

Phase 2 Study of Olaparib in Malignant Mesothelioma and Correlation of Efficacy With Germline or Somatic Mutations in *BAP1* Gene



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ABSTRACT

Introduction: PARP inhibition may enhance antitumor responses in *BAP1*-associated mesothelioma by inducing synthetic lethality.

Methods: A single-center, nonrandomized, phase 2 trial was conducted, in which patients with refractory mesothelioma were given olaparib 300 mg twice daily in a 21-day cycle until disease progression or intolerable toxicity. The primary objective was to determine the objective response rate on the basis of somatic or germline mutation status of DNA repair genes. The secondary objectives were to assess safety and tolerability and to determine progression-free survival (PFS) and overall survival (OS). Whole-exome sequencing was performed on blood and tumor.

Results: A total of 23 previously treated patients with pleural and peritoneal mesothelioma were enrolled and treated (germline *BAP1*, n = 4; germline *MRE11A*, n = 1; somatic *BAP1*, n = 8 mutations). There was one (4%) partial response, 18 (78%) with stable disease at 6 weeks, and four (17%) with progressive disease. The median overall PFS and OS were 3.6 months (95% confidence interval [CI]: 2.7–4.2 mo) and 8.7 months (95% CI: 4.7 mo–not estimable), respectively. The median PFS of germline *BAP1* mutants (n = 4) was 2.3 months (95% CI: 1.3–3.6 mo) versus 4.1 months (95% CI: 2.7–5.5 mo) for wild-type (n = 19; p = 0.019). The median OS was 4.6 months (95% CI: 3.1–4.9 mo) for germline *BAP1* mutation versus 9.6 months (95% CI: 5.5 mo–not estimable) in no germline mutation (p = 0.0040). Olaparib was safe with no new safety concerns.

Conclusions: Olaparib has limited activity in previously treated mesothelioma including patients with *BAP1* mutations. Germline *BAP1* mutations were associated with decreased PFS and OS.

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Keywords: Mesothelioma; PARP1; Olaparib; *BAP1*; *MRE11A*

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Introduction

Mesothelioma is a neoplasm originating from the mesothelial cells, often occurring in the pleura and peritoneum, and, rarely, the pericardium and tunica vaginalis.¹ Malignant mesothelioma (MM) is an aggressive disease with a poor prognosis. Most patients present with advanced unresectable disease, and treatment options for these patients are limited. Until recently, the combination of pemetrexed and cisplatin was the only approved first-line therapy, yielding a median overall survival (OS) of 12.1 months.² Nivolumab plus ipilimumab was approved recently as initial treatment for malignant pleural mesothelioma (MPM) on the basis of a phase 3 clinical trial that resulted in a median OS of 18.1 months.^{3,4} There are no approved therapies for patients with tumor relapse after first-line therapies.

Risk factors in developing mesothelioma include exposure to asbestos⁵ and other carcinogenic fibers such as erionite,⁶ and previous radiation therapy.^{7,8} Studies of familial clusters of mesothelioma have revealed genetic predisposition to develop MM.^{9,10} Recent work has identified germline mutations in *BAP1* that can predispose to mesothelioma^{11,12} and other cancers such as uveal and cutaneous melanoma, basal cell carcinoma, meningioma, and renal cell cancers.^{13,14} We previously identified deleterious germline mutations in 12% of 241 consecutive patients with MM who enrolled on a prospective natural history study, with *BAP1* being the most frequent germline mutation.¹⁵ *BAP1* was also recurrently inactivated at the somatic level, suggesting *BAP1* variants undergoing positive selection in the context of the classic “two-hit” model.

BAP1, a nuclear deubiquitylase, was initially discovered as an interaction partner of the tumor suppressor *BRCA1*.¹⁶ Subsequent studies revealed that *BAP1* binds to *BARD1*, which, in turn, binds to *BRCA1*, forming the *BRCA1*-*BARD1*-*BAP1* complex that is crucial for the homologous recombination (HR)-mediated repair of DNA double-strand breaks (DSBs).¹⁷ PARP enzymes play a major role in DNA single-strand break repair and base excision repair pathways. PARP inhibition leads to the accumulation of single-strand breaks that are converted to lethal DNA DSBs in cells deficient in HR-mediated DNA DSB repair pathways by synthetic lethality.¹⁸ Accordingly, mutations in *BRCA* genes, which are essential for high-fidelity repair of DNA DSBs through the HR repair pathway render tumors sensitive to PARP inhibitors.^{19,20}

PARP inhibitors are approved across many cancer types and their use can be biomarker-dependent. Olaparib monotherapy is approved by the Food and Drug Administration in several settings including the first-line maintenance therapy of *BRCA*-mutated advanced ovarian

cancer, the maintenance therapy of recurrent ovarian cancer, and after three or more lines of chemotherapy in advanced germline *BRCA*-mutated ovarian cancer. It is also approved for germline *BRCA*-mutated HER2-negative metastatic breast cancer, as maintenance treatment for germline *BRCA*-mutated metastatic pancreatic cancer in the first-line, and HR gene-mutated metastatic castration-resistant prostate cancer.^{21–26} Studies of olaparib in cancers driven by other DNA HR repair deficiencies beyond *BRCA* mutations have also been approved.^{27,28}

We hypothesized that patients with mesothelioma carrying germline or somatic *BAP1* mutations or other DNA repair genes deficiencies may clinically benefit from olaparib monotherapy. To address this hypothesis, we enrolled patients with mesothelioma on a non-randomized open-label, single-arm, phase 2 clinical trial to receive the PARP inhibitor olaparib at 300 mg twice daily until progression or intolerable toxicity. Assessment of the efficacy of PARP inhibition was based on the presence or absence of germline or somatic loss-of-function mutations of DNA repair genes or *BAP1*.

Materials and Methods

Study Design and Eligibility

This phase 2 single-arm, open-label study enrolled patients with progressive, histologically or cytologically confirmed mesotheliomas previously treated with platinum and pemetrexed chemotherapy ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03531840) NCT03531840). Eligible patients were 18 years or older with Eastern Cooperative Oncology Group performance status less than or equal to 1 and life expectancy of at least 16 weeks. Patients were enrolled regardless of previous tumor response to platinum-based therapy and could have received any number of previous systemic treatments. The study was conducted in accordance with the principles of the International Conference on Harmonization-Good Clinical Practice guidelines. The study protocol was approved by the local Institutional Review Boards and written informed consent was obtained before patients were enrolled in the study.

Treatment

Patients were administered olaparib 300 mg in tablet form by mouth twice daily in 3-weekly cycles until disease progression, patient request for withdrawal from the study, intolerable toxicity, or by physician's discretion. Toxicities observed during the course of the study were managed by treatment interruption or dose reductions. Two dose reductions were allowed to 250 mg twice daily (dose level 1) and 200 mg twice daily (dose level 2). Once the olaparib dose was reduced, escalation

was not permitted, and no further dose reduction was allowed, and study treatment was to be discontinued. In general, grade 3 or 4 hematologic or nonhematologic toxicities or both, required dose interruptions and dose reduction on recovery. Management of prolonged hematologic toxicities while receiving olaparib involved more frequent blood count monitoring, blood product transfusion, and further hematologic work-up if warranted.

Outcomes

The primary objective was to determine the objective response rate (ORR) of olaparib in the overall intent-to-treat patients and assess its association in three subgroups according to their mutation status: group 1 consisted of patients with a germline mutation in DNA repair genes, group 2 included patients with *BAP1* somatic mutations, and group 3 with neither germline DNA repair mutations nor *BAP1* somatic mutations. Secondary objectives included determining the safety and tolerability of olaparib and estimation of progression-free survival (PFS) and OS. ORR was defined as the proportion of partial and complete responses using Response Evaluation Criteria in Solid Tumors (RECIST 1.1)²⁹ for peritoneal mesothelioma and modified RECIST for pleural mesothelioma patients.³⁰ PFS was defined as the time from starting olaparib to radiographic (RECIST 1.1) or clinical progression, or death from any cause. OS was defined as the time from starting treatment to death from any cause. The data cutoff date for analysis was January 21, 2020. After completion of whole-exome sequencing (WES), patients were retrospectively analyzed in the three separate comparison groups. All patients were assessable for toxicity graded by Common Terminology Criteria for Adverse Events version 5.0 from the time of their first treatment with olaparib.

Assessments

Clinical response was assessed by computed tomography or magnetic resonance scan every two cycles (or 6-wk). Patients with measurable disease at baseline who had received at least one cycle of therapy and had taken at least 50% of the doses per given cycle were considered assessable for response.

Germline and Tumor WES

Germline and tumor WES were previously described.³¹ Briefly, formalin-fixed, paraffin-embedded tumor tissue samples and peripheral blood mononuclear cells were used for DNA extraction for tumor and germline WES. A total of 100 nanograms of DNA was sheared to approximately 200 base pairs by sonication (Covaris, Woburn, MA). Exome enrichment was

performed using SureSelect Clinical Research Exome Kits according to the manufacturer's instructions (Agilent Technologies, Santa Clara, CA). Paired-end sequencing (2 × 75 base pairs) was performed on an Illumina NextSeq500 (Illumina, San Diego, CA) instrument. Raw sequences in FASTQ format were aligned against the human reference genome (hg19) with Burrows-Wheeler Alignment tool³² and then processed through a custom NCI ClinOmics Bioinformatic Pipeline version 3.1.³¹ The Genome Analysis Toolkit (Broad Institute, Cambridge, MA) and HaplotypeCaller (Broad Institute) were used for germline single nucleotide variant and insertion and deletion calling; whereas MuTect (Broad Institute) and Strelka (Illumina) were used for somatic single nucleotide variant and small insertion and deletion calling, respectively.

Statistical Analysis

It was considered desirable if, overall, there was a minimum of approximately 20% response rate. The study initially planned to enroll 30 assessable patients to estimate the ORR with a maximum two-sided 90% confidence interval (CI) width of plus and minus 16%. However, if in a planned interim analysis of the initial 20 patients, there were 0 to 1 responses noted, then no further patients would be enrolled. The probability of OS and PFS as a function of time was determined by the Kaplan-Meier method.³³ Comparisons of OS and PFS were made between those with and without somatic *BAP* mutations, with and without germline mutations, and with and without any *BAP* mutations using a two-tailed log-rank test.

Results

Patient Characteristics

A total of 23 patients, 16 with pleural and seven with peritoneal mesothelioma were enrolled between July 2018 and May 2019 (Table 1). The median age was 63 years (range: 40–75 y) and most were men (60%). All patients had Eastern Cooperative Oncology Group 0 or 1. Two patients (9%) had biphasic mesothelioma and the rest (91%) were epithelioid mesothelioma. Previous surgeries consisted of pleurectomy and decortication (13%) or extrapleural pneumonectomy (13%) and cytoreductive surgery with heated intraperitoneal chemotherapy for peritoneal disease (17%) among all the patients enrolled. Eight patients (35%) were considered platinum-sensitive with a platinum-free interval greater than 6 months from previous platinum-based chemotherapy. The median number of previous treatments received was three (range: 1–5) and 14 (60%) had received more than three previous lines of

Table 1. Baseline Patient Characteristics (N = 23)

Patient Characteristics	Number (%)
Age, y, median (range)	63 (40-75)
Sex	
Male	14 (60)
Female	9 (40)
ECOG performance status	
0	2 (9)
1	21 (91)
Tumor location	
Pleural	16 (70)
Peritoneal	7 (30)
Histology	
Epithelioid	21 (91)
Biphasic	2 (9)
<i>BAP1</i>	
Germline mutation ^a	4 (17)
Somatic mutation ^b	8 (42)
Prior Surgery	
P/D	3 (13)
EPP ± HIOC	3 (13)
CRS ± HIPEC	4 (17)
Previous platinum-free interval	
<6 mo	15 (65)
≥6 mo	8 (35)
Previous lines of systemic therapy	
1	4 (17)
2	5 (22)
≥3	14 (60)

^aA total of 23 patients were sequenced for germline mutations.

^bA total of 19 patients were sequenced (DNA or RNA) in the tumor for somatic *BAP1* mutation. This included two patients with no copies of *BAP1*, as determined by RNA sequencing.

CRS, cytoreductive surgery; ECOG, Eastern Cooperative Oncology Group; EPP, extrapleural pneumonectomy; HIOC, hyperthermic intraoperative chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy P/D, pleurectomy and decortication.

systemic therapy. The median number of olaparib cycles received was 4 (range: 2–21).

Germline and Somatic Mutation Status

All 23 patients enrolled underwent germline WES and 19 patients (83%), whose archival tumor samples were available, underwent somatic tumor WES. Four of 23 patients (17%) carried pathogenic germline *BAP1* mutations, whereas eight of the 19 (42%) had somatic *BAP1* mutations in the tumor. One patient with a germline *MRE11A* mutation also carried a somatic *BAP1* mutation in the tumor (Table 2).

Efficacy

All 23 enrolled patients received at least two cycles of olaparib and were included in the intention-to-treat analyses for response, survival, and toxicity. None of them were receiving treatment at the data cutoff. Of the four patients with germline *BAP1* mutation, three had

radiologic progression, whereas the fourth patient had clinical progression, defined as clinical progression of disease-related symptoms without radiologic progression (Supplementary Fig. 1). Of these four patients, two progressed after receiving two cycles of olaparib. Of the 19 patients with wild-type germline *BAP1*, two withdrew owing to intolerable toxicities, 15 patients had radiographic progression, and two patients had clinical progression. Of the 23 assessable patients enrolled, one patient experienced a partial response (PR) (4%), 18 had stable disease (78%), and four (17%) had progressive disease. The primary end point ORR was 4%. Four patients had disease progression after two cycles of treatment, of whom two harbored a germline *BAP1* mutation. There was no substantial difference in PFS among these patients. On the contrary, only two of the 18 patients with stable disease had germline *BAP1* mutation, with the median PSF being 3.6 and 3.2 months, four (22%) with somatic *BAP1* mutation, and 12 (67%) with no *BAP1* mutation (Table 2).

The bar chart illustrates the PFS and mutation status of all enrolled patients (Fig. 1). There was one response in this study—a patient with a germline *MRE11A* mutation and somatic *BAP1* mutation. This 63-year-old woman with heavily pretreated and refractory MPM achieved a durable response to olaparib. The patient was initially diagnosed with right-sided pleural mesothelioma of biphasic subtype, mostly epithelioid pattern of disease. After initial tumor resection with pleurectomy and decortication, she had disease progression in the pleura within three months of completing adjuvant carboplatin and pemetrexed. She then enrolled on a phase 1 clinical trial of a novel mesothelin targeting immunotoxin, LMB-100 (Fab fragment fused to *Pseudomonas* exotoxin),³⁴ combined with four cycles of nab-paclitaxel chemotherapy. After progression of the disease on trial, she received pembrolizumab off-label but had progression within 3 months of commencing. Despite being treatment-refractory, she was enrolled on this phase 2 trial, in which she received olaparib and achieved a partial radiologic and metabolic response after approximately 12 weeks of treatment and clinical improvement of her disease-related symptoms of dyspnea and cough (Fig. 2A and B). The duration of her radiologic response lasted 30 weeks. She had a PFS of 6.9 months. Retrospectively, this patient had undergone germline (hereditary) DNA testing and was found to have a pathogenic mutation in the *MRE11* cancer susceptibility gene with a frameshift mutation within the nuclease domain (L169Rfs*14) (Table 2). This mutation has rarely been described in the literature for human solid malignancies.

Secondary outcomes of PFS and OS in the overall intention-to-treat population were conducted using the

Table 2. Clinical Characteristics, Mutations, and Response to Olaparib

Pt. ID	Age/Sex	Site	Mutations				C ^e	Best Response ^f	PFS ^g	OS ^h
			Germline ^a	Germline Variations ^b	Somatic ^c	Somatic Variations ^d				
1	65/M	Peri	WT	NA	<i>BAP1</i>	c.1891delG E631Sfs*5	C4	SD	2.8	4.1
2	75/M	Peri	<i>BAP1</i>	c.155G>A p.W52X* stopgain	WT	NA	C5	SD	3.6	4.5
3	59/M	Pleu	WT	NA	ND	NA	C4	SD	2.7	4.0
4	68/M	Pleu	WT	NA	WT	NA	C8	SD	5.5	17.7 ^j
5	50/F	Peri	WT	NA	<i>BAP1</i>	0 copy ⁱ	C6	SD	4.1	16.7 ^j
6	75/M	Pleu	WT	NA	WT	NA	C4	SD	2.7	16.7 ^j
7	59/M	Peri	WT	NA	WT	NA	C13	SD	9.0	16.7 ^j
8	72/F	Pleu	WT	NA	WT	NA	C21	SD	14.5	16.1 ^j
9	70/M	Peri	WT	NA	ND	NA	C4	SD	2.7	15.8 ^j
10	60/F	Pleu	WT	NA	<i>BAP1</i>	c.1679dupG L561Pfs*5	C4	SD	2.7	5.4
11	42/M	Pleu	WT	NA	WT	NA	C3	SD	1.8	4.0
12	63/F	Pleu	<i>MRE11A</i>	c.504_511del L169Rfs*14	<i>BAP1</i>	c.581-2A>G splice variant	C10	PR	6.9	14.4 ^j
13	66/M	Pleu	WT	NA	ND	NA	C8	SD	5.7	6.9
14	74/M	Pleu	WT	NA	<i>BAP1</i>	0 copy ⁱ	C2	PD	1.5	8.8
15	66/M	Pleu	WT	NA	ND	NA	C5	SD	4.8	7.5
16	42/F	Pleu	<i>BAP1</i>	c.2056+1G>C splice variant	WT	NA	C2	PD	1.3	3.1
17	70/F	Pleu	WT	NA	WT	NA	C11	SD	8.2	9.6
18	40/M	Peri	<i>BAP1</i>	c.898_899del R300Gfs*5	WT	NA	C4	SD	3.2	4.9
19	49/M	Pleu	WT	NA	<i>BAP1</i>	c.376-1_387 delins A	C6	SD	4.1	11.2 ^j
20	72/F	Peri	WT	NA	<i>BAP1</i>	c.253C>T p.Q85X stopgain	C2	SD	3.9	8.7
21	62/M	Pleu	WT	NA	WT	NA	C6	SD	4.2	9.9 ^j
22	59/F	Pleu	WT	NA	WT	NA	C2	PD	1.5	2.6
23	61/F	Peri	<i>BAP1</i>	c.587G>A stopgain p.W196A	<i>BAP1</i>	c.1889delA K630Rfs*6 frameshift deletion	C2	PD	1.4	4.7

^aGermline *BAP1* or *MRE11A* mutations.

^bReference cDNA sequences: *BAP1*: NM_004656; *MRE11*: NM_001330347.2.

^cSomatic *BAP1* mutation.

^dReference cDNA sequences: *BAP1*: NM_004656.

^eCycles of olaparib received.

^fResponse at 6-week restaging: SD; PR; PD.

^gPFS: start of treatment till PD in months.

^hOS: start of treatment till death or last follow-up (January 21, 2020) in months.

ⁱ0 copy as determined by RNA sequencing.

^jPatients alive.

C, cycle; cDNA, complementary DNA; F, female; fs, frameshift; ID, identification document; M, male; NA, not applicable; ND, not determined; OS, overall survival; PD, progression of disease; peri, peritoneal; PFS, progression-free survival; pleu, pleural; PR, partial response; Pt., patient; SD, stable disease; WT, wild-type.

cutoff date for primary analysis of January 21, 2020 (Fig. 3A and B). The median potential follow-up was 14.5 months. Median PFS in the overall population was 3.6 months (95% CI: 2.7–4.2 mo). The 6-month PFS probability was 17.4% (95% CI: 5.4%–35%). The median OS in the overall population was 8.7 months (95% CI: 4.7 mo–not estimable). The 6-month and 9-month OS probabilities were 60.9% (95% CI: 38.7%–77.4%) and 43.5% (95% CI: 23.3%–62.1%), respectively.

We conducted a prespecified exploratory analysis of PFS and OS in patients with germline *BAP1*, somatic *BAP1*, and both somatic and germline *BAP1* mutations versus others. We found that the PFS and OS for patients harboring germline *BAP1* mutation versus wild-type germline *BAP1* were significantly different (Fig. 3C and D). The median PFS for the patient with germline *BAP1*

mutation was 2.3 months (95% CI: 1.3–3.6 mo) compared with 4.1 months (95% CI: 2.7–5.5 mo) with wild-type germline *BAP1* ($p = 0.019$). The median OS was better in the *BAP1* wild-type cohort compared with germline *BAP1* mutation; median OS was 4.6 months (95% CI: 3.1–4.9 mo) for patients with germline *BAP1* versus 9.6 months (CI: 5.5–not estimable) for patients with wild-type *BAP1* ($p = 0.004$).

There was no statistical difference in PFS and OS in patients with somatic *BAP1* mutations versus wild-type cohort (Supplementary Fig. 2A and B). The median PFS for somatic *BAP1* was 3.3 months (95% CI: 1.4–4.1 mo) compared with 3.6 months (95% CI: 1.5–8.2 mo) for no somatic *BAP1* mutation ($p = 0.28$). Similarly, when we compared OS between patients with somatic *BAP1* and no somatic *BAP1* mutations, we did not observe a

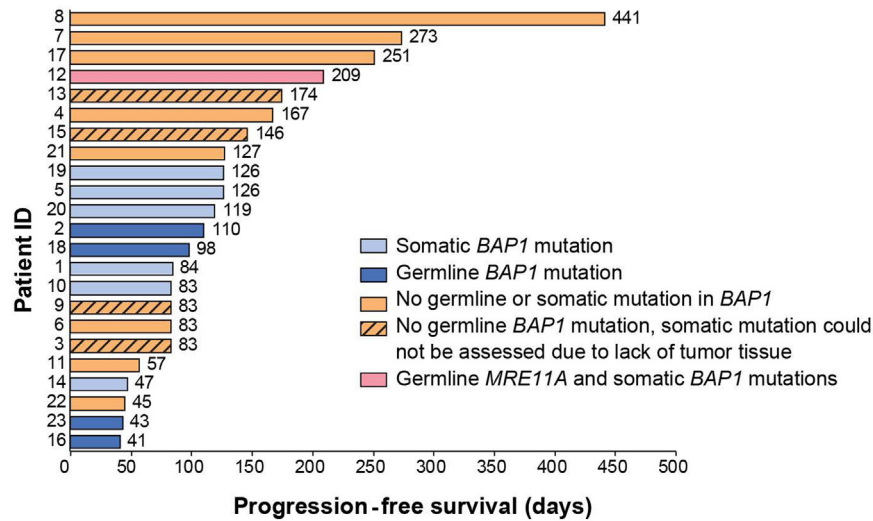


Figure 1. Progression-free survival and mutation status in the intention-to-treat population. Progression-free survival of patients in days is plotted from the start of therapy until the progression of the disease. Germline and somatic *BAP1* status and germline *MRE11A* mutation are indicated. Light blue bars indicate patients with somatic *BAP1* mutation, dark blue with germline *BAP1* mutation, yellow with no somatic or germline *BAP1* mutations, and yellow hashed bar with no germline *BAP1* mutation. However, in these patients (yellow hashed bar) tumor sequencing was not performed owing to insufficient tissues; hence, somatic *BAP1* status was not assessed. Pink bar shows the only patient with germline *MRE11A* and somatic *BAP1* mutations. y axis: Patient identification number (N = 1-23). ID, identification document.

difference; the median OS were 8.8 months (95% CI: 4.1 mo–not estimable) and 9.6 months (95% CI: 3.1 mo–not estimable), ($p = 0.98$), respectively. Similar PFS and OS observations were seen in subset analysis with any *BAP1* mutation (somatic or germline) with no somatic and germline mutations (Supplementary Fig. 3A and B).

Safety

All patients who were treated with at least one dose of olaparib experienced an adverse event (AE) related to the drug. The most common all-grade, non-hematologic AEs associated with olaparib were nausea (70%), renal toxicity (48%), and fatigue (48%) (Table 3). There were two (9%) grade 3 AEs (fatigue) and no grade 4 or higher nonhematologic toxicities. Decreased lymphocyte count (78%) and anemia (52%) were the most common all-grade, hematologic AEs associated with olaparib. Among these, there were seven grade 3 AE (six decreased lymphocyte count, one anemia) but no grade 4 or higher hematologic toxicities. A total of 12 patients (52%) underwent olaparib dose reductions. Four patients were dose-reduced to 250 mg twice daily (dose level 1) and eight to 200 mg twice daily (dose level 2). Two patients were removed from the study owing to intolerable toxicities (nausea/vomiting and intolerable fatigue). Overall, AEs were consistent with the known profile of olaparib used in other malignancies.^{21–25}

Discussion

Although PARP inhibitors have been approved and widely used for the treatment of cancers with defective HR genes,³⁵ their efficacy in mesothelioma, characterized by germline and somatic alterations in DNA repair genes including *BAP1* has not been explored in the past. In this study, we find that olaparib monotherapy has limited antitumor activity in mesothelioma patients, with an ORR of 4%, median PFS of 3.6 months, and median OS of 8.7 months.

In subset analyses comparing outcomes in patients with *BAP1* germline or somatic mutations, versus patients with wild-type *BAP1*, the median PFS and OS in the germline *BAP1* mutant cohort were much shorter compared with the wild-type *BAP1* cohort. Although this difference in PFS and OS is based on a limited number of patients, the shortened survival outcomes in patients harboring a germline *BAP1* mutation are antithetical to our original hypothesis. These results are consistent with our recent preclinical findings in mesothelioma cell line models wherein *BAP1* loss induced by CRISPR-Cas9 was not a determinant of sensitivity to PARP inhibitors.³⁶ Overall, the efficacy of PARP inhibition in *BAP1*-mutated MM is unclear in preclinical studies reporting mixed results.^{37–40} No differential sensitivity to PARP inhibition in *BAP1*-mutant compared with *BAP1* wild-type MPM cell lines was noted in a previous study.¹² Taken together, our findings suggest that *BAP1* status is not a determinant of

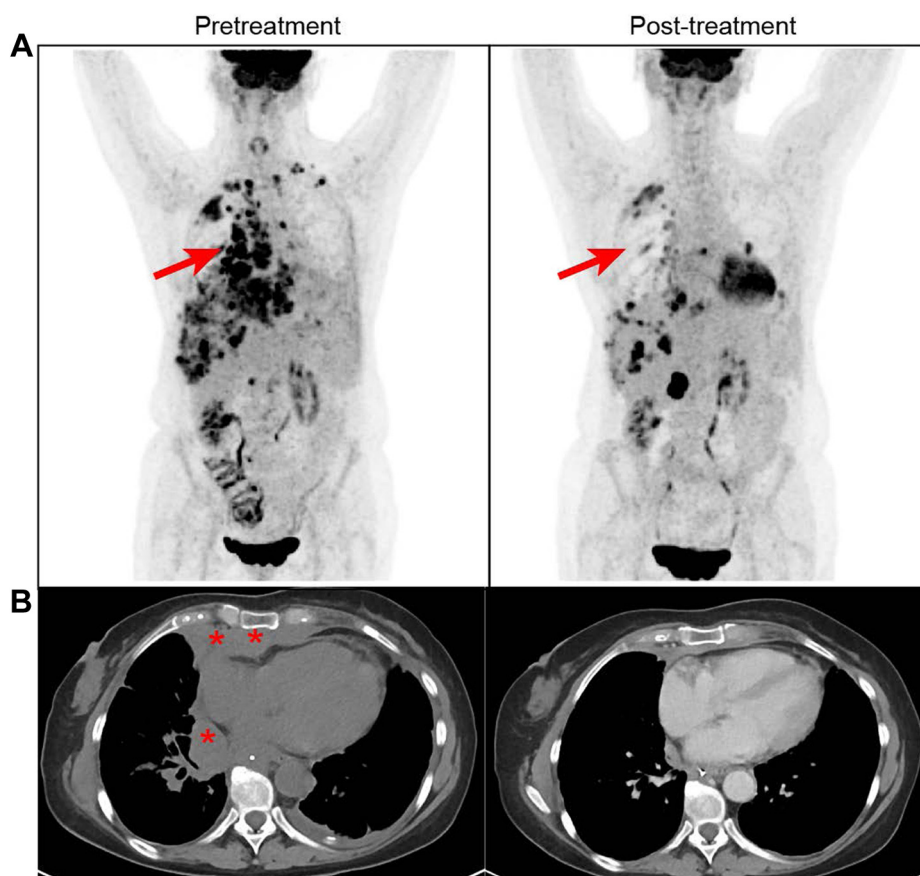


Figure 2. A partial response seen in a patient with germline *MRE11A* mutation. A 63-year-old woman with heavily pretreated pleural mesothelioma harboring germline *MRE11A* and somatic *BAP1* mutations achieved a durable (>6 mo) partial response. (A) Pretreatment and posttreatment PET scans and (B) CT scans revealed tumor regression. The response was achieved approximately after 12 weeks of treatment, with immediate clinical improvement of disease-related dyspnea and cough. The duration of the radiologic response lasted 30 weeks. CT, computed tomography; PET, positron emission tomography.

sensitivity to PARP inhibitors, and patients with germline *BAP1* mutation may, in fact, have worse outcomes with PARP inhibition.

There are other phase 2 clinical studies exploring PARP inhibitors rucaparib and niraparib in MM with mutations in HR genes, which are ongoing or have recently been completed. Mesothelioma stratified therapy 1 (MiST1, NCT03654833), a phase 2a trial, was designed to test the efficacy of rucaparib in patients with MM harboring either *BAP1* deficiency (loss of nuclear staining or protein expression) or *BRCA1* deficiency or both.⁴¹ The primary end point was a 12-week disease control rate. Patients were molecularly prescreened for eligibility on the basis of immunohistochemistry-based loss of *BAP1* or *BRCA1* protein expression in tumor tissue. Germline mutation status was not determined for *BAP1*, *BRCA1*, or other DNA repair pathway genes. The study revealed promising efficacy by meeting its primary end point of 58% disease control rate with three PRs; however, *BAP1* immunohistochemistry status did not predict response to PARP inhibition, and the outcome of

patients with *BAP1* mutations alone was not presented. The lack of predictive biomarkers failed to answer if molecular alterations in *BAP1* sensitizes to PARP inhibition, and thus, require a broader correlative analysis between PARP inhibitor response and mutational (somatic and germline) profile. Two phase 2 trials of niraparib in *BAP1* and other DNA damage response-deficient neoplasms including MM (NCT03207347)⁴² and in combination with programmed cell death protein-1 checkpoint inhibitor in MPM are ongoing.⁴³ A phase 2 study at the University of Chicago assessing efficacy of olaparib in patients with HR repair deficiencies mesothelioma is about to commence (NCT04515836). Participants harboring germline or somatic *BAP1* mutations are eligible for enrolment. The primary objective is to determine ORR and the secondary objectives are to determine PFS, OS, and adverse effects. The outcome of this study will further elucidate the efficacy of olaparib in *BAP1*-mutated mesothelioma.

The only patient who responded to our study has germline *MRE11A* mutation. *MRE11* is a vital component

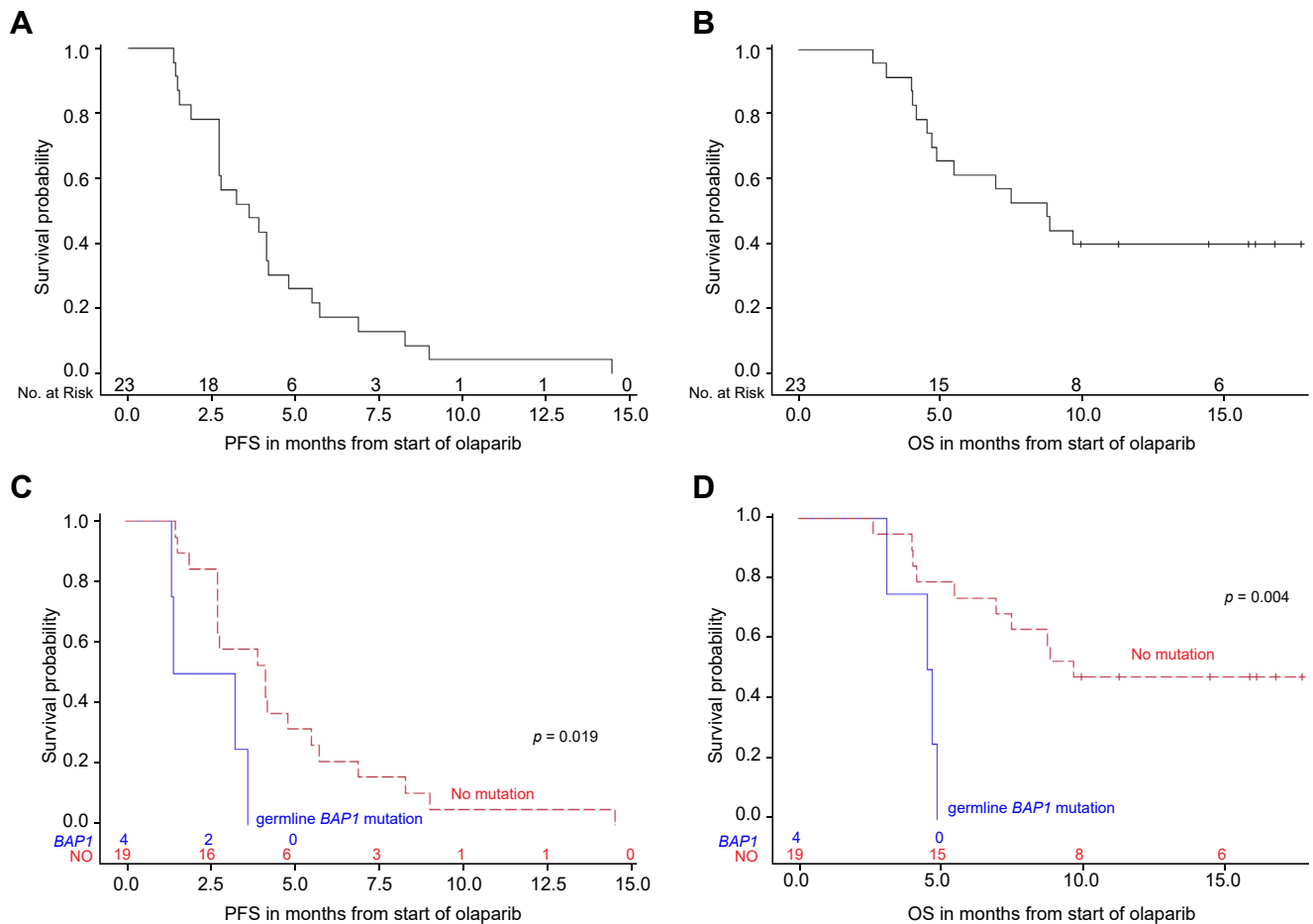


Figure 3. Kaplan-Meier curves for PFS and OS in the overall intention-to-treat population and the germline *BAP1* cohort. PFS and OS were measured in months from the start of olaparib treatment. The median potential follow-up was 14.5 months. (A) In the overall cohort (N = 23), the median PFS was 3.6 months (95% CI: 2.7-4.2 mo) and the 6-month PFS was 17.4% (95% CI: 5.4%-35.0%). (B) The median OS was 8.7 months (95% CI: 4.7 mo-not estimable), the 6-month OS was 60.9% (95% CI: 38.7%-77.4%), and the 9-month OS was 43.5% (95% CI: 23.3%-62.1%). (C) In the germline *BAP1* cohort (n = 4), the median PFS was 2.3 months (95% CI: 1.3-3.6 mo) and the 6-month PFS was not reached. In the cohort with wild-type germline *BAP1* (n = 19), the median PFS was 4.1 months (95% CI: 2.7-5.5 mo) and the 6-month PFS was 21.1% (95% CI: 6.6%-41.0%) ($p = 0.019$). (D) In the germline *BAP1* cohort (n = 4), the median OS was 4.6 months (95% CI: 3.1-4.9 mo) and the 6-month OS was not reached. In the cohort with wild-type *BAP1* (n = 19), the median OS was 9.6 months (95% CI: 5.5 mo-not estimable) and the 6-month OS was 73.7% (95% CI: 47.9%-88.1%) (** $p = 0.0040$). CI, confidence interval; OS, overall survival; PFS, progression-free survival.

of the upstream DNA damage response-MRE11 complex, which regulates DSB repair by promoting homology-directed repair (HR) and alternative nonhomologous end-joining pathway in conjunction with CtIP^{44,45} and restart of stalled replication fork along with PARP.⁴⁶ Preclinical studies have revealed synthetic lethality between *MRE11* and PARP inhibitors. Loss of *MRE11* expression has been found to render colorectal, endometrial, and myeloid-derived cancer cells sensitive to PARP inhibitors owing to reduced HR-directed DNA repair and replication fork stalling.⁴⁷⁻⁴⁹ To the best of our knowledge, there are no documented clinical responses to PARP inhibition with an underlying germline *MRE11A* pathogenic mutation. However, a preclinical study screening for genes other than *BRCA1*, whose

transcription levels were associated with sensitivity to olaparib in breast cancer cell lines, has identified *MRE11A* as a candidate.⁵⁰ Although the occurrence of this mutation is rare in human cancers, preclinical studies support the scientific rationale to target *MRE11A* mutations with PARP inhibitors. Given the strong preclinical evidence and our clinical experience with the patient with germline *MRE11A* mutations who attained a PR, it is worth exploring the efficacy of PARP inhibitors in patients with cancer having *MRE11A* mutations through a prospective clinical trial.

In summary, olaparib as a single agent has limited antitumor efficacy in previously treated MM and unexpectedly exhibits a decreased PFS and OS in germline *BAP1*-mutant patients. The only patient with a durable

Table 3. Treatment-Associated AEs

AEs	Grade 1	Grade 2	Grade 3	All Grades (N = 23)
Nonhematologic				
Nausea	15 (65)	1 (4)	0	16 (70)
Renal ^a	9 (39)	2 (9)	0	11 (48)
Fatigue	3 (13)	6 (26)	2 (9)	11 (48)
Anorexia	6 (26)	4 (17)	0	10 (43)
Vomiting	6 (26)	1 (4)	0	7 (30)
Dysgeusia	5 (22)	1 (4)	0	6 (26)
Weight loss	3 (13)	3 (13)	0	6 (26)
Diarrhea	5 (22)	0	0	5 (22)
Dyspepsia	4 (17)	1 (4)	0	5 (22)
Abdominal pain	3 (13)	0	0	3 (13)
Dizziness	2 (9)	0	0	2 (9)
Headache	2 (9)	0	0	2 (9)
Gastroesophageal reflux disease	0	1 (4)	0	1 (4)
Hematologic				
Lymphocyte count decreased	2 (9)	10 (43)	6 (26)	18 (78)
Anemia	2 (9)	9 (39)	1 (4)	12 (52)
White blood cell decreased	2 (9)	0	0	2 (9)
Platelet count decreased	1 (4)	0	0	1 (4)

Note: Values given are in number (%). AE's definition and grading were assessed using the NCI CTCAE, version 5.0.

^aEither an elevation of baseline creatinine or decreased creatinine clearance since starting olaparib treatment.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

PR harbored a germline *MRE11A* mutation, suggesting a possible synthetic lethality with PARP inhibition warranting further studies in patients with germline *MRE11A* mutations.

CRediT Authorship Contribution Statement

Azam Ghafoor: Conceptualization, Data curation, Investigation, Methodology, Roles/writing - original draft.

Idrees Mian: Investigation.

Cathy Wagner, Yvonne Mallory, Maria Garcia Agra: Methodology, Project administration.

Betsy Morrow: Data curation, Methodology, Writing - review & editing.

Jun S. Wei: Data curation, Formal analysis, Methodology, Software.

Javed Khan: Formal analysis, Methodology, Software, Validation, Visualization, Writing - review & editing.

Anish Thomas: Investigation, Writing - review & editing.

Manjitha Sengupta: Data curation, Writing - review & editing.

Seth M. Steinberg: Formal analysis, Investigation, Methodology, Software, Validation, Writing - review & editing.

Raffit Hassan: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Visualization, Writing - review & editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at <https://doi.org/10.1016/j.jtocrr.2021.100231>.

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