Author's response to reviews

Title: Phase II Study of Olaparib in Patients with Refractory Ewing Sarcoma Following Failure of Standard Chemotherapy

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Author's response to reviews: see over
Dear Dr. Ratin,

Thank you so much for considering our manuscript entitled, “Phase II Study of Olaparib in Patients with Refractory Ewing Sarcoma Following Failure of Standard Chemotherapy.” We were delighted to read that your reviewers noted that our findings were “important, if sobering, direct clinical evaluation of very promising preclinical data,” that they “enjoyed reading this well written manuscript,” and that we “should be congratulated for conducting this academic study in a rare cohort of patients translating a sound biological hypothesis into a proof-of-concept clinical trial.”

I believe that the changes suggested by the reviewers make this a stronger manuscript. I hope that you consider these improvements sufficient for publication in your journal.

Below are point-by-point responses to the comments by your reviewers:

Reviewer 1:

Minor Essential Revisions

Statistical design and methods

1. Was pathology centrally reviewed. If it was, could the authors include this information into the manuscript

   Pathology was re-reviewed at one of the participating site institutions, but they were not reviewed centrally. We added clarification language in the text.

Results

1. Line 173 mentioned there were 6 occurrences of grade 3 AEs but table 2 indicated 4 events. Were there events not captured in the table (i.e. selected toxicities) or were there recurrent events in the same patient. Please clarify

   Only 4 of the grade 3 AEs were attributed to the study drug or treatment procedures. We made this clarification in the text.

Discretionary Revisions
1. Could the authors include the period of study accrual.

   Yes, we added this in the text.

2. Could the authors provide more information about the grade 4 event encountered in this study

   Yes, we added this in the text.

Reviewer 2:

Minor Essential Revisions:

1. Under “Methods”: The authors should state the diagnostic criteria for Ewing sarcoma used to accrue patients. Specifically, it should be mentioned if molecular testing for the EWS translocation was performed, as one of the mechanisms underlying the preclinical efficacy of PARP inhibitors in Ewings centers around the interaction between the Ewings-defining FET-ETS fusion transcript and PARP.

   Molecular testing was not required other than what was required for the pathologist to make a pathologic diagnosis of Ewing sarcoma. This clarification was added to the text.

2. Line 207: In spite of the fact that some of the preclinical data may be based on cell lines derived from tumors that have yet to develop resistance, it should be mentioned that there is some data for PARP efficacy in cell lines derived from resistant, pretreated tumors, as described in Brenner et al Cancer Research 2012 (ref 13).

   We added the qualifier “some” in the language of the text to describe these cell lines.

Again, I’d like to thank you and the reviewers for helping to improve this report of our clinical trial results. I hope that with these improvements, this manuscript will be acceptable for publication in your journal.

Yours truly,
Edwin Choy, MD