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A Phase I Study of Veliparib in Combination with Metronomic Cyclophosphamide in Adults with Refractory Solid Tumors and Lymphomas

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Abstract

Purpose—Oral administration of the alkylating agent cyclophosphamide at low doses, metronomic dosing, is well tolerated, with efficacy in multiple tumor types. Poly(ADP-ribose) polymerase (PARP) inhibition potentiates effects of cyclophosphamide in preclinical models. We conducted a phase I trial of the PARP inhibitor veliparib and metronomic cyclophosphamide in patients with refractory solid tumors and lymphoid malignancies.

Experimental Design—Objectives were to establish the safety and maximum tolerated dose (MTD) of the combination; characterize veliparib pharmacokinetics; measure poly(ADP-ribose) (PAR), a product of PARP, in tumor biopsies and peripheral blood mononuclear cells (PBMCs); and measure the DNA-damage marker γH2AX in PBMCs and circulating tumor cells (CTCs). Cyclophosphamide was administered once daily in 21-day cycles in combination with veliparib administered once daily for 7, 14, or 21 days.

Results—Thirty-five patients were enrolled. The study treatment was well tolerated, and the MTD was established as veliparib 60 mg with cyclophosphamide 50 mg given once daily. Seven

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patients had partial responses; an additional six patients had disease stabilization for at least six cycles. PAR was significantly decreased in PBMCs (by at least 50%) and tumor biopsies (by at least 80%) across dose levels; γH2AX levels were increased in CTCs from seven of nine patients evaluated after drug administration.

Conclusions—The combination of veliparib with metronomic cyclophosphamide is well tolerated and shows promising activity in a subset of patients with *BRCA* mutations. A phase II trial of the combination compared to single-agent cyclophosphamide is ongoing in *BRCA*-positive ovarian cancer, triple-negative breast cancer, and low-grade lymphoma.

Keywords

PARP inhibitor; DNA damage; BRCA mutations; chemopotentiation; DNA repair defects

INTRODUCTION

Poly(ADP-ribose) polymerase (PARP) enzymes are characterized by the ability to poly(ADP-ribosyl)ate protein substrates (1, 2). PARP-1 and PARP-2 help maintain genomic stability by regulating the repair of DNA damage; PARP inhibition potentiates the DNA-damaging effects of alkylating agents, including cyclophosphamide, by interfering with the repair of DNA damage (3, 4). PARP inhibition in homozygous *BRCA*-deficient cells produces synthetic lethality, making PARP inhibitors attractive therapeutic agents for patients with *BRCA* mutations (5-7). Veliparib (ABT-888), a potent, oral small molecule, inhibits PARP activity significantly in tumors at clinically achievable concentrations (4, 8). We hypothesized that co-administration of a PARP inhibitor with metronomic cyclophosphamide would be well tolerated and might enhance the therapeutic index because of the known modest toxicity of cyclophosphamide administered on a daily, oral schedule.

Chronic administration of the alkylating agent cyclophosphamide at low doses, known as metronomic dosing, is effective in lymphoma and multiple tumor types, including ovarian, prostate, and breast cancer (9-12). In addition to inducing DNA damage, metronomic cyclophosphamide may target tumor angiogenesis by reducing tumor endothelial cell proliferation through activation of thrombospondin 1 (13, 14). It has also been reported to reduce the population of CD4+CD25+ regulatory T cells that suppress antitumor immunity (15).

We conducted a phase I trial of the combination of veliparib with metronomic oral cyclophosphamide in patients with refractory solid tumors and lymphoid malignancies. The objectives were to establish the safety, tolerability, and maximum tolerated dose (MTD) of the combination; to determine the pharmacokinetics (PK) of veliparib; and to examine the effects on PARP activity and phosphorylated histone H2AX (γH2AX) levels, a marker of DNA double-strand breaks, in peripheral blood mononuclear cells (PBMCs), tumor biopsies, and circulating tumor cells (CTCs).

PATIENTS AND METHODS

Eligibility criteria

Patients (age ≥ 18 years) were eligible if they had pathologically confirmed metastatic solid tumor or low-grade lymphoma for which there was no acceptable standard therapy; a Karnofsky performance status ≥ 60%; and adequate liver, kidney, and marrow function defined as absolute neutrophil count ≥ 1,500/μL, platelets ≥ 100,000/μL, total bilirubin ≤ 1.5 X the upper limit of normal (ULN), aspartate aminotransferase and/or alanine

aminotransferase < 2.5 X ULN, creatinine < 1.5 X ULN. Prior exposure to PARP inhibitors or cyclophosphamide was allowed.

Previous anticancer therapy or surgery must have been completed at least 4 weeks prior to enrollment; patients were required to have evidence of disease progression on previous therapy by staging scans. Patients unable to swallow pills or those with uncontrolled intercurrent illness; brain metastases within the past 3 months; history of seizures (high-dose veliparib caused seizures in a preclinical model); or gastrointestinal conditions that might predispose to drug intolerability or poor drug absorption were excluded. Documentation of *BRCA* mutation status was not required.

This trial was conducted under a National Cancer Institute (NCI)-sponsored IND with institutional review board approval at each participating site. Protocol design and conduct followed all applicable regulations, guidances, and local policies. [ClinicalTrials.gov Identifier: NCT00810966].

Trial design

This was an open-label, multicenter, single-arm phase I combination study of veliparib and metronomic oral cyclophosphamide in patients with advanced malignancies. The Division of Cancer Treatment and Diagnosis, NCI, supplied veliparib under a Collaborative Research and Development Agreement with Abbott Laboratories. Cyclophosphamide was obtained through commercial sources.

Cyclophosphamide was administered orally once daily throughout a 21-day cycle. Veliparib was administered orally once daily, with cyclophosphamide, for the first 7, 14, or 21 days of the cycle, depending on dose level (DL). Starting doses were veliparib 20 mg daily and cyclophosphamide 50 mg daily (Table 1). Dose escalation did not follow the Fibonacci schema due to low anticipated toxicity and desire to provide uninterrupted PARP inhibition coverage to the majority of patients given the potential for clinical benefit.

A standard phase I dose escalation design (3 + 3) was employed. Higher DLs were not opened until the last patient in the previous cohort had completed one cycle. Intrapatient dose escalation was allowed once three new patients completed that dose level without grade 2 or higher toxicity and the given patient was tolerating therapy well. Adverse events were graded according to NCI Common Toxicity Criteria version 3.0. Dose-limiting toxicity (DLT) was defined as an adverse event that occurred in the first cycle, was felt to be related to the study drugs, and fulfilled one of the following criteria: grade 3 or greater nonhematologic toxicity (except grade 3 nausea/vomiting and diarrhea without maximal symptomatic treatment, grade 3 creatinine and electrolyte abnormalities that corrected to grade 1 or baseline within 24 hours); grade 4 neutropenia; grade 4 thrombocytopenia; or a ≥ 2-week delay in starting the next cycle due to toxicity. Any degree of anemia, leucopenia in the absence of neutropenia, or lymphopenia was not considered dose limiting. Patients were considered evaluable for cohort dose escalation decisions if they either experienced DLT or completed one full cycle without DLT and received at least 80% of the planned dose.

Toxicities had to resolve to grade 1 or less for non-hematologic toxicities (except electrolyte abnormalities, which had to resolve to grade 2 or less) and grade 2 or less for hematologic toxicities, before starting the next cycle. Treatment could be delayed for a maximum of 2 weeks to allow resolution of toxicities. If toxicities did not resolve as defined above, patients were taken off study treatment. DLT resulted in a reduction in DL. The MTD was defined as the DL at which zero or one of six patients experienced DLT, and the DL below one in which two or more patients experienced DLT. Six additional patients were accrued at the MTD to further evaluate PK and pharmacodynamics (PD).

Safety and efficacy evaluations

History and physical examination, including performance status and vital signs, were performed at baseline and repeated at the start of every cycle. Complete blood counts with differential and serum chemistries were performed at baseline, weekly during cycle 1, and the start of every cycle from cycle 2 onwards. In the studies conducted with veliparib, there has been no indication of cardiac toxicity related to study drug, therefore, EKG was performed at baseline only and repeated as clinically indicated. Radiographic evaluation was performed at baseline and every two cycles to assess tumor response based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (16).

Pharmacokinetic evaluations

Veliparib PK analysis was performed over a 24-hour period (samples collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours post-dose) on day 1 of cycle 1 and on the last day veliparib was administered in cycle 1 (day 7, 14, or 21, depending on dose level). Blood samples were centrifuged at 1,000 × *g* and plasma stored at -70°C until analysis. Plasma veliparib concentrations were quantified with a liquid chromatography-mass spectrometry assay validated to FDA guidelines (17). See Supplementary Data for additional details.

Pharmacodynamic evaluations

PBMC samples for PD analysis were obtained in 8-mL Cell Prep Tubes (Becton Dickinson, Franklin Lakes, NJ) on days 1 and 21 of the first cycle over a 24-hour period (pre-dose and 2, 4, 6, and 24 hours post-dose). Optional tumor biopsies were collected pre-dose and 2 to 6 hours (or 24 hours for the MTD expansion cohort) after the last dose of veliparib in cycle 1. Poly(ADP-ribose) (PAR), a product of PARP, was measured in PBMCs and tumor biopsies using a validated immunoassay as previously described (8, 18). Levels of γH2AX were measured in PBMCs and CTCs using standard operating procedures previously described for the validated immunofluorescence assays (19-21).

Statistical analyses

Statistical analyses for PK parameters and concentration values were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL). Values were compared using a two-tailed, paired exact Wilcoxon signed-rank test; $P < 0.05$ was considered significant.

Blyth-Still-Casella 95% confidence intervals were calculated for the true probability across patients for change in PAR levels using StatXact 4.0 (Cytel, Inc., Cambridge, MA) (22, 23). These confidence intervals were for descriptive purposes only, as PAR threshold values were influenced by the observations.

RESULTS

Demographics

Thirty-five patients with advanced malignancies were enrolled (Table 2). Two patients on DL 7 did not complete a full cycle of therapy and were not included in the MTD determination. One patient developed a small bowel obstruction shortly after enrollment that was considered secondary to disease progression and adhesions from prior surgeries, and was taken off study. One patient required intervention for pericardial involvement by tumor, necessitating discontinuation of study therapy. Patients were heavily pretreated; 16 had received prior intravenous cyclophosphamide and three received prior oral cyclophosphamide, in combination with other therapeutic agents. Three patients had prior single-agent PARP inhibitor therapy (one received veliparib, two received olaparib).

Toxicity

The study regimen was well tolerated. Grade 2 myelosuppression (with some higher grade lymphopenia) was the most common toxicity across dose levels (Table 1). At DL 8, two patients developed DLTs. One patient with advanced breast cancer and baseline dyspnea on exertion developed worsening dyspnea, hypoxia, and eventually acute respiratory failure during the first week of treatment. No clear evidence of cardiac dysfunction or disease progression in the lungs was documented. This patient died a few days later despite best supportive care. The treating physician felt the cause of death was likely disease progression, but the possibility that the study drug combination may have contributed to the respiratory failure could not be excluded. A second patient with metastatic breast cancer and extensive liver involvement presented with worsening abdominal pain and distension in the middle of cycle 1; radiologic assessment was consistent with mild bowel loop dilatation without evidence of obstruction. The patient did not have a prior history of ileus or small bowel obstruction, and there was no known intestinal or peritoneal involvement by disease. Study drugs were held, and the patient was managed conservatively, with resolution of symptoms. Study therapy was re-initiated at the next lower DL with no recurrence of symptoms. Due to the two DLTs at DL 8, additional patients entered on DL 7 (veliparib 60 mg daily with cyclophosphamide 50 mg daily), which was established as the MTD.

Efficacy

Seven patients experienced a partial response, and an additional six patients had prolonged stable disease (six or more cycles), including one patient (patient 1) with low-grade lymphoma who received a total of 42 cycles of study treatment with resolution of B symptoms (Table 3, Fig. 1). He was enrolled on DL 1 and eventually escalated to DL 7 following discussions with the study sponsor, lack of significant toxicity, and establishment of the safety of DL 7, to assess whether chronic PARP inhibition would provide additional clinical benefit. One patient with *BRCA2*-positive ovarian cancer (patient 23; DL 7), who had received multiple lines of prior chemotherapy (including cisplatin, paclitaxel, liposomal doxorubicin, and irinotecan), had disappearance of target lesions on follow-up scans, and received a total of 17 cycles with eventual disease progression. However, CA 125 levels, although improved, remained above normal; thus, this patient was not considered a complete response by RECIST 1.0. One of the patients with urothelial malignancy and Muir-Torre syndrome had prolonged disease stabilization for 17 cycles.

Thirteen patients had known *BRCA* mutations; of these, six had partial responses and three had prolonged stable disease. The *BRCA* status of the remaining patients was unknown; therefore, no comparisons to wild-type *BRCA* could be made.

Pharmacokinetics

Veliparib PK data were available for 35 patients, and data were available for 30 patients on both day 1 and the last day of veliparib dosing (day 7, 14, or 21) (Supplementary Table S1). Dose linearity assessment for maximum plasma concentration (C_{max}) resulted in a coefficient of 1.098 (95% CI: 0.784-1.41; 90% CI: 0.720-1.48). Dose linearity assessment for area under the curve (AUC) resulted in a coefficient of 1.15 (95% CI: 0.882-1.42; 90% CI: 0.828-1.47).

No statistically significant changes in PK parameters between baseline and day 7, 14, or 21 were observed. The accumulation index was 1.04 (SD ± 0.23) for AUC_{0-24} and 1.12 (SD ± 0.40) for C_{max}; these were not statistically significant. In the three patients on DL 5 (100 mg cyclophosphamide), PK behavior of veliparib was not different from other DLs.

PAR levels in patient PBMC and tumor samples

Mean PAR levels in patient PBMCs over the first 24 hours of cycle 1 are shown in Fig. 2A. Of the 33 evaluable patients with PBMCs available at 4 hours post-dose, 21 (64%) had at least a 50% decrease in PAR; six of these 21 patients had PAR levels below the level quantifiable by the assay. The Blyth-Still-Casella 95% confidence interval, indicating the true probability of such a decrease across patients, without accounting for dose level (a limitation imposed by the small sample numbers), ranged from 0.45 to 0.79. PBMC PAR levels also decreased by at least 50% from baseline on day 21 of cycle 1 in all seven patients for whom samples were available; these patients were on DL 6-8 (Supplementary Fig. S1). Five of the seven patients were known to have a *BRCA* mutation, but no conclusions can be made concerning *BRCA* status due to the small sample size. Due to the small number of patients treated per dose level, statistical comparisons of the degree of inhibition at day 21 compared to baseline could not be performed.

All five patients with pre- and post-dose (after 7 or 21 days of treatment) paired tumor biopsies had greater than 80% decreases in PAR levels (Fig. 2B). The Blyth-Still-Casella 95% confidence interval, indicating the true fraction of patients who had more than an 80% decrease in tumor biopsy PAR levels on either day 7 or 21, ranged from .50 to 1.0.

γH2AX levels in patient PBMC and CTC samples

We measured γH2AX levels, expressed as percent nuclear area positive (%NAP), in PBMCs collected over 24 hours from 17 patients on day 1. Fifteen of 17 patients had post-treatment γH2AX levels at or below baseline (Supplementary Fig. S2). Two patients had a slight increase in γH2AX %NAP at the 4-hour time point that returned to near baseline by 6 hours. We also measured γH2AX in CTCs. CTCs were detectable in nine patients; most samples had fewer than 10 detectable CTCs, a number that remained relatively constant over the first 5 days of cycle 1 (Fig. 2C). Seven of nine patients had an increased percentage of γH2AX-positive CTCs on day 2 (Fig. 2D), but these data are difficult to interpret in regard to response given the small numbers of CTCs. For patient 8, the number of CTCs increased from 0 at baseline to 33 at day 2; 64% of these cells were γH2AX positive. Patient 17, a 56-year-old man with colonic adenocarcinoma, had considerably more CTCs than other patients, and received two cycles of therapy before disease progression. The percentage of γH2AX-positive CTCs for this patient increased slightly from 3.9% at baseline to 6.2% on day 2.

In one patient, a 57-year-old man with small lymphocytic lymphoma/chronic lymphoid leukemia who had prolonged stable disease (patient 1), PAR levels in PBMCs and tumor, and γH2AX in PBMCs were measured (Fig. 3). This patient was on DL 1 for cycle 1.

DISCUSSION

This is the first clinical trial to evaluate once-daily dosing of veliparib in combination with a chemotherapeutic agent. Given its short half-life (5.0 ± 1.5 hours), veliparib has been administered twice daily in all other combination trials. We evaluated once-daily dosing based on PD data from our phase 0 trial, which showed greater than 48% inhibition of PARP activity in tumor biopsies 24 hours after a single 50 mg dose (8), and because of better patient compliance with once-daily dosing (24, 25). Enhanced myelotoxicity has been observed with PARP inhibitor combination regimens with cytotoxic chemotherapy, requiring dose reduction of the chemotherapy (26-28). This has raised questions about the relative contribution of the addition of PARP inhibitors to combination regimens and whether administration of full doses of chemotherapy alone would provide similar benefit. Therefore, we designed a regimen that would be well tolerated and have low levels of

toxicity and good patient compliance, a potentially better therapeutic ratio, and we were able to safely escalate the PARP inhibitor dose with metronomic cyclophosphamide dosing. The regimen was well tolerated, and the MTD was established at 60 mg veliparib with 50 mg cyclophosphamide administered daily in 21-day cycles.

Six of seven partial responses were observed in patients with known *BRCA* mutations, and an additional three patients with BRCA mutations had prolonged disease stabilization. Evidence of clinical benefit and PARP inhibition was observed across dose levels, suggesting that even at lower doses, veliparib produced sufficient inhibition of PARP activity to provide benefit in *BRCA*-positive patients receiving DNA-damaging chemotherapy. Two of the partial responses, and two of the prolonged stable diseases, occurred in patients who had received prior cyclophosphamide. One patient with metastatic ovarian cancer and a known *BRCA* mutation had complete disappearance of radiologic evidence of disease, even though tumor markers remained elevated. To our knowledge, this is the first report of the disappearance of radiologic evidence of disease in a patient treated with veliparib. Due to the unknown *BRCA* status of the remaining patients, no comparative analysis with wild-type *BRCA* patients can be performed. However, these preliminary data support the hypothesis that tumors with DNA repair defects may be sensitive to PARP inhibitors. Interestingly, a patient with Muir-Torre syndrome, an autosomal dominant genetic disorder likely caused by microsatellite instability (29), and urothelial malignancy had prolonged disease stabilization for 17 cycles, further supporting the potential therapeutic role of PARP inhibitors in the treatment of tumors with DNA repair defects.

We observed a statistically significant inhibition of PARP activity in PBMCs and tumor biopsy samples across dose levels. The degree and duration of PARP inhibition in tumor required for clinical benefit has not been established. A comparative study of the effects of treatment with other PARP inhibitors, MK-4827, olaparib, and PF-01367338, on PBMCs has recently been reported, and decreases in PAR levels ranged from 65% to 92% (30). The PAR levels at baseline and the degree of inhibition in PBMCs is variable as evidenced by our observations in this study. In the small subset of patients who underwent tumor biopsies and PBMC sampling on the same day (patients 20, 22, and 34), there appeared to be concordance in the inhibition of PAR in both sample sets. Although there is inherent variability in the baseline levels of PAR in PBMCs and the degree of PARP inhibition for a given dose level as shown in Fig. 2A, overall PAR levels were significantly decreased in PBMCs across all dose levels.

We did not observe consistent increases in γH2AX, a sensitive marker of DNA damage (20, 31), in PBMCs. As previously reported in our phase 0 study of veliparib (8), PARP activity is more easily inhibited in tumor cells than PBMCs; therefore, we evaluated the number of CTCs and the presence of γH2AX as a marker of drug effect in tumor. Though we observed increases in the fraction of CTCs positive for γH2AX after treatment, definitive conclusions cannot be made due to the few patients who underwent CTC sampling (as this was added later to the study) and low number of CTCs recovered per sample. We did not observe increases in γH2AX in PBMCs in the majority of patients evaluated, but did observe increases in γH2AX in CTCs, which is consistent with the minimal myelosuppression and promising antitumor activity observed with this regimen.

We were concerned about the potential for co-administration of cyclophosphamide to increase PARP inhibitor metabolism, because cyclophosphamide can induce CYP3A4 expression in human hepatocytes and liver slices (32). However, no effect of metronomic cyclophosphamide on veliparib PK was observed between the first and last days of treatment (days 1 and 7, 14, or 21). These results are consistent with our previous report where 31% to 115% of the veliparib dose was recovered in urine as unchanged parent drug (8).

Because of the encouraging activity and tolerability of this combination in patients with DNA repair deficiencies, the activity of metronomic cyclophosphamide alone and in combination with veliparib is being compared in a multicenter, randomized phase II study in patients with advanced ovarian cancer and *BRCA* mutations, high-grade serous ovarian cancers, triple-negative breast cancers, and low-grade lymphomas [ClinicalTrials.gov Identifier: NCT01306032]. The trial includes a detailed genetic analysis of underlying DNA repair defects for the ovarian cancer cohort. Veliparib as a single agent is being evaluated in a separate phase I clinical trial in patients with cancer carrying the *BRCA* mutation [ClinicalTrials.gov Identifier: NCT00892736]. Data from the single-agent trial were not available at the time of designing the phase II trial of the combination to add single-agent veliparib as a comparator arm.

The phase II trial, as currently designed, should help define the contribution of PARP inhibition to the activity of this combination, and will begin to establish whether a true increase in the therapeutic ratio of a cytotoxic is possible with the use of PARP inhibitors in the clinic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TRANSLATIONAL RELEVANCE

The development of combinations of cytotoxic chemotherapy regimens with poly(ADP-ribose) polymerase (PARP) inhibitors have been hampered by increased toxicity, limiting the dose of chemotherapy. This report describes a phase I study of an oral PARP inhibitor, veliparib, administered once daily, in combination with low-dose, continuous administration of oral cyclophosphamide in patients with refractory solid tumors and lymphoid malignancies. This regimen was designed with the goal of enhancing the antitumor effect while maintaining an acceptable toxicity profile, resulting in a favorable therapeutic ratio. The combination was tolerable and showed encouraging activity in patients with DNA repair defects, further supporting the role of PARP inhibitors in that population. We measured changes in markers indicative of PARP inhibition and DNA damage in clinical samples. The promising results of this trial have informed a randomized phase II trial of the combination versus cyclophosphamide alone in *BRCA*-positive ovarian cancer and triple-negative breast cancer.

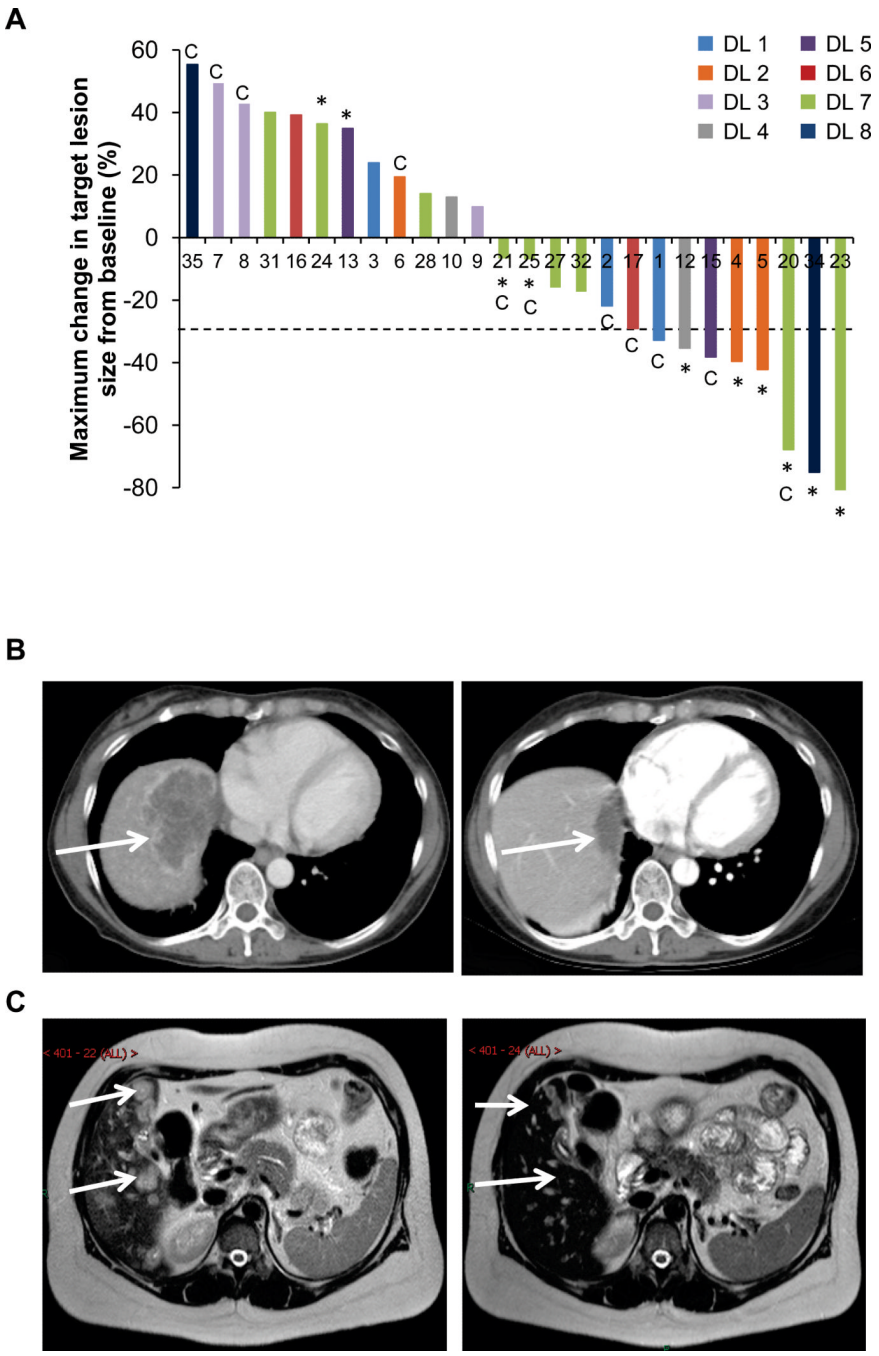

Figure 1.

Antitumor activity. A, maximum change in target lesion size from baseline assessed according to RECIST 1.0 (n=26). Six patients had non-measurable, evaluable disease only; one patient was taken off study for clinical progression. Dotted line indicates 30% decrease as defined by RECIST 1.0 for partial response. Patient numbers are displayed along the x-axis. *Patients with *BRCA* mutation. [C]Patients who had prior oral (patients 21 and 25) or intravenous cyclophosphamide. Patient 21 received prior veliparib and patient 3 received prior ifosfamide. B, computed tomography scans from patient 4, a 57-year-old woman with *BRCA2*-positive ovarian cancer at baseline (left) and after four cycles of treatment on DL 2 (right); patient achieved a partial response. C, magnetic resonance imaging scans from

patient 20, a 44-year-old woman with ER-positive, *BRCA2*-positive breast cancer on DL 7 at baseline (left) and after two cycles (right); patient achieved a partial response (status post doxorubicin/cyclophosphamide, taxane, letrozole, trastuzumab, fulvestrant, gemcitabine, and bevacizumab). Arrows indicate pre- and post-treatment tumor sites.

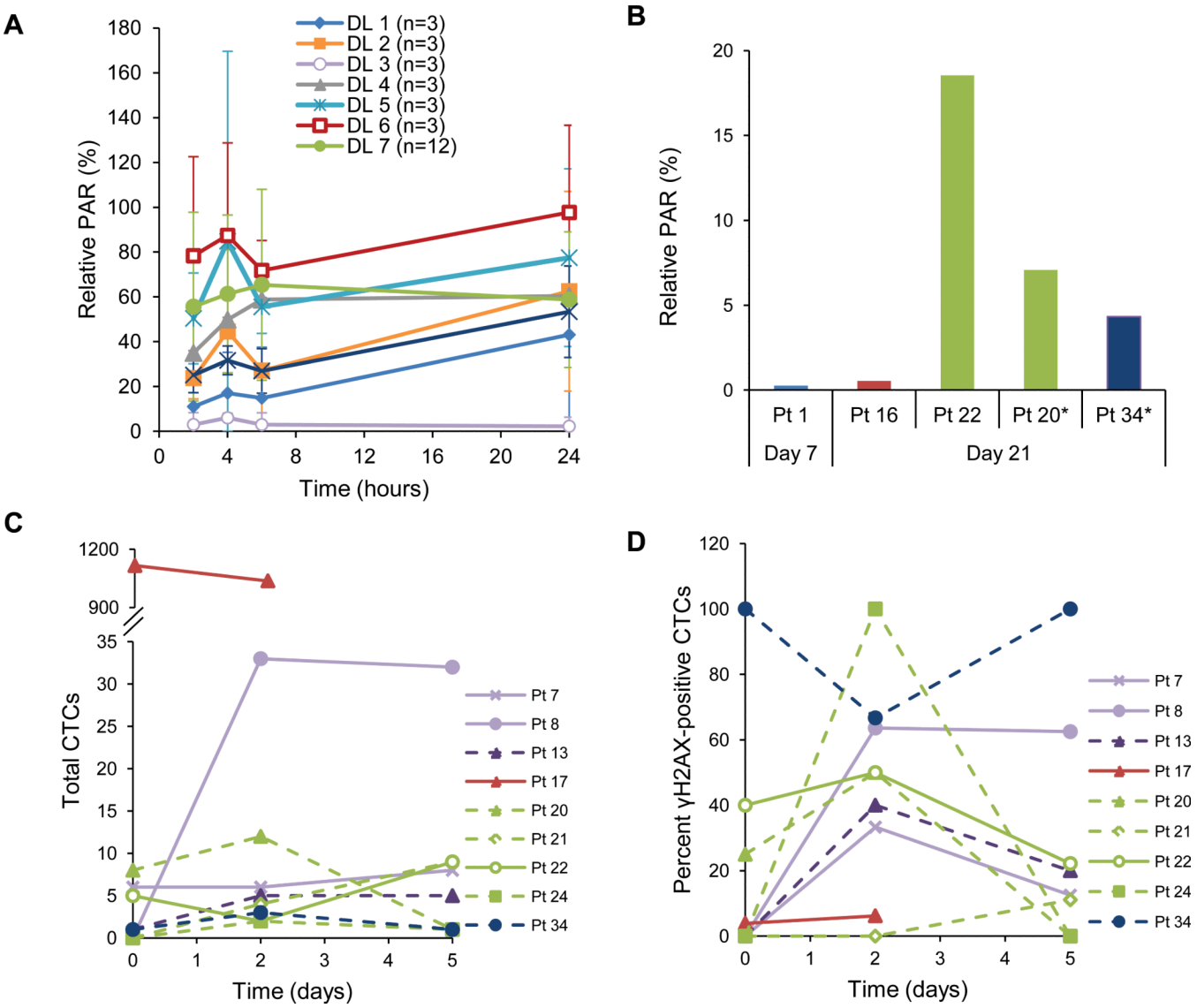

Figure 2.

A, mean PAR levels relative to baseline (100%) by DL in PBMC samples collected at baseline and 2, 4, 6, and 24 hours post-dose on day 1. Error bars represent the standard deviation. B, PAR levels relative to baseline (100%) in tumor biopsy samples collected 2 to 6 hours post-dose on day 7 for patient 1 (DL 1), 4 to 6 hours post-dose on day 21 for patients 16 (DL 6), 22 (DL 7), and 20 (DL 7), and 24 hours after the day 21 dose for patient 34 (DL 8). *Patients with *BRCA* mutation. Total number of CTCs (C) and percent γH2AX-positive CTCs (D) isolated from nine patients during cycle 1 at baseline and post-treatment on days 2 and 5. Color coding indicates DL; DL 3 (Pt 7-8), DL 5 (Pt 13), DL 6 (Pt 17), DL 7 (Pt 20-22, 24), DL 8 (Pt 34). Dotted lines indicate samples from patients with *BRCA* mutations.

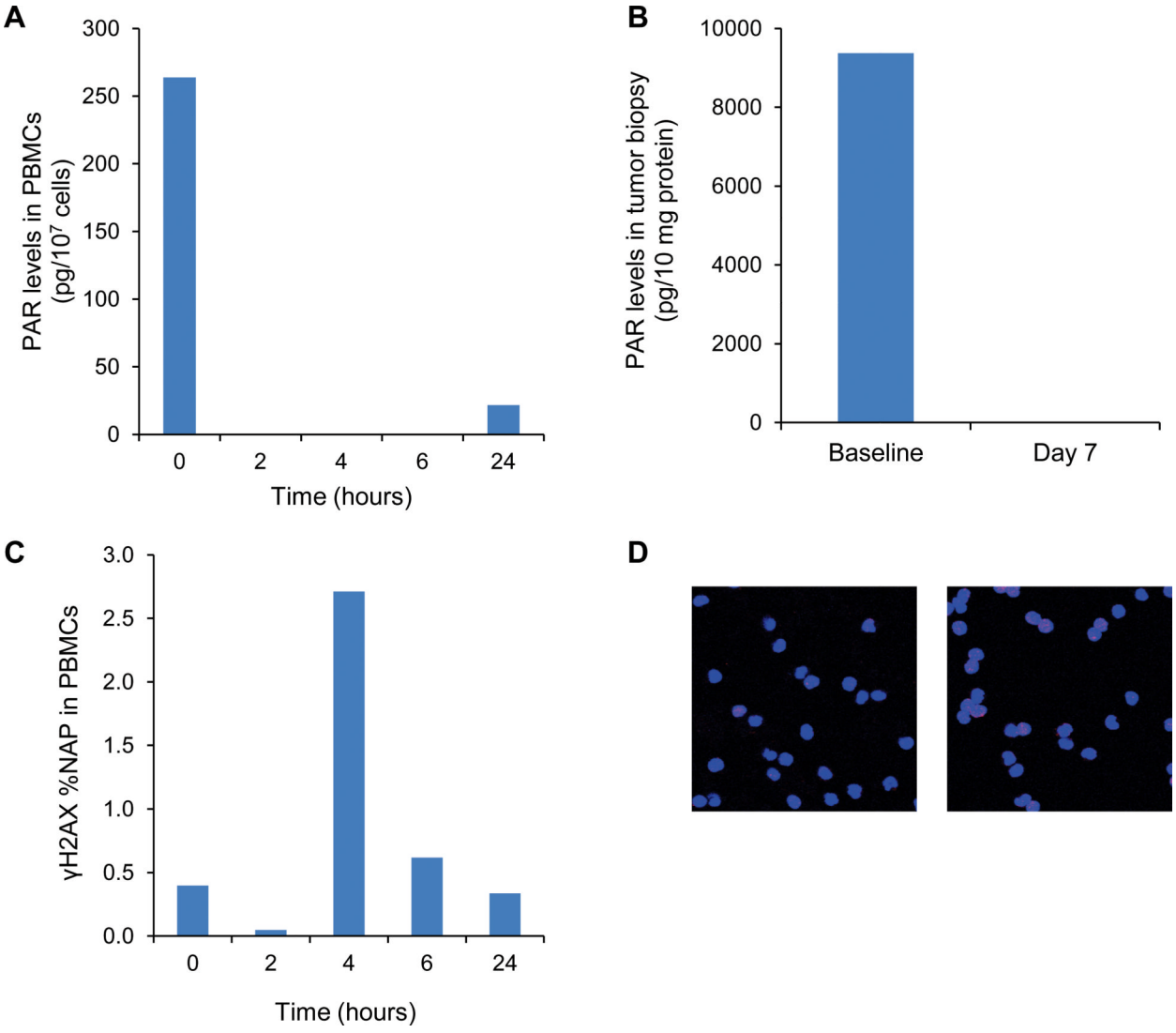

Figure 3.

Pharmacodynamic data from a 57-year-old man with small lymphocytic lymphoma/chronic lymphoid leukemia on DL 1 during cycle 1 (dose escalated to DL 7 in subsequent cycles) who experienced prolonged stable disease and received a total of 42 cycles of therapy. A, PAR levels in serial PBMC samples collected on day 1 of cycle 1. PAR levels were undetectable at 2, 4, and 6 hours post-dose. B, PAR levels in tumor at baseline and on day 7 of cycle 1. C, γH2AX levels measured as percent nuclear area positive (%NAP) in serial PBMC samples collected on day 1 of cycle 1. D, representative γH2AX staining in PBMCs at baseline (left) and 4 hours after combined treatment during cycle 1 (right).

Table 1

Dose cohorts and adverse events of at least grade 2, at least possibly related to study medication

Dose level	Veliparib (QD)	Cyclophosphamide (QD × 21 days)	Total No. of patients	Adverse event	Grade[a]	No. of patients
1	20 mg × 7 days	50 mg	3	Lymphopenia	2	1
					3	1
2	30 mg × 7 days	50 mg	3	Lymphopenia	2	2
				Leucopenia	2	1
				Neutropenia	2	2
				Thrombocytopenia	2	1
3	30 mg × 14 days	50 mg	3	Lymphopenia	2	2
				Leucopenia	2	1
				Anemia	2	1
4	40 mg × 21 days	50 mg	3	Lymphopenia	2	1
					3	1
				Leucopenia	2	1
				Neutropenia	2	1
				Allergic reaction	2	1
5	40 mg × 21 days	100 mg	3	Lymphopenia	2	1
					3	2
				Fatigue	3	1
6	50 mg × 21 days	50 mg	3	Lymphopenia	3	2
				Leucopenia	2	1
7	60 mg × 21 days	50 mg	14	Lymphopenia	2	2
					3	3
					4	3
				Leucopenia	2	4
				Neutropenia	2	2
				Anemia	2	4
				Thrombocytopenia	2	2
				Fatigue	2	2
				Hypophosphatemia	3	1

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Dose level	Veliparib (QD)	Cyclophosphamide (QD × 21 days)	Total No. of patients	Adverse event	Grade[a]	No. of patients
				Hypoalbuminemia	2	1
				Nausea	2	1
				Vomiting	2	1
				Upper respiratory infection	2	1
				Urinary tract infection	2	1
				Urinary tract obstruction	3	1
8	80 mg × 21 days	50 mg	3	Lymphopenia	2	1
				Leucopenia	2	1
				Neutropenia	2	1
				Acute respiratory failure	4	1[b]
				Abdominal distension, abdominal pain	3	1[b]

Abbreviation: QD, once a day.

[a]Worst grade reported per patient.

[b]Dose-limiting toxicity. The patient with acute respiratory failure died; the treating physician felt the cause of death was likely disease progression, but the possibility that the study drug combination may have contributed to the respiratory failure could not be excluded.

Table 2

Patient characteristics

No. of patients	35
Male	6
Female	29
Age, years	
Median	56
Range	42-82
Tumor types	
Ovarian	11
Carcinoid	1
Breast	12
Colon	1
Pancreas	1
Urothelial	2
Melanoma	1
Sarcoma	1
Endometrial	2
Lymphoma	2
Unknown primary	1
Karnofsky performance status	
80%-100%	33
70%	2
No. of lines of prior systemic therapies	
Median	6
Range	1-22

Table 3

Responses to treatment by tumor type

Responses and histology	Patient No.	Dose level	Total No. of cycles
Partial response			
BRCA2+ ovarian cancer	12	4	32
BRCA2+ ovarian cancer	4	2	20
BRCA2+ ovarian cancer	23	7	17
BRCA2+ ovarian cancer	34	8	10
BRCA2+ ovarian cancer	5	2	8
BRCA2+ triple-negative breast cancer	20	7	8
Breast cancer	15	5	4
Prolonged stable disease[a]			
SLL/CLL	1	1-7	42
BRCA2+ breast cancer (male)	14	5	15
Urothelial cancer	32	7	17
BRCA2+ ovarian cancer	25	7	11
Urothelial cancer	31	7	8
BRCA+ breast cancer	29	7	6

Abbreviation: SLL/CLL, small lymphocytic lymphoma/chronic lymphoid leukemia.

[a]Stable disease for at least six cycles.