A Phase I Study of Veliparib (ABT-888) in Combination with Low-Dose Fractionated Whole Abdominal Radiation Therapy in Patients with Advanced Solid Malignancies and Peritoneal Carcinomatosis

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Abstract

Purpose: The combination of low-dose radiotherapy with PARP inhibition has been shown to enhance antitumor efficacy through potentiating DNA damage. We combined low-dose fractionated whole abdominal radiation (LDFWAR) with escalating doses of veliparib (ABT-888), a small-molecule PARP inhibitor, in patients with peritoneal carcinomatosis from advanced solid tumor malignancies.

Experimental Design: Patients were treated with veliparib (80–320 mg daily) for a total of 3 cycles. LDFWAR consisted of 21.6 Gy in 36 fractions, 0.6 Gy twice daily on days 1 and 5 for weeks 1–3 of each cycle. Circulating tumor cells (CTC) were collected and evaluated for γ-H2AX. Quality of life (QoL) was assessed using the EORTC-QLQ-C30 questionnaire.

Results: Twenty-two patients were treated. Treatment-related grade 3 and 4 toxicities included lymphopenia (68%), anemia (9%), thrombocytopenia (14%), neutropenia (4%), leukopenia (9%), ascites (4%), vomiting (4%), and dyspnea (4%). No objective responses were observed. Disease stabilization (≥24 weeks) was observed in 7 patients (33%). Median progression-free survival (mPFS) was 4.47 months and median overall survival (mOS) was 13.04 months. In the subset of 8 ovarian and fallopian cancers, mPFS was 6.77 months and mOS was 17.54 months compared with mPFS 2.71 months and mOS 13.01 months in others. Patients with ovarian and fallopian cancers had better QoL over time than those with other cancers. An increased percentage of γ-H2AX–positive CTCs was observed in a subset of patients (3/6 with >2 CTCs at baseline).

Conclusions: Combined veliparib and LDFWAR is a well-tolerated regimen that resulted in prolonged disease stability for some patients with advanced solid tumors and carcinomatosis, particularly in the ovarian and fallopian cancer subpopulation.

Introduction

Peritoneal carcinomatosis presents a difficult clinical challenge, with significant morbidity as well as poor prognosis (1–3). Whole abdominal radiation has not often been used because of toxicity concerns (4–8). However, laboratory data suggest that using low-dose fractionated radiotherapy as a chemo sensitizer might improve efficacy with only a minimal increase in treatment toxicity (8, 9). Phase I data combining chemotherapy with low-dose fractionated whole abdominal radiation (LDFWAR) in patients with advanced small bowel, pancreatic, and ovarian cancers have demonstrated good tolerability (10, 11).

The PARP are an essential group of enzymes in base excision DNA repair that are swiftly activated by cells in response to DNA damage (12). PARP-1 and PARP-2 localize to the sites of DNA damage and catalyze the transfer and polymerization of PAR (13–17). Increased PARP activity is a well-described mechanism by which tumor cells avoid apoptosis caused by DNA damaging agents; it has been linked to drug resistance and the ability of tumor cells to withstand genotoxic stress (18–20).

PARP inhibitors interrupt the catalytic effects of PARP (21). PARP inhibition has been exploited particularly in cancers with BRCA mutations (16, 22–25). However, even in the absence of...
Translational Relevance

In this phase I multi-institutional trial, we pursued a novel strategy of combining two DNA-damaging modalities, both in low doses. Our primary endpoint was toxicity of this regimen. Secondary endpoints included progression-free survival, overall survival, and quality of life, as evaluated by the EORTC-QLQ-C30 questionnaire. As an exploratory measure, circulating tumor cells were serially collected from each patient at four time points in treatment and were evaluated for expression of γ-H2AX, a marker of DNA damage.

We hypothesized that our regimen might result in a tolerable palliative regimen for patients in this challenging patient population with typically poor outcomes. To the best of our knowledge, this is the first study that combines low-dose fractionated whole abdominal radiotherapy with systemic therapy.

BRCAl/2 mutations, it has been shown that PARP inhibitors may function as sensitizing agents for chemotherapy and radiotherapy that cause DNA damage (26–31). Preclinical studies have shown that the inhibition of PARP enhances the cytotoxic effects of radiation as well (17, 25, 32–38).

On the basis of these preclinical and clinical data, we hypothesized that LDFWAR with PARP inhibition might be a tolerable combination and provide clinical benefit to patients with peritoneal carcinomatosis, a group of patients with minimal therapeutic options (8–10, 17).

Patients and Methods

Study design

The primary objective of this multi-institutional phase I study was to assess the safety profile of the combination of veliparib and LDFWAR in patients with advanced solid tumor malignancies and peritoneal carcinomatosis. Secondary objectives included assessment of the antitumor effect and evaluation of quality of life (Qol). Serial circulating tumor cell (CTC) analysis of γ-H2AX levels in these cells were included as exploratory objectives.

Eligibility criteria

Eligible patients had an unresectable or metastatic solid tumor malignancy with the presence of peritoneal carcinomatosis documented either via imaging, operative notes, clinical notes, or symptoms. Measureable disease was not required as an eligibility criterion. Extra-abdominal disease was permitted so long as peritoneal disease was dominant. Patients had adequate organ function, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, and a life expectancy of more than 3 months. Exclusion criteria included prior abdominal radiotherapy (prior pelvic radiation was acceptable as long as there was no overlap between radiation fields), previous malignant bowel obstruction (except if at diagnosis) or uncontrolled ascites. The protocol was approved by the institutional review boards of the participating institutions, and written informed consent was obtained from all patients before performing study-related procedures in accordance with federal and institutional guidelines.

Drug administration, radiotherapy, and dose-escalation procedures

Veliparib was provided by the Cancer Therapy Evaluation Program (CTEP) through a Clinical Trials Agreement between Abbott Laboratories and the NCI Division of Cancer Treatment and Diagnosis. Patients were treated with veliparib by mouth in four escalating doses [dose levels (DL) 1–4: 40 mg per os, twice a day (DL1), 80 mg per os, twice a day (DL2), 120 mg per os, twice a day (DL3), and 160 mg per os, twice a day (DL4)]. Patients received veliparib on days 5 to 21 of the first 28-day cycle and on days 1 to 21 of the subsequent 2 cycles. LDFWAR was delivered using anterior and posterior open fields, in two daily fractions of 60 cGy on days 1 and 5 (minimum 4 hours between fractions) for weeks 1 to 3 of each cycle, with posterior kidney shielding used to keep kidney doses <20 Gy. The field borders were as follows: superiorly 1 cm above the dome of the diaphragm at the patient’s maximum comfortable expiration and inferiorly either at the inferior border of the obturator foramina or 2 cm below the lowest extension of disease. Lateral borders extended at least 2 cm beyond skin. In some cases, an extended source to skin distance (SSD) was needed to cover the entire area.

The trial was amended during the accrual period to allow ovarian/fallopian tube cancer patients who had obtained substantial benefit from the treatment to continue on single-agent veliparib at a dose of 400 mg per os, twice a day until progression of disease at the discretion of the principal investigator. These patients were required to either have a BRCA mutation or a strong family history of BRCA-associated malignancies.

We enrolled successive cohorts of 3 patients each using a standard 3+3 design (39). Dose escalations occurred no sooner than 4 weeks after the last patient on the dose level had begun therapy. Dose-limiting toxicities (DLT) were defined as any grade 4 toxicity, any grade 3 toxicity with the exception of nausea, vomiting, or diarrhea that improved to grade 2 within 3 days of receiving maximal medical support, and any grade 3 electrolyte abnormality that did not correct to grade ≤2 within 48 hours. Asymptomatic lymphopenia or leukopenia of any grade was not considered to be a DLT.

Clinical evaluation and safety assessment

Patients underwent a history and physical examination, performance status assessment, vital signs, blood work, and EKG at baseline. A baseline CT scan with contrast (unless contraindicated) was required within 28 days of beginning study treatment. While on study treatment during weeks 1 to 3 of each 4-week cycle, patients underwent weekly evaluations including brief history and physical examinations, adverse event evaluation, vital signs, CBC, and chemistries. Adverse events (AE) were classified/graded weekly according to the NCI Common Terminology Criteria of Adverse Events, version 4.0. Response and/or progression was assessed every 8 weeks by CT scan using RECIST 1.1 criteria (40), including by clinical and radiological assessment in cases wherein carcinomatosis was obviously present but no discreet lesions >1.0 cm were available for RECIST response evaluation.

Circulating tumor cells

Our exploratory, translational hypothesis was that γ-H2AX would increase from baseline with DNA-damaging radiation.
and the increase would be greater with combination ABT-888 and radiation than just radiation alone. Blood draws for CTCs were taken at baseline, on cycle 1 day 1 after the first radiation dose, at cycle 1 day 3, at cycle 1 day 5 preradiation dose, and on cycle 1 day 12. Samples were evaluated for number of CTCs and for γ-H2AX positivity. Specimens were only evaluated if there was ≥1 CTC in the sample. Samples were analyzed using the CellSearch Circulating Tumor Cell Epithelial Kit (Veridex Cat. no. 7900000) and Control Kit, as per the manufacturer’s protocol.

Quality-of-life assessment
QoL, as measured by the EORTC-QLQ-C30, was assessed at baseline and then every 2 cycles. Only patients who remained on treatment completed the follow-up questionnaires.

Statistical analysis
Proportions are reported with exact 95% binomial confidence intervals (CI). Event time distributions were estimated with the method of Kaplan and Meier (41) and compared using the log-rank statistic (42) and the proportional hazards regression model (43). QoL at baseline and during cycle 2 of treatment was assessed with the EORTC core QoL questionnaire, QLQ-C30. Item scores were linearly transformed to a 0 to 100 scale with the five functional scales and global QoL coded so that higher scores represent a better level of functioning while symptom scales were coded so that higher scores correspond to worsening of symptoms. There was no imputation of missing data. Changes in QoL and subdomains of the QLQ-C30 standardized questionnaire pretreatment and during cycle 2 of treatment were analyzed with paired t tests. QoL comparisons between independent groups were made with two-sample t tests.

Results

Patients and treatment
Twenty-two patients were enrolled in the study between September 8, 2011, and August 16, 2013. Of the 22 patients, 8 were men and 14 were women with a median age of 58 (range, 40–86). Patients had received a median of 4 prior anticancer therapies (range, 1–7). The baseline characteristics and demographics of the patients are further summarized in Table 1.

Table 1. Baseline characteristics of all treated patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dose level 1 (40 mg twice a day)</th>
<th>Dose level 2 (80 mg twice a day)</th>
<th>Dose level 3 (120 mg twice a day)</th>
<th>Dose level 4 (160 mg twice a day)</th>
<th>All dose levels</th>
</tr>
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<tbody>
<tr>
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<td>N = 6</td>
<td>N = 6</td>
<td>N = 7</td>
<td>N = 22</td>
</tr>
<tr>
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<td>65</td>
<td>57</td>
<td>59</td>
<td>56</td>
<td>58</td>
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<tr>
<td>Range</td>
<td>62–86</td>
<td>50–75</td>
<td>40–78</td>
<td>42–74</td>
<td>40–86</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
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<td>3 (50)</td>
<td>3 (43)</td>
<td>8 (36)</td>
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<td>6 (100)</td>
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</tr>
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<td>Ethnicity, n (%)</td>
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<td>5 (83)</td>
<td>4 (66)</td>
<td>5 (71)</td>
<td>15 (68)</td>
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<td>1 (14)</td>
<td>2 (9)</td>
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<td>1 (4)</td>
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<td>0</td>
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<td>0</td>
<td>1 (4)</td>
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<td>ECOG performance status, n (%)</td>
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<td>1</td>
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<td>6 (100)</td>
<td>3 (50)</td>
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<td>17 (77)</td>
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<td>Primary site of disease, n (%)</td>
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<td></td>
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<td>3 (43)</td>
<td>1 (14)</td>
<td>7 (32)</td>
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<td>2 (33)</td>
<td>1 (14)</td>
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<td>0</td>
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<td>1 (17)</td>
<td>0</td>
<td>1 (4)</td>
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<td>1 (17)</td>
<td>0</td>
<td>1 (4)</td>
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<td>0</td>
<td>1 (4)</td>
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<td>1 (17)</td>
<td>0</td>
<td>1 (4)</td>
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<td>0</td>
<td>1 (14)</td>
<td>2 (29)</td>
<td>2 (9)</td>
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<td>0</td>
<td>0</td>
<td>1 (14)</td>
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<tr>
<td>Disease stage, n (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
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<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (100)</td>
<td>6 (100)</td>
<td>5 (83)</td>
<td>3 (43)</td>
<td>17 (77)</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>3 (43)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Prior therapies, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (66)</td>
<td>3 (50)</td>
<td>1 (17)</td>
<td>2 (29)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>2–3</td>
<td>0</td>
<td>0</td>
<td>3 (50)</td>
<td>5 (71)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>4 or more</td>
<td>1 (33)</td>
<td>5 (50)</td>
<td>2 (33)</td>
<td>0</td>
<td>6 (27)</td>
</tr>
</tbody>
</table>
Of the 22 patients, 8 had a primary ovarian or fallopian cancer. Two patients with primary peritoneal cancers (primary peritoneal mesothelioma and disseminated peritoneal adenomucinosis) were not included in this group. Two patients were BRCA 1/2 mutation carriers, two were known mutation negative. Of the four other patients for whom BRCA status was unknown, family history did not reveal a strong signal of BRCA-associated malignancies in 3 of the patients. The fourth patient withdrew consent, so family history was not obtained.

The patients with primary ovarian or fallopian tube cancer had received a median of 4 prior anticancer therapies (range, 1–7) and of these, a median of 1.5 platinum-containing therapeutic regimens (range, 1–4). At the time of enrollment, 4 patients were considered to be platinum-sensitive and 4 were considered to be platinum-resistant (Supplementary Table S1).

The protocol allowed for a total of 3 cycles of veliparib plus LDFWAR to be administered. A total of 49 complete cycles of veliparib plus LDFWAR were administered with a mean number of cycles per patient being 2.0 (range, 0–3); 50% of the patients received all 3 planned cycles. Two of these patients went on to enter the maintenance phase with full-dose veliparib (400 mg twice a day) upon completion of therapy (for 2 cycles and 5 cycles, respectively).

Reasons for discontinuation of therapy included progression of disease (7 patients), withdrawal of consent (1 patient) and AEs (3 patients). Although not stipulated by the protocol, no patients received any further anticancer treatments until there was evidence of disease progression. Once progression was confirmed, 6 patients went on to have another line of therapy. One patient withdrew consent so follow-up data was unable to be obtained. One additional patient’s follow-up treatment data was unable to be obtained despite multiple attempts.

Dose escalation

Three patients were treated at dose level 1 without significant toxicity. Of the first 3 patients treated at dose level 2, 1 experienced protracted grade 2 thrombocytopenia that lasted 2 weeks. Therefore, 3 more patients were enrolled at this dose level. The next 3 patients were treated at dose level 3. Two patients required replacement due to early clinical progression following less than one cycle of veliparib. Therefore, 3 more patients were enrolled at this dose level to fully establish a side-effect profile of the regimen. At dose level 4, 7 patients were enrolled, as one patient at that dose level required replacement. A maximum tolerated dose (MTD) was not reached. A summary of dosing is found in Table 2.

Safety

Twenty-two patients were evaluable for toxicity (Table 3). The most common treatment-related AEs of all grades across all cohorts included lymphopenia in 68%, anemia in 45%, thrombocytopenia in 50%, leukopenia in 54%, neutropenia in 41%, nausea in 68%, diarrhea in 41%, and fatigue in 41%. Grade 3 or 4 toxicities included lymphopenia in 68%, anemia in 9%, thrombocytopenia in 14%, neutropenia in 4%, leukopenia in 9%, ascites in 4%, vomiting in 4%, small bowel obstruction in 4%, and dyspnea in 4%. One patient experienced pneumonitis that was possibly related to infection as a result of immunosuppression caused by veliparib; this patient elected not to be intubated or resuscitated and died due to respiratory failure.

Of the twenty-two patients, one experienced protracted grade 2 thrombocytopenia at dose level 2 requiring permanent discontinuation of veliparib after only 3 doses of drug during cycle 1. Although this toxicity was not considered a DLT by the definitions within the parameters of the protocol, this event was considered a DLT by the investigators at their discretion. The dosing schedule and DLT is summarized in Table 2.

Seven patients required either a temporary suspension (n = 4) or permanent discontinuation (n = 3) of veliparib due to an AE though not all these AEs were related to study treatment. Discontinuation of veliparib was due to multiple intolerable grade 2 AEs, small bowel obstruction, and biliary obstruction; the latter two due to disease progression, not study treatment. Dizziness, leukopenia, and thrombocytopenia were the reasons for temporary holds in veliparib.

Clinical activity

Twenty-one patients were evaluable for disease response. Eighteen of these patients were able to be assessed for response by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (19) and the remaining 3 patients were assessed by clinical and radiological assessment of carcinomatosis (i.e., peritoneal studding and/or ascites). The remaining patient, who was treated at dose level 2, discontinued the study during cycle 1 and did not undergo response assessment.

No objective responses were observed. Twelve patients (57%) achieved stable disease throughout treatment and disease stability of ≥24 weeks (range, 24.8–101.6 weeks) was seen in 7 patients (33%; Table 4). Median progression-free survival (PFS) and overall survival (OS) were calculated from date of first therapeutic intervention to date of progressive disease (Fig. 1 and Fig. 2). Overall, median PFS was 4.47 months (range, 0.46–23.26 months) and median OS was 13.04 months (range, 0.82–24.27 months).

At the time of study enrollment, 16 of 22 patients had exclusively abdominal disease and 6 of 22 patients had both intra-abdominal and extra-abdominal (lung) disease. Of the 6 patients with known intra- and extra-abdominal disease at study onset, 3 progressed in both sites, 2 progressed in the abdomen.

Table 2. Patient dosing and DLT assessment

<table>
<thead>
<tr>
<th>Dose cohort</th>
<th>ABT-888 (mg, days 5–21 of cycle 1 and 1–21 of subsequent cycles)</th>
<th>XRT (cGy, days 1 and 5, weeks 1–3 for 3 cyclesa)</th>
<th>N</th>
<th>Median no. of completed cycles (range)</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40 mg twice a day</td>
<td>60 cGy</td>
<td>3</td>
<td>2.66 (2–3)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>80 mg twice a day</td>
<td>60 cGy</td>
<td>6</td>
<td>2.16 (0–3)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>120 mg twice a day</td>
<td>60 cGy</td>
<td>6</td>
<td>2.00 (0–3)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>160 mg twice a day</td>
<td>60 cGy</td>
<td>7</td>
<td>1.71 (1–2)</td>
<td>0</td>
</tr>
</tbody>
</table>

a Cycle is 28 days.

b Grade 2, protracted thrombocytopenia. By the original protocol, this would not have met the requirement for a DLT. However, this was considered a DLT at the discretion of the principal investigators.
alone, and 1 progressed in the lungs only. Of the 16 patients with exclusively intra-abdominal disease at study enrollment, 1 developed new lung lesions at the time of progression while abdominal disease was stable. The remaining patients progressed in the abdomen alone (Supplementary Table S2).

In a post hoc analysis, patients with primary ovarian/fallopian tube cancers (n = 8) achieved a median PFS of 6.8 months and a median OS of 17.5 months compared with a median PFS of 2.7 months and a median OS of 13.0 months in the non-gynecological (non-GYN) cancer patients. Of these patients, the two with known

<table>
<thead>
<tr>
<th>Event</th>
<th>Level 1 (40 mg twice a day); n (%)</th>
<th>Level 2 (80 mg twice a day); n (%)</th>
<th>Level 3 (120 mg twice a day); n (%)</th>
<th>Level 4 (160 mg twice a day); n (%)</th>
<th>All dose levels; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GR 1/2</td>
<td>GR 3/4</td>
<td>GR 1/2</td>
<td>GR 3/4</td>
<td>GR 1/2</td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>66</td>
<td>0</td>
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<td>0</td>
<td>3</td>
<td>50</td>
<td>1 (17)</td>
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<td>Lymphopenia</td>
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<td>5</td>
<td>83</td>
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<td>66</td>
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<td>3 (100)</td>
<td>0</td>
<td>3</td>
<td>50</td>
<td>1 (17)</td>
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</table>

In a post hoc analysis, patients with primary ovarian/fallopian tube cancers (n = 8) achieved a median PFS of 6.8 months and a median OS of 17.5 months compared with a median PFS of 2.7 months and a median OS of 13.0 months in the non-gynecological (non-GYN) cancer patients. Of these patients, the two with known

Table 4. Patients who achieved durable disease stability (≥24 weeks): Demographics, PFS, and OS

<table>
<thead>
<tr>
<th>Patient identifier</th>
<th>Primary disease</th>
<th>Age, y</th>
<th>Prior therapies, n</th>
<th>BRCA status</th>
<th>Veliparib dose, mg/day</th>
<th>Continued veliparib maintenance?, yes/no</th>
<th>PFS, mo</th>
<th>OS, mo</th>
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<td>Peritoneal mesothelioma</td>
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<td>2</td>
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<td>No</td>
<td>23.26</td>
<td>24.27</td>
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<td>55</td>
<td>7</td>
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<td>8</td>
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BRCA mutations had PFS 4.47 and 7.92 months, respectively, and OS 4.47 and 8.64 months, respectively. The two patients who were known to be BRCA wild-type had PFS 6.77 and 0.46 months, respectively, and OS 10.58 and 0.82 months, respectively. At the data cutoff, 2 patients (colorectal carcinoma and cholangiocarcinoma) had not yet progressed and 10 patients (45%) had died. All deaths were disease-related with the exception of the patient above who developed pneumonitis.

Figure 1.
OS and PFS: all patients by ovarian versus non-ovarian cancers. Kaplan-Meier survival curves of OS (A) and PFS (B) in all patients and OS (C) and PFS (D) by ovarian and non-ovarian cancers.

Figure 2.
PFS for evaluable patients. Ovarian and fallopian tube patients are differentiated by the red and maroon colored bars.
QoL assessment
Twenty patients completed QoL assessment before starting treatment and 13 of these patients completed a second QoL assessment at cycle 2. Of the 7 patients who did not complete the second QoL assessment at cycle 2, 4 had come off study before cycle 2 due to toxicity, 2 had come off study before cycle 2 for disease progression, and 1 patient did not complete the QoL questionnaire but remained on study.

The data for patients who completed at least 2 QoL assessments were analyzed for change of QoL during the treatment phase. The baseline characteristics of patients who did and did not complete both questionnaires were also compared. On the basis of Osoba and colleagues, a change in score on the EORTC-QLQ-C30 of less than 10 corresponds to a "small" clinical change. Changes of 10–20 correlate with a "moderate" clinical change and changes in scores >20 correlate with "large" clinical changes (44).

Thirteen patients completed QoL questionnaires at baseline and at cycle 2; the overall average decrease in global QoL during treatment [change of −8.9; CI (−16.23 to −1.72)] was small. A moderate clinical decrease in role function occurred between baseline and cycle 2 [change of −19.23; P = 0.007; CI (−32.13 to −6.33)], and moderate increases in symptoms between baseline and cycle 2 occurred in fatigue [change of +12.82; P = 0.01; CI (3.39–22.26)], and appetite loss [change of +12.82; P = 0.02; CI (2.62–23.02); Supplementary Table S3].

There were no statistically significant differences between the baseline characteristics of patients who did and did not complete both questionnaires at the outset of treatment. However, in the group of patients who ultimately did not complete cycle 2, there were statistically nonsignificant moderate elevations in fatigue (mean difference of 16.00; P = 0.18), pain (mean difference of 16.85; P = 0.14), and appetite loss (mean difference of 16.12; P = 0.16) and nonsignificant large elevations in insomnia (mean difference 27.11; P = 0.09) and constipation (mean difference 20.15; P = 0.16) as compared with the group of patients who did complete cycle 2 (Supplementary Table S3).

The mean global QoL and physical function decreases in the non-GYN patients were clinically moderate, (average changes approximately −13.0) and marginally worse compared with the GYN patients. Increased fatigue was reported exclusively by non-GYN patients.

CTC data
Many (16/22; 73%) patients were found to have ≤2 CTCs at baseline evaluation. Six patients had >2 CTCs at baseline evaluation. Of these patients, 3 had an increase in percent γ-H2AX expression after veliparib and LDFWAR had been administered together, an event that occurred between the cycle 1, day 5 cell CTC collection and the cycle 1, day 12 CTC collection. Of the 3 patients who had an increase in their percent γ-H2AX expression, these were of the following magnitudes: +3.6%, +16.4%, and +37.14%, respectively. An additional patient who had >2 CTCs at baseline had a drop in percent γ-H2AX expression of 40% accompanied by a notable rise in total number of CTCs, possibly suggestive of treatment failure. This patient indeed had nearly immediate progressive disease (Supplementary Fig. S1).

Discussion
The treatment of patients with peritoneal carcinomatosis is an important and unmet need in oncology, as these individuals have a significantly poorer prognosis and suffer more complications than those without peritoneal disease (1, 2). For example, in colorectal cancer, a recent report found that overall survival from the time of diagnosis for patients with peritoneal carcinomatosis was 12.7 months versus 17.6 months in a post hoc analysis of two large randomized studies (1). Beyond a poor prognosis, these patients also suffer considerably from challenging complications of peritoneal disease, including intractable pain and vomiting from bowel obstruction as well as abdominal distension from ascites. Our goal for this study was to identify a palliative regimen that was (i) well tolerated, (ii) had a defined, short course of treatment, and (iii) would then allow patients a treatment holiday while providing disease control.

We aimed for a substantially lower MTD dose of veliparib than the established monotherapy dose of 800 mg per os daily. This decision was based on the phase 0 study by Kummar and colleagues showing significant inhibition (>95%) of PAR levels in tumor biopsies at doses of 25 and 50 mg per day doses of veliparib (44). These data suggested that higher doses of veliparib were not necessary for pharmacodynamic effect and thus would possibly add toxicity without substantial benefit. Our regimen was well tolerated by measures of toxicity and by our QoL data. The majority of grade 3 and 4 treatment-related toxicities were largely limited to myelosuppression. Nonhematologic grade 3 and 4 toxicities were seen in no more than one patient each. There was one possibly treatment-related case of fatal infectious pneumonitis that may have been caused by lymphopenia.

Regarding QoL, we interpreted our data based on a study by Osoba and colleagues (45). Our QoL measure revealed only moderate adverse changes in role function, fatigue, and appetite during treatment. However, only patients who remained on therapy completed the serial questionnaires. Although there were no statistically significant baseline QoL differences between those who remained on therapy and those who did not, there was a trend toward increased baseline symptoms in who ultimately did not complete cycle 2. Those who discontinued therapy early, either due to progression of disease, adverse effects, or a global inability to tolerate further treatment, may have had inferior QoL while on this regimen as compared with those who were able to continue the regimen. It is difficult to assess whether this is due to intrinsic patient and disease factors or due to the treatment itself.

The tolerability of our regimen can at least partially be attributed to the LDFWAR. Historically, the toxicities associated with full-dose whole abdominal radiotherapy have precluded its combination with systemic therapy (8, 11, 18, 38, 45). However, prior phase I data by Regine and colleagues demonstrated that hyperfractionated low-dose radiation was tolerable in patients with pancreatic cancer when combined with LDFWAR; we chose the identical dosing and fractionation schedule. In addition, in a recent study by Kunos and colleagues (11), low-dose, fractionated radiation was shown to be well tolerated and affords the combination of radiation plus systemic docetaxel therapy. Our data combining LDFWAR plus low-dose veliparib demonstrates similar tolerability, making it a particularly attractive option in the palliative setting.

Our CTC data are worth commenting. γ-H2AX is a marker of double-stranded DNA damage. In our exploratory analysis, we hypothesized that radiation, as a DNA-damaging agent, would increase γ-H2AX in CTCs, and that the addition of veliparib to radiation would increase γ-H2AX further. A majority of patients
had ≤2 CTCs at baseline, finding likely attributable to the epithelial cell adhesion molecule (EpCAM) capture, which would miss cells with a more mesenchymal phenotype seen in patients with advanced cancer (46). Of the 6 patients with ≥2 CTCs, 3 demonstrated an increase in γ-H2AX after veliparib and LDFWAR were combined, suggesting increased DNA damage to tumor cells. One patient had a rise in CTCs and a drop in γ-H2AX suggestive of treatment failure and this patient indeed had immediate progressive disease. This measure was exploratory and any conclusions are highly limited; further testing in larger studies of this regimen will be necessary to assess the potential validity of the hypothesis.

Regarding efficacy, no objective responses were seen, but 1 of 3 patients was progression-free at 24 weeks in this heavily pretreated patient population. Disease stabilization was seen across all dose levels and durable disease stabilization of ≥24 weeks was seen in 7 patients, 4 of whom had ovarian or fallopian tube cancers. In post hoc analysis, patients in the GYN cancer subset had an OS of 17.5 months compared with 13.0 months in the non-GYN group. Patients who demonstrated stable disease did not go on to have further anticancer therapy of any kind until they developed progressive disease. Of the evaluable patients, two developed interval progression of disease exclusively in the lungs while intra-abdominal disease remained stable, suggesting a possible benefit to the radiotherapy in these 2 patients. Overall, there was no pattern of location of treatment failure (within vs. outside of the radiation field).

Our lack of objective responses may be attributable to a heavily pretreated population, patients with ovarian cancer concentrated in the lower dosing cohorts and the recently described phenomenon of PARP trapping (47). The clinical relevance of PARP trapping has not fully been established and it is uncertain whether the doses of veliparib needed for PARP trapping are the same as those needed for PAR inhibition. We may have aimed for dose too low for that mechanism to engage.

The slightly longer PFS observed in the heavily pretreated ovarian cancer group could be a reflection of better disease biology of this histology rather than any treatment effect. The prolonged disease stability in the ovarian cancer subset is further complicated by the fact that PARP inhibitor monotherapy has been shown to be effective for patients with ovarian cancer with known BRCA mutations and the sporadic setting (16, 22). Gelmon and colleagues treated patients with serous ovarian cancer with full doses of the PARP inhibitor olaparib, regardless of BRCA status (18). In the post hoc analysis of the study by Gelmon and colleagues, median time to progression (mTTP) in patients with BRCA mutation was 221 days (7.4 months) and was 192 days (6.4 months) in those without a BRCA mutation. The median PFS of 6.9 months among our patients with ovarian and fallopian tube cancer, the majority of whom had negative or unknown BRCA status, is comparable with that reported by Gelmon and colleagues, and at significantly lower doses than its single-agent MTD. Of course, our study was much smaller, and our results can only be viewed as hypothesis-generating for further evaluation of this regimen.

Any conclusions that we draw are limited by our very small sample size, our lack of data on tumor growth kinetics before enrollment on this study, and by the fact that this is not a randomized, controlled trial. The overall survival in this trial, albeit a small study, is worth commentary. In pretreated ovarian cancer, the expected OS is approximately 13 months, based on multiple studies. Our small study with a heterogeneous group of tumors types had a median OS of 13.0 months overall and 17.5 months in the ovarian subset.

Several questions regarding this regimen of low-dose veliparib plus LDFWAR remain unanswered. Would we see greater benefit, especially for patients with ovarian cancer, if we escalated veliparib to its single-agent dosing, and could we preserve the tolerability of the regimen in that setting? Is LDFWAR as monotherapy all that is required to stabilize disease in some patients? We are presently exploring increasing doses of veliparib in patients with ovarian, fallopian tube or peritoneal cancers with LDFWAR in an ongoing extension study, with the intention of opening a subsequent, randomized trial of veliparib with and without LDFWAR when that extension study has completed.

In conclusion, our data from this phase I trial of palliative low-dose veliparib combined with LDFWAR demonstrates that this is a well-tolerated treatment regimen that may result in durable disease stabilization, especially in the ovarian cancer patient subset.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.A. Reiss, J.M. Herman, M. Zahurak, A. Brade, L.A. Dawson, L. Wang, S. Temkin, N.A. Azad

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Other (research nurse responsible for collecting, reporting and organizing data during and after patient visits): A. Scardina

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A Phase I Study of Veliparib (ABT-888) in Combination with Low-Dose Fractionated Whole Abdominal Radiation Therapy in Patients with Advanced Solid Malignancies and Peritoneal Carcinomatosis

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