Author’s response to reviews

Title: A multicenter open-label phase II trial to evaluate Nivolumab and Ipilimumab for 2nd line therapy in elderly patients with advanced esophageal squamous cell cancer (RAMONA)

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Author’s response to reviews:

Dear Editors,

Many thanks for the opportunity to answer the referees’ comments on our manuscript entitled “A multicenter open-label phase II trial to evaluate Nivolumab and Ipilimumab for 2nd line therapy in elderly patients with advanced esophageal squamous cell cancer (RAMONA)”. We are convinced that the consideration of the comments significantly improved our paper.

Prof. Lin brought the very recent data published November 2018 into play, highlighting the effectiveness of second-line pembrolizumab-based PD-1 inhibition for ESCC patients. In our opinion, this publication highly supports the potential of the RAMONA trial. To our knowledge, RAMONA is the only trial to date evaluating second-line treatment of ESCC patients with combined PD-1/CTLA-4-inhibition worldwide.
For rebuttal, please find below our careful point-by-point response to each comment of both referees. Also, find the improved manuscript attached to this letter. We highlighted all changes by ‘track changes’.

Thank you for considering the publication of our manuscript in your journal. I am looking forward to your reply.

Yours sincerely,
Nadja Meindl-Beinker

Reviewer reports:

Chia-Chi Lin (Reviewer 1): This is the protocol summary of a multicenter (in Germany) phase II trial to evaluate nivolumab plus ipilimumab as the second-line therapy in elderly (> or = 65 year-old) patients with advanced esophageal squamous cell cancer (RAMONA).

The unique aspects of this phase II trial is that, (1) The primary endpoint of this phase II trial is one-year overall survival (OS) rate (landmark analysis); (2) For patient screening, the G8 screening tool and the Deficit Accumulation Frailty Index (DAFI) will be used to exclude "frail" patients; (3) The addition of ipilimumab is conditional.

Background

1. The authors stated that, "...effectiveness of second-line chemotherapy is discouraging". The authors could add the following updated information in this paragraph. "On 14 November, 2018, MSD announced that pembrolizumab significantly improved OS compared to chemotherapy (paclitaxel, docetaxel or irinotecan) in patients with advanced esophageal or esophagogastric junction carcinoma whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10), regardless of histology."

We thank Prof. Li for this valuable comment. We are convinced that adding this very recent data to our manuscript improved the relevance of this manuscript significantly. Please find the respective information on page 4.


We totally agree that this trial nicely highlights the beneficial effect of immunotherapy in ESCC. So, we added the information to our introduction (page 4). We also discuss this publication at the very end of our discussion section (see page 15).

Yasuo Hamamoto (Reviewer 2): This paper was about the study protocol of RAMONA trial which is a multicenter open-label phase II trial to assess nivolumab and ipilimumab combination therapy for elderly ESCC patients. Improving treatment for elderly ESCC patients was needed, thus this trial seemed to be of value for publishing. Some revises would be necessary for publication.

Major point

1. Authors limited elderly patients for this study, however the rationale is weak. It could be easily expected that the selected patients will be mainly fit-healthy elderly patients. They planned to exclude frail patients from the immune combination. It is hard to understand what kind of clinical and immunological questions. To investigate most promising second-line immune treatments, they SHOULD conduct healthy patients. If authors try to clarify immunological behavior for elderly frail ESCC patients, they need to conduct immunotherapy focus on frail patients. This study does not simplify the question and mixed. If there are more strong rationale for the design and immunological assessments, please explain.

The referee is correct, the choice of the patient cohort is critical for the value of a clinical trial. The principal investigator of the trial is head of a geriatric oncology network and his experience reports a limited number of HEALTHY patients, at least in western countries.

As explained in our manuscript, Caucasian ESCC patients usually present different comorbidities. Thus, the patients show a reduced performance status, especially in the second line setting. However, our experience demonstrates that elderly frail patients often refuse any therapy in centers and prefer best supportive care approaches. Thus, the potential to recruit FRAIL patients to a clinical trial is very poor. In the RAMONA trial, we instead decided to enroll Slow-Go patients as far as possible. After a run-in phase and subsequent safety assessment, they also have access to the combined nivo/ipi treatment. Half of the ESCC patient population is older than 65 years with a clear medical need, letting us focus on this patient subset. The objective of the study is to show that, for our cohort, the combination of nivo and ipi is more feasible than chemotherapy.

However, we acknowledge that the referee does have an important point. Indeed, during recruitment, investigators asked to allow recruitment of younger patients to the study due to a similarly high medical need. However, as this would change the scope of the study dramatically,
this might raise critical concerns by local regulatory authorities and ethics committees. Still, RAMONA was planned as a first phase II study. If effectiveness and safety are proven in our vulnerable patient cohort, it would definitely be necessary to analyze this treatment combination in larger and more diverse cohorts.

2. Why do they select second-line setting? Several study already conducted immune-check point inhibitor compared with weekly paclitaxel. Weekly paclitaxel were one of established second-line treatment for ESCC. Why author do not discuss about wPTX?

We apologize that we did not explain this well enough in our manuscript. The main target cohort of this trial has received first-line treatment according to the CROSS protocol (chemoradiation with carboplatin and paclitaxel) which is the preferred treatment scheme in Germany. This approach is also considered effective as definite chemoradiation and in the palliative setting. Thus, the weekly administration of paclitaxel is no option for most of our patients. We now included a more detailed explanation of this argument in the manuscript on page 12.

3. What kind of phase 3 study could be planned after this study? Comparison with wPTX or Nivolumab/Pembrolizumab?

As described in our reply to comment number 1 of this referee, we would plan to test the combination therapy in a larger and more diverse patient cohort as the next step. With respect to our answer to comment 2 of this referee, there is no standardized chemotherapy in this setting in Germany so far. Thus, we would suggest to randomize against ‘investigator’s choice’. However, we would define ‘investigator’s choice’ for specific options (wPTX, vinorelbine as single agent etc.).

4. Statistical assumption is too poor. Is there any limited data of elderly ESCC patients in second-line setting?

To our knowledge, there is no prospective data available on elderly ESCC patients in the second-line setting, e.g. due to the rarity of this disease in Western countries. Accordingly, we estimated a recruitment maximum of 2 patients per center per year in 34 centers all over Germany (see page 6).

(Only) Limited data of elderly ESCC patients is accessible and summarized by Thallinger et al. Statistical estimation of the sample size for the explorative phase 2 RAMONA study is based on this data. (See reference 4 of our manuscript. We added the reference in the paragraph ‘statistical analysis and sample size’ on page 11.) However, we agree that, after approved effectiveness in RAMONA, a larger randomized trial is important.
5. Kudo et al. reported that of the 65 patients included in the study, grade 3 or 4 adverse events occurred in 26%. Is there possibility that the probability of adverse events could increase in patients with esophageal cancer than patients with other carcinomas?

As described above, ESCC patients represent a vulnerable cohort with many comorbidities (e.g. nicotine and alcohol abuse and related diseases) which indeed can increase adverse events as compared with patients with other carcinomas. We included a run-in phase and a safety assessment in our trial design to address this point. This is described in the manuscript on page 6 (bottom).

6. Did authors take into consideration the estimated timing of immune related adverse events occurrence, to determine the timing of the first safety assessment?

The referee is absolutely right, and timing of safety assessment was one of the most important points when the trial design was planned. Many adverse events occur after 6 weeks of immunotherapy as described e.g. by Kähler et al. We added the respective citations accordingly on page 6 of the manuscript to clarify this decision for the reader.

7. In Figure 1, it seems that a restaging examination is repeated every 12 weeks (2 cycles in nivolumab/ipilimumab combination therapy and 6 cycles in nivolumab monotherapy). Is it equal to four treatment cycles as authors mentioned in page 7, line 1-2?

The referee is absolutely right. We corrected the figure and the figure legend according to the text.

8. In this trial, patients with G8 score >14 will be included into the study. Is there any possibility that these patients could benefit from standard second line chemotherapy than nivolumab/ipilimumab combination therapy?

This screening tool was chosen to discriminate between go-go and slow-go patients and allows distinct subgroup definition for additional explorative data analysis. For the complete cohort, treatment options (second-line) are limited as discussed for comments 1 and 2 above. Furthermore, very recent data for pembrolizumab vs. chemotherapy (paclitaxel, docetaxel, irinotecan) highlight PD-1 inhibition as more effective for these patients (Kojima et al., J Clin Oncol). In that trial, ECOG 0-1 patients were recruited. We added this reference in the background information section of the revised manuscript on page 4.

9. Are patients with nivolumab monotherapy (those who are not eligible to nivolumab/ipilimumab combination therapy) subject to statistical analysis?
Of course, also these patients are subject to statistical analysis. We will analyze ALL (elderly) patients recruited according to the ITT principle. This information was added to the manuscript on page 11 to the paragraph describing statistical analysis and sample size.

Differentiation between mono or combination therapy allows an additional explorative subgroup analysis. In line with toxicity data, we expect about 2/3 of the patients to develop toxicity grades \(\geq 2\), explaining the number of patients that will be finally recruited to arm A of the trial.

Minor points

1. CROSS trial included only patients with clinical stage T1N1 or T2-3N0-1, so it is controversial to extrapolate the result of CROSS trial directly to patients with locally advanced or metastatic ESCC.

We agree with the referee in this point. Especially in Germany, experience with the CROSS protocol used in the curative and palliative setting (ESCC Stage IV patients) is favorable. We addressed this important issue at the beginning of the discussion section citing Noronha et al. (page 12), who demonstrated the effectiveness of carboplatin/paclitaxel (CROSS scheme) as definite chemoradiation. We rephrased this sentence to make this point clearer for the reader.

2. Authors should mention the source of historical control for standard chemotherapy.

Thanks for this obvious missing piece of information in the paragraph ‘statistical analysis and sample size’. The respective citation was added on page 11.