and due to development of grade III thrombocytopenia and gastrointestinal bleeding in another patient). Two patients had partial response (PR), 13 stable disease (SD) with a median duration of 20 weeks (range, 6–114 weeks) and 6 progressive disease. Although patients were not screened for mutations in BRCA1 and BRCA2, 2 patients were known to have BRCA abnormalities. One patient with ovarian cancer had a variant of BRCA1 of unknown significance. She completed 6 cycles of therapy at DL−1 with SD. CA125 decreased from 311 U/mL at baseline to 12 U/mL after completion of treatment. The second patient was a male with pancreatic cancer, a past history of breast cancer and an extensive family history of breast cancer. He had a known BRCA2 mutation, completed 6 cycles of therapy at DL1, and had a confirmed PR. CA19-9 levels decreased from 3,841 U/mL at baseline to 667 U/mL at the end of treatment. Both patients received olaparib for 4 days in 21-day cycles. One patient with NSCLC had a PR and completed 6 cycles of treatment at DL−1.

## Discussion

This phase I study shows that combining olaparib with cisplatin and gemcitabine results in significant thrombocytopenia and neutropenia. The degree of myelosuppression was related to the duration of treatment with olaparib. The etiology of myelosuppression remains unclear although it could be a result of potentiation of cisplatin activity due to PARP inhibition (7). Other studies evaluating administration of PARP inhibitors with chemotherapy have also shown an association between the schedule of administration of the PARP inhibitor and the occurrence of myelosuppression. DLTs of neutropenia and thrombocytopenia have been described with a 7-day course of olaparib in combination with dacarbazine administered in 21-day cycles (5). A higher degree of myelosuppression than



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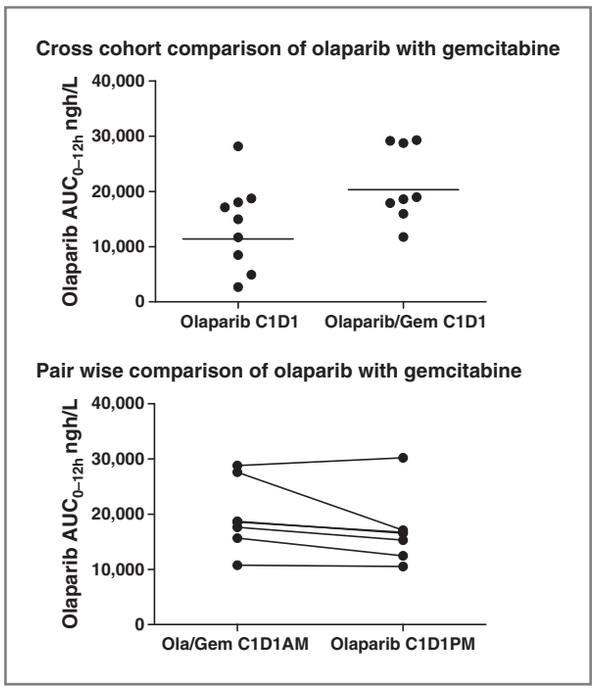


Figure 3. Cross cohort and pairwise comparison of olaparib (Ola) $AUC_{0-12hr}$ following the first dose with and without coadministration of 500 mg/m$^2$ gemcitabine (Gem, $P = 0.047$ and $P = 0.0469$).

expected has also been noted with a 5-day course of the PARP-1 inhibitors AG014699 and INO-1001 administered every 4 weeks in combination with temozolomide (9, 10). Higher than expected thrombocytopenia was also seen in a phase II study evaluating the PARP inhibitor veliparib (ABT888) used for 7 days in combination with temozolomide given concurrently for 5 days of a 28-day cycle (11). Interestingly, in a randomized phase 2 study of 123 patients with metastatic triple-negative breast cancer evaluating carboplatin and gemcitabine with or without the PARP inhibitor iniparib administered on days 1, 4, 8, and 11 of a 21-day cycle, there was no significant difference in the frequency of adverse events, including myelosuppression between the 2 treatment arms. This study showed that the addition of iniparib to chemotherapy improved the rate of clinical benefit and survival (12). However a randomized phase III study of the same combination in 519 patients with metastatic triple-negative breast cancer failed to show a statistically significant improvement in progression-free and overall survival (13). Because iniparib is thought to be a much weaker PARP inhibitor than the other agents under development, the lesser potency may well be a factor mitigating the hematologic toxicity (14–16).

In our study, olaparib pharmacokinetics appeared to be influenced by coadministration of gemcitabine and olaparib exposure may be modestly increased by concomitant gemcitabine administration at doses of at least 400 mg/m$^2$. Increased sensitivity to DNA-damaging agents has been showed in PARP knockout mice (17). Hence, an increase in olaparib exposure in the presence of cisplatin, which causes DNA double-strand breaks, could potentially explain the higher degree of myelosuppression due to an effect on rapidly dividing bone marrow cells. Pharmacodynamic data from our study suggest that multiple doses of olaparib are required for sustained inhibition of PARP during the course of a 21-day cycle with an intermittent schedule of administration to prevent dose-limiting myelosuppression. Maximum inhibition of PAR was seen between 6 and 24 hours after the first dose of olaparib administration with 2 doses in one day. PAR levels had started approaching baseline values within 36 hours of the last dose of olaparib and exceeded baseline values in 80% of cases before the next cycle of treatment.

Of the 2 patients who had PR observed in our study, one patient was known to have a mutation in BRCA2. The benefits of adopting a synthetic lethal approach using PARP inhibition in cancers harboring BRCA mutations are well described (4, 18, 19). However, tumor cells can be susceptible to PARP inhibition in the presence of other defects in DNA repair by homologous recombination, such as loss of function of the Fanconi anemia repair pathway and mutations in the ataxia telangiectasia gene (20–23). Screening tumors for non-BRCA defects in the homologous recombination pathway could help identify patients with tumors sensitive to PARP inhibition.

Development of significant myelotoxicity prevents the use of standard doses of cisplatin and gemcitabine chemotherapy in combination with olaparib. Newer schedules of administration, the selection of a PARP inhibitor based on specificity for PARP isoforms and potency and patient selection based on genotypic factors affecting DNA repair, need to be explored in future trials.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## References

1. Ame JC, Spenlehauer C, de Murcia G. The PARP superfamily. Bioessays 2004;26:882–93.

2. Dantzer F, de La Rubia G, Menissier-De Murcia J, Hostomsky Z, de Murcia G, Schreiber V. Base excision repair is impaired in mammalian



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cells lacking Poly(ADP-ribose) polymerase-1. Biochemistry 2000;39: 7559–69.
3. Menear KA, Adcock C, Boulter R, Cockcroft XL, Copsey L, Cranston A, et al. 4-[3-(4-cyclopropanecarbonylpiperazine-1-carbonyl)-4-fluorobenzyl]-2H-phth alazin-1-one: a novel bioavailable inhibitor of poly(ADP-ribose) polymerase-1. J Med Chem 2008;51:6581–91.
4. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123–34.
5. Khan OA, Gore M, Lorigan P, Stone J, Greystoke A, Burke W, et al. A phase I study of the safety and tolerability of olaparib (AZD2281, KU0059436) and dacarbazine in patients with advanced solid tumours. Br J Cancer 2011;104:750–5.
6. Zamble DB, Lippard SJ. Cisplatin and DNA repair in cancer chemotherapy. Trends Biochem Sci 1995;20:435–9.
7. Miknyoczki SJ, Jones-Bolin S, Pritchard S, Hunter K, Zhao H, Wan W, et al. Chemopotentiation of temozolomide, irinotecan, and cisplatin activity by CEP-6800, a poly(ADP-ribose) polymerase inhibitor. Mol Cancer Ther 2003;2:371–82.
8. Jacob DA, Bahra M, Langrehr JM, Boas-Knoop S, Stefaniak R, Davis J, et al. Combination therapy of poly (ADP-ribose) polymerase inhibitor 3-aminobenzamide and gemcitabine shows strong antitumor activity in pancreatic cancer cells. J Gastroenterol Hepatol 2007;22:738–48.
9. Bedikian AY, Papadopoulos NE, Kim KB, Hwu WJ, Homsi J, Glass MR, et al. A phase IB trial of intravenous INO-1001 plus oral temozolomide in subjects with unresectable stage-III or IV melanoma. Cancer Invest 2009;27:756–63.
10. Plummer R, Jones C, Middleton M, Wilson R, Evans J, Olsen A, et al. Phase I study of the poly(ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumors. Clin Cancer Res 2008;14:7917–23.
11. Isakoff SJ, Overmoyer B, Tung NM, Gelman RS, Giranda VL, Bernhard KM, et al. A phase II trial of the PARP inhibitor veliparib (ABT888) and temozolomide for metastatic breast cancer. J Clin Oncol 28:15s, 2010 (suppl; abstr 1019).
12. O'Shaughnessy J, Osborne C, Pippen JE, Yoffe M, Patt D, Rocha C, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. N Engl J Med 2011;364:205–14.
13. O'Shaughnessy J, Schwartzberg LS, Danso MA, Rugo HS, Miller K, Yardley DA, et al. A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). J Clin Oncol 29:2011 (suppl; abstr 1007).
14. Carey LA, Sharpless NE. PARP and cancer–if it's broke, don't fix it. N Engl J Med 2011;364:277–9.
15. Maegley KA, Bingham P, Tatlock JH, Thomas HD. All PARP inhibitors are not equal: an *in vitro* mechanistic comparison of PF-01367338 to iniparib. J Clin Oncol 29: 2011 (suppl; abstr e13576).
16. Mendeleyev J, Kirsten E, Hakam A, Buki KG, Kun E. Potential chemotherapeutic activity of 4-iodo-3-nitrobenzamide. Metabolic reduction to the 3-nitroso derivative and induction of cell death in tumor cells in culture. Biochem Pharmacol 1995;50:705–14.
17. Shall S, de Murcia G. Poly(ADP-ribose) polymerase-1: what have we learned from the deficient mouse model?Mutat Res 2000;460: 1–15.
18. Ashworth A. A synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol 2008;26: 3785–90.
19. Kaelin WG Jr. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 2005;5:689–98.
20. McCabe N, Turner NC, Lord CJ, Kluzek K, Bialkowska A, Swift S, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res 2006;66:8109–15.
21. Wang Z, Li M, Lu S, Zhang Y, Wang H. Promoter hypermethylation of FANCF plays an important role in the occurrence of ovarian cancer through disrupting Fanconi anemia-BRCA pathway. Cancer Biol Ther 2006;5:256–60.
22. Marsit CJ, Liu M, Nelson HH, Posner M, Suzuki M, Kelsey KT. Inactivation of the Fanconi anemia/BRCA pathway in lung and oral cancers: implications for treatment and survival. Oncogene 2004;23: 1000–4.
23. Lo YL, Hsiao CF, Jou YS, Chang GC, Tsai YH, Su WC, et al. ATM polymorphisms and risk of lung cancer among never smokers. Lung Cancer 2010;69:148–54.



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# A Phase I Combination Study of Olaparib with Cisplatin and Gemcitabine in Adults with Solid Tumors

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