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; PARP inhibitors; 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. 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. 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. There are no approved therapies for patients with relapse after first-line therapies.

Risk factors in developing mesothelioma include exposure to asbestos and other carcinogenic fibers such as erionite, and previous radiation therapy. Studies of familial clusters of mesothelioma have revealed genetic predisposition to develop MM. Recent work has identified germline mutations in BAP1 that can predispose to mesothelioma and other cancers such as uveal and cutaneous melanoma, basal cell carcinoma, meningioma, and renal cell cancers. 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. 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. 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). 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. 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.

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.

Studies of olaparib in cancers driven by other DNA HR repair deficiencies beyond BRCA mutations have also been approved. 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 NCT035931840). 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) for peritoneal mesothelioma and modified RECIST for pleural mesothelioma patients. 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. 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 tool and then processed through a custom NCI ClinOmics Bioinformatic Pipeline version 3.1. 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. 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)      |
| BAP1                    |            |
| Germline mutation *     | 4 (17)     |
| Somatic mutation *      | 8 (42)     |
| Prior Surgery           |            |
| P/D                     | 3 (13)     |
| EPP ± HIPEC             | 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)    |

* A total of 23 patients were sequenced for germline mutations.
* A 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.

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), 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
The 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%–35.0%). The median OS in the overall population was 8.7 months (95% CI: 4.7–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
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 \textit{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 \textit{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 \textit{BAP1} germline or somatic mutations, versus patients with wild-type \textit{BAP1}, the median PFS and OS in the germline \textit{BAP1} mutant cohort were much shorter compared with the wild-type \textit{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 \textit{BAP1} mutation are antithetical to our original hypothesis. These results are consistent with our recent preclinical findings in mesothelioma cell line models wherein \textit{BAP1} loss induced by CRISPR-Cas9 was not a determinant of sensitivity to PARP inhibitors.\(^{36}\) Overall, the efficacy of PARP inhibition in \textit{BAP1}-mutated MM is unclear in preclinical studies reporting mixed results.\(^{37–40}\) No differential sensitivity to PARP inhibition in \textit{BAP1}-mutant compared with \textit{BAP1} wild-type MPM cell lines was noted in a previous study.\(^{12}\) Taken together, our findings suggest that \textit{BAP1} status is not a determinant of
sensitivity to PARP inhibitors, and patients with germ-line 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. 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) and in combination with programmed cell death protein-1 checkpoint inhibitor in MPM are ongoing. A phase 2 study at the University of Chicago accessing 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 enrollment. 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 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.
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\textsuperscript{44,45} and restart of stalled replication fork along with PARP.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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
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

**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.

**Manjistha 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](http://www.jtocrr.org) and at [https://doi.org/10.1016/j.jtocrr.2021.100231](https://doi.org/10.1016/j.jtocrr.2021.100231).

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