Peer Review File

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Reviewer Comments

Response to Major points

Comment 1: There are no data about the lines of treatment. Neither it is described which therapies were given frontline nor in which line of treatment D+R was used? Had there been patients treated by immune-checkpoint inhibitors (ICI) or chemotherapy plus ramucirumab. Data should be at least given in the results part.

Reply 1: We thank the reviewer for their comment. We agree with the reviewer and have incorporated these suggestions throughout our paper.
Related to comment 2, the efficacy of DOC plus RAM may be affected by a previous immunotherapy treatment. In addition, data on treatment line may have a significant impact on the OS, and therefore should be described. In Japan, DOC is the only drug that can be used in combination with RAM in standard therapy for advanced NSCLC patients. Therefore, we did not use any combination therapy of immune-checkpoint inhibitors or chemotherapy plus ramucirumab.

Changes in the text: We added data regarding treatment line both Table 1 and the Results section (see Page 10, line 161). We also added information on the types of treatment to both Table S1 and the Results section (see Page 10, line 162).

Comment 2: This fact is relevant as there are nowadays some papers published about the synergistic effect of anti-angiogenesis and chemotherapy followed immediately after ICI. A most recent one was published by Brueckl et al., BMC Cancer 2020 and includes a summary of the papers published to this theme. Of note, there do not only data exist to ramucirumab but also to nintedanib in combination to docectaxel, which is another anti-angiogenic agent directed against VEGFR (and additionally FGF/PDGF). In addition, there is a prospective trial VARGADO (NCT02392455) aiming to give answers to N+D in different lines and after ICI or chemo plus ICI 1st line (Grohe et al., Future Oncol 2019; Proc ASCO 2020). These information should be mentioned and completed in the introduction and discussion parts.

Reply 2: We thank the reviewer for their comment. As mentioned in Comment 2, the efficacy may improve depending on whether or not immunotherapy was previously carried out.

Changes in the text: We quoted the report by Brueckl et al. and Grohe et al. and added an explanation in the Discussion section to outline that immunotherapy as a front-line treatment may also affect our study as 40% of patients underwent prior immunotherapy (see Page 15, line 281).

Comment 3: In addition, there is no information given, whether clinical factors, which

are of prognostic value in terms of PFS are also relevant for OS? However, it might be interesting whether those factors are specific for R+D therapy are generally prognostic. Especially, liver and brain mets are of negative prognostic value for chemotherapy and ICI based therapy. Therefore, factors relevant to OS should be named in the results part und further discussed in the discussion.

Reply 3: We thank the reviewer for their comment. We agree that OS data should be given as it is the most reliable endpoint. Unfortunately, prognostic factors such as MPE and brain metastasis were not consistent between PFS and OS. Since the number of prior treatments and immunotherapy pre- and post-DOC plus RAM may affect OS, we added the contents to the Discussion section. A possible explanation could be that PFS showed high maturity (82.3%) whereas OS showed relatively lower maturity (62.4%). Therefore, in assessing the efficacy of DOC plus RAM, we focused on PFS.

Changes in the text: We added OS data to Table 3 and the above comments to the Results and Discussion section (see Page 12, line 204, Page 15, line 252 and Page 16, line 273).

Comment 4: Furthermore, it should be described who many patients had been on treatment with D+R at the cut-off (minimal follow-up was 3 months!) and how many patients received further therapies after progression to R+D?

Reply 4: We thank the reviewer for their comment. At the time of cut off, 13 patients were receiving DOC plus RAM treatment. We showed that the median follow-up time in sensor patients was 12.5 months, which is sufficient to follow PFS. Unfortunately, we did not collect data on line treatments after DOC plus RAM, and further investigation on this is needed in the future.

Changes in the text: We added text to the Results section (see Page 10, line 169).

Comment 5: The number of cycles of D+R or even R as monotherapy should be described and associated with the ECOG-PS. Had patients with a lower PS had received less therapy, or less ramucirumab monotherapy? Due to ECOG PS it should be described how many patients were split up in PS 2, 3 and 4, respectively. Probably, there had been only few patients in the later PS categories.

Reply 5: We thank the reviewer for their suggestion. We apologize for not examining the number of cycles of DOC plus RAM. It is important to investigate the association between ECOG-PS and continuation rate to accurately reflect the prognosis. Instead of the number of cycles, we examined the discontinuation rate and analyzed the association between good and poor PS. In the results of the $\chi 2$ test, there was no difference discontinuation rate due to adverse events between good and poor PS patients. Therefore, the reason why poor PS patients showed shorter survival remains unclear.

Changes in the text: We added comments to both Table 1 and the Discussion section (see Page 13, line 226).

Response to Minor points

Comment 6: p.4 line 70 should be changed into most.

Reply 6: We thank the reviewer for their comment. We have modified our text as advised (see Page 6, line 88).

Comment 7: p.5 line 91. A combination of BEV in combination with chemotherapy and the ICI atezolizumab showed a significant benefit for liver metastases in the ImPOWER 150 study and was approved for this type of metastases (Socinski et al. NEJM 2018). This information should be added.

Reply 7: We thank the reviewer for their comment. In response to this, we have added reference number 4 (see Page 7, line 108).

Comment 8: p.9 line 159. A RR of 30.3% will not be termed “high”. This should be changed

Reply 8: We thank the reviewer for their comment. In response to this, we have modified our text as advised (see Page 11, line 184).

Comment 9: p.9 line 161. Do not mix ORR and RR, as ORR means a confirmation of RR at a further staging not earlier than 4 weeks after the first detection o aRR.

Reply 9: We thank the reviewer for their comment. In response to this, we have modified our text as advised (see Page 4, line 60, 63, 64, Page 6, line 92; Page 11, line 181, 184, 185; Page 15, line 256 and Page 17, line 292)

Comment 10: p.10 line 170. Correlation should be changed into association as correlation is a defined statistical term.

Reply 10: We thank the reviewer for their comment. In response to this, we have modified our text as advised (see Page 12, line 196).

Comment 11: p14. Line 247. First-line and further lines of treatment before R+D are not further analyzed and may had been resulted in confounding data.

Reply 11: We thank the reviewer for their comment. In response to this, we have added this limitation to our text (see Page 16, line 284).