Peer Review File

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Reviewer A:

This is a retrospective study of FOLFIRI+Ramucirumab for advanced gastric cancer. However, it is very difficult to draw some conclusion from this study due to the following issues.

Comment 1: Because there are some issues of patient background which seem to affect the efficacy of FOLFIRI plus Ramucirumab, such as prior use of fluoropyrimidine and treatment line, it is very difficult to evaluate its efficacy in overall pupulation. The comparison between irinotecan and FOLFIRI may be affected by the prior use of fluoropyrimidine and treatment line.

Reply 1: We clearly agree that prior use of 5-FU and number of therapy lines may influence efficacy. Ramucirumab plus FOLFIRI or irinotecan was used as palliative first or second line therapy. Only one patient had been pretreated with more than two therapy lines as participant of a clinical trial. The majority of patients receiving irinotecan-RAM had been pretreated with palliative intent, whereas FOLFIRI-RAM was mostly administered as first-line therapy. All patients had been pretreated with 5-FU based therapy either perioperatively or with palliative intent.

Changes in the text: We added detailed data regarding treatment line in table 1, pretreatment with 5-FU on page 7 (line 88) and page 9 (lines 124-127).

2. The rule of counting the treatment line should be added because it generally depends on the interval between perioperative chemotherapy and recurrence.

Reply 2: Systemic palliative treatment was defined as systemic therapy in the presence of metastases independent of the interval between perioperative chemotherapy and disease recurrence.

Changes in the text: We added the rule of counting the treatment line in our text as advised (see page 4, lines 59-61).

3. Because the tumor progression is rapid and the prognosis is poor in patients experiencing early recurrence after peri-operative chemotherapy with FLOT, it is highly recommended to add the data of patients with early recurrence after FLOT who were treated with other patients.

Reply 3: Progression during or rapid disease recurrence after FLOT in the perioperative setting is one of the main considerations that prompted us to perform this analysis of alternative treatment strategies. RAM plus FOLFIRI or IRI was chosen due to early recurrence in 63% (n=10), which was defined as disease progression within 6 months after perioperative chemotherapy. Clinical outcome did not differ between patients with rapid disease recurrence or progression during perioperative therapy when compared to the rest of our cohort (median OS: 7.6 months versus 7.2 months, p=0.8). Median time to relapse in patients with initially curative setting was 3.8 months in our cohort.

Changes in the text: We integrated the information on early relapse in the text as recommended (see page 7, lines 97-101).

Reviewer B:

I would like to congratulate the authors for sharing their retrospective analysis. I have a few minor suggestions:

1. Did all patients have biopsy-proven adenocarcinoma. Please mention that in your manuscript.

Reply 1: This is an important information we missed to mention. All patients had biopsy-proven adenocarcinoma.

Changes in the text: We modified the text as advised (see page 4, lines 56-57)

2. How many patients received this regimen because of pre-existing neuropathy vs progression during peri-operative chemotherapy? Please mention that in your manuscript.

Reply 2: FOLFIRI-RAM or irinotecan-RAM was chosen due to progression during or rapid disease recurrence after FLOT in the perioperative or first-line setting in 63% (n=10) and preexisting PNP in 31% (n=5). In one patient treatment was chosen due to other reasons.

Changes in the text: We modified the text as advised (see page 7, lines 90-92) and added detailed information in the table with baseline characteristics.

3. Did any patient die or discontinue the regimen because of toxicity? Please mention that in your manuscript.

Reply 3: Only one patient discontinued the regimen because of toxicity.

Changes in the text: We added information as suggested on page 7, line 95).

4. Was there any difference in PFS among patients receiving FOLFIRI and RAM vs Irinotecan and RAM?

Reply 4: There was no statistically significant difference in PFS (median: 5.4 months versus 4.6 months, p=0.2).

Changes in the text: We modified the text as advised (see page 7, lines 104-105)

5. If possible, please add a table describing the baseline characteristics of the overall population, patients receiving FOLFIRI and RAM/Irinotecan and RAM.

Reply 5: We added a table summarizing baseline characteristics as suggested.

Changes in the text: See table 1 on page 6.

Reviewer C:

1. Those who had received FOLFIRI plus RAM might have been more feasible for intensive chemotherapy than those who received irinotecan plus RAM. Authors should mention the selection bias.

Reply 1: Unexpectedly, age and ECOG PS were balanced between the subgroups. However, the majority of patients who received irinotecan as chemotherapy backbone were pretreated with one palliative therapy line, whereas the majority of patients who received FOLFIRI had not been pretreated in palliative intention.

Changes in the text: We added detailed information concerning overall patient characteristics as well as the mentioned chemotherapy backbone subgroups in table 1 and pages 7 and 8 lines 104-18. Considerations on selection bias are mentioned on page 9, lines 124-127.

2. The information about the metastatic sites and the number of the metastases is poor. As Vogl et al described in the manuscript, the peritoneum metastasis may influence the results.

Reply 2: The presence of peritoneal metastases was assessed and did not have an impact on survival in our cohort.

Changes in the text: We added detailed information about peritoneal metastases in table 1 and modified the text (see page 7, lines 95-97).

3. Authors should describe the grade of peripheral neuropathy at the initiation of FOLFIRI plus RAM. Authors also should clarify the definition of ‘rapid recurrence following FLOT’ (e.g. during the treatment, or recurrence within the 6 months after the last administration of FLOT).

Reply 3: The grade of peripheral neuropathy was not captured in our retrospective analysis. Patients suffering from PNP >1 were considered eligible for a taxane-free therapy regimen. As correctly assumed, ‘rapid recurrence’ was defined as progression during or recurrence within

6 months after perioperative or first-line FLOT.

Changes in the text: We modified the text as advised (see page 7, lines 90-92 and 97-100).

4. The efficacy of the addition of 5-fluorouracil beyond progression was unknown in the treatment of the gastric cancer, although it is a common strategy for the treatment of the metastatic colorectal cancer (J Clin Oncol. 2003 Jun 1;21(11):2059-69. doi:10.1200/JCO.2003.11.126). Authors referred to the phase 2/3 trial which compares FOLFIRI plus RAM versus paclitaxel plus RAM. However, this design could not clarify the utility of 5-Fu beyond progression.

Reply 4: The primary scope of our analysis was to report feasibility and clinical efficacy of RAM plus FOLFIRI or IRI in pretreated gastric/GEJ cancer. We fully agree with the reviewer that use of 5-FU beyond progression in gastric/GEJ cancer should be further investigated.

Changes in the text: Efficacy data of the RAMIRIS trial have been added to the Discussion section (see page 9, lines 132-135).

5. Is the dose of irinotecan in FOLFIRI plus RAM regimen same to the irinotecan plus RAM?

Reply 5: We used the same dose of irinotecan (180 mg/m^2 every two weeks) alone or in combination with 5-FU as chemotherapy backbone.

Changes in the text: We added information about dosing on page 4, lines 57-59.

6. How about the median PFS in each subgroup? Patients who had received FOLFIRI plus RAM might have received the subsequent chemotherapy, which affected the prolonged OS.

Reply 6: PFS did not significantly differ between FOLFIRI plus RAM and irinotecan plus RAM (median: 5.4 months versus 4.6 months, p=.2) and the number of subsequent therapy lines was balanced between groups.

Changes in the text: We reported on PFS and subsequent therapy lines as advised (see pages 7 and 8, lines 104-108) and added detailed information in table 1.