Dear Editor,

We would like to thank the reviewers for a thorough review of our manuscript. All your comments are constructive and have been helpful in revising and improving our manuscript. We did our best to respectfully follow your detailed advice. As requested, we have addressed each reviewer comment point by point in the text below.

All of the authors have read and approved the revised manuscript.

We also would like to thank you for considering our manuscript “Comprehensive molecular and clinical characterization of Asian melanoma patients treated with anti-PD-1 antibody” for publication in your journal.

Please contact us if you have any additional questions or issues regarding this paper.
We look forward to receiving your positive final decision on this manuscript.

Sincerely,

Su Jin Lee, MD, PhD

Division of Hematology-Oncology, Department of Internal Medicine, Ewha Womans University College of Medicine, 260, Gonghang-daero, Gangseo-gu, Seoul, 07804, Republic of Korea

Tel: +82-2-2650-5890, Fax: +82-2-2648-5890

Email: sujinlee421@gmail.com

Response to comments from Rodabe Amaria (Reviewer 1)

The incidence of BRAF mutations in this cohort seems abnormally high considering this is a mostly mucosa/acral population, additionally the incidence of KIT mutations seems low. Additionally, the OS seems very long if the median duration of treatment was only 2.6 months. Not surprising to find that the BRAF mutated patients who previously had BRAF/MEK didn’t respond well to anti-PD1.

I think one important thing you omitted here is that response rates are lower because you have a high percentage of mucosal melanoma patients. We know from the CheckMate 067 study that mucosal patients have lower response rates/benefits from PD-L1 or ipi/nivo than cutaneous patients – this should be mentioned. Would be beneficial to break down response by subtype of melanoma: mucosal vs acral vs other instead of just lumping the whole population together.

Response to Reviewer: Thank you for raising this important issue. We have analyzed the data, and found that neither the response rates or survival outcomes significantly differed for mucosal vs. acral vs. other (including cutaneous) subtypes.

The pooled analysis by Angelo et al., which analyzed the efficacy and safety of nivolumab alone or nivolumab/ipilimumab combination in patients with mucosal melanoma, included patients from five studies, two of which only recruited previously untreated patients (CheckMate 066; n=206, CheckMate 067; n=313). In comparison, our study included heavily pre-treated patients, 20% of whom received more than two lines of previous therapy. We have also included patients with poor performance status and baseline brain metastases, which are exclusive criteria in most clinical trials.
Hence, we believe that the low response rates are attributable to the patients’ treatment lines, ECOG, and CNS metastasis. This was mentioned in the first paragraph of the Conclusion section in the original manuscript. With all due respect, the authors think that breaking down response by subtype would not accrue additional information regarding response or survival outcomes in our report.

You should add a sentence about M staging of patients, presence of brain mets, elevated LDH in the methods/patients section instead of just referring to Table 1.

Response to Reviewer: Thank you for your comment. The following sentence was added in the Result section, ‘1. Patient characteristics,’ line 7.

M staging was based on cutaneous melanoma criteria for all patients– 42 (28%) with stage M1c and 11 (7%) with stage M1d (with brain metastases).

Comments on elevated LDH was stated in the original manuscript (Results section, 1. Patient characteristics, line 9), with a sentence beginning with “A total of 32 patients (21%) had elevated baseline LDH …”.

I don’t think table 3 is all that helpful since the BRAF/KIT status shouldn’t influence PD1 response.

Response to Reviewer: Thank you again for your comment. Table 3 was deleted from the manuscript, and instead we revised a sentence in the Result section, 4. Genomic analysis, line 21.

Response rate was not associated with BRAFV600 (ORR 19 vs 13%, p=0.493; DCR 65 vs 44%, p=0.060; DCB 42 vs 39%, p=0.812) or KIT (ORR 16 vs 29%, p=0.231; DCR 64 vs 57%, p=0.608; DCB 42 vs 43%, p=0.933) mutational status.

Other tables in the manuscript were re-numbered accordingly.