Author’s response to reviews

Title: Correlation of skin rash and overall survival in patients with pancreatic cancer treated with gemcitabine and erlotinib – results from a non-interventional multi-center study

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Change independent of the reviews:
Although "erlotinib" may suggest the indication “pancreatic cancer”, we would prefer to explicitly name the disease in the title. We therefore propose to expand the title accordingly (p.1): "Correlation of skin rash and overall survival in patients with pancreatic cancer treated with gemcitabine and erlotinib – results from a non-interventional multi-center study".

We thank both reviewers for their in-depth review and the valuable comments to strengthen the manuscript.

Reviewer 1:

1. HOWEVER, IT IS APPARENT THAT THERE IS IMPROVEMENT IN THE PFS AND THAT PATIENTS WHO EXPERIENCE A RASH GRADE EQUAL TO OR GREATER THAN 2, OR OVER THE AGE OF 65 PARTICULARLY BENEFIT. THIS IS CLEARLY STATED BUT UNFORTUNATELY THE NUMBERS ARE NOT SUFFICIENT TO STATISTICALLY AFFIRM
THESE FINDINGS. STILL AN IMPORTANT OBSERVATION WHICH COULD BE FURTHER EMPHASIZED.
We thank the reviewer for this important point to put more emphasis on patients potentially benefiting form gemcitabine/erlotinib.
Indeed, we observed an improvement in PFS in the subgroup of patients with rash grade ≥2 (vs. grade 1 and vs. no rash) as well as in the subgroup of patients aged ≥65 years (vs. ≤65 years) and this improvement was found to be statistically significant.
We have stated this this in the “Results”, “Effectiveness” section, para 2 (“Subgroup analyses revealed a statistically significant benefit in PFS of patients with rash grade ≥2 …”; p.10). We have also stated the benefit observed in these two subgroups in the Abstract, Results, Discussion, and Conclusions. In the latter section, we now include the information that the favorable PFS was “significant”, to further emphasize this result (p.14).
In contrast to PFS, improvement in OS observed in the same subgroups did not reach statistical significance. However, we found a trend towards better median OS in the subgroup of patients with rash grade ≥2 and in patients aged ≥65 years (see “Results”, “Effectiveness” section, para 1; p.9). Moreover, we now include the OS data more clearly in the Conclusions (p.14).

2. THE LACK OF DATA ON 2ND AND 3RD LINE THERAPY IS A PROBLEM IN ASSESSING OS.
WITH THE DEVELOPMENT OF BOTH FOLFIRINOX AND GEMCITABINE/NAB-PACLITAXEL REGIMENS, IT IS LIKELY THAT SOME OF THESE PATIENTS MAY HAVE CROSSED OVER TO OTHER THERAPY AND THIS IS NOT ACCOUNTED FOR OR DEFINED IN THE MANUSCRIPT. THIS COULD HAVE PROFOUND EFFECTS ON THE OS AND MOST READERS WOULD LIKE TO SEE DATA ON THIS. IN THIS TYPE OF STUDY WITH SUBSEQUENT THERAPIES, THE DFS MAY BE THE ONLY WAY TO GAUGE THE PERFORMANCE OF THE REGIMEN UNDER STUDY.
We agree with the reviewer that further line treatment has an important effect on the outcome of patients.
Accordingly, we went back to the primary data of the study to address this point as comprehensively as possible.
Of the full analysis set (n=270), 21.5% of patients (n=58) had received previous palliative chemotherapy. Out of the 338 patients in the full safety set, 130 patients were alive after premature termination of the study. Of those patients, 33.1% (n=43) started further line treatment. The type of further line treatment has not been recorded. These data are now included in a new paragraph on follow-up and further line treatment (“Safety and treatment satisfaction”, para 1; p.11) as well as in a new table (Table 3, p.11).
Accordingly, we agree that progression-free survival might be a more appropriate measure to assess the effectiveness of a regimen tested. In this light, the positive results observed in elderly patients and in patients with rash ≥2 might gain some additional importance.

3. I AM ALSO PUZZLED BY THE APPARENTLY LONG TIME TAKEN TO INITIATE THERAPY - UP TO 71 DAYS. WHILE THIS MAY HAVE NO EFFECT ON THE STUDY, IT CATCHES ONE'S ATTENTION AND DESERVES AT LEAST A COMMENT. IN THE USA IT WOULD BE UNUSUAL TO START LATER THAN 14 DAYS FROM DIAGNOSIS.
We agree with the reviewer that, with a mean of 71 days and a median of 27 days, the time from diagnosis of metastatic disease to informed consent seems rather long. Accordingly, we have explored the primary data set to seek insights into this issue.
The median (27 days) and range (1 to 792 days) are shown in Table 2. The arithmetic mean of 71 days
is likely to be distorted by the outlier of 792 days. The median of 27 days shows that 50% of the patient population gave informed consent within 27 days or less after diagnosis of metastatic disease. Furthermore, 21.5% of patients in the full analysis set received previous palliative chemotherapy before receiving gemcitabine/erlotinib as part of this NIS. This fact might further explain the seemingly long time from diagnosis of metastatic disease to informed consent. We have added this fact in the Results section, Study population, para 1; p.7.

Reviewer 2:

1. I DO NOT LIKE THE PHRASE 'REAL WORLD DATA' IN KEYWORDS. ITS TOO DRAMATIC AND EVEN SARCASTIC!

We intended to use "real-world data" as a technical term for data obtained in a non-interventional (i.e. observational) study - as opposed to data from a clinical trial with narrowly defined selection criteria. Instead of “real-world data” we now use “clinical practice” in the abstract (p.3) and “Non-interventional study” in the keywords (p.4).

2. THE BACKGROUND IS JUST ONE LONG PARAGRAPH. I SUGGEST BREAKING IT DOWN INTO 2 PARAGRAPHS FOR EASE OF READING, AND BETTER PRESENTATION.

We have divided the background section into three paragraphs to make it easier to read (p.5).

3. ONE IMPORTANT ASPECT THAT IS NOT VERY CLEAR IS THE STATUS OF PATIENTS - DID ALL OF THE PATIENTS EVENTUALLY SUCCUMB TO THIS DISEASE? WAS DEATH ONE OF THE INCLUSION CRITERIA? IF SOME OF THE PATIENTS ARE STILL ALIVE, PLEASE PROVIDE CLEAR ANALYSES ON HOW MANY PATIENTS WITH RASHES VS NO-RASHES ARE STILL ALIVE AND HOW MANY FROM EACH CATEGORY ARE DEAD.

We have added a paragraph and a new table (Table 3) to the manuscript that expands on premature study termination (including reasons) and on deaths before regular study end (including causes) (section on “Safety and treatment satisfaction”, first para; p.11).

It has to be noted, that the pre-specified observation period in this study was 12 months. Out of the 338 patients in the full safety set, 39 patients completed the full 12 months of observation. Out of the remaining 292 patients, 133 (45.5%) had died and 130 (44.5%) had prematurely terminated study participation due to tumor progression or other reasons (see new Table 3, p.11).

Death was an outcome as reflected by overall survival analyses. Mortality (Kaplan-Meier estimates) at end of follow-up (12 months) was as follows:

<table>
<thead>
<tr>
<th>Rash grade</th>
<th>None</th>
<th>Grade 1</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (FAS population)</td>
<td>171</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>Died (%)</td>
<td>61 (58%)</td>
<td>23 (66%)</td>
<td>16 (46%)</td>
</tr>
<tr>
<td>Survived (%)</td>
<td>(42%)</td>
<td>(34%)</td>
<td>(54%)</td>
</tr>
</tbody>
</table>

Note that Kaplan-Meier mortality estimates are higher than raw percentages, since censoring of events (loss to follow-up) was noteworthy.

4. DID AUTHORS FIND ANY GENDER-SPECIFIC DIFFERENCES?

Unfortunately, we did not conduct subgroup analyses according to patients’ gender, as gender was not a pre-specified variable for the Cox regression model used in PFS and OS analyses.

However, based on the results of NCIC CTG PA.3 presented in the original publication of the combination of gemcitabine/erlotinib, we would not expect gender to influence the clinical outcome or
the appearance of skin rash. In NCIC CTG PA.3, younger patients \( (p = 0.01) \) and patients with better performance status \( (p = 0.03) \) were significantly more likely to develop a skin rash.

5. **AUTHORS CLEARLY CONCLUDE THAT SKIN RASHES DO NOT CORRELATE WITH BETTER OVERALL SURVIVAL.** THIS CLEARLY GOES AGAINST EARLIER STUDIES THAT SHOWED OTHERWISE (CITED ARTICLES 8 THROUGH 11). TO DISCUSS THIS FURTHER AND MEANINGFULLY, AUTHORS NEED TO CLEARLY POINT OUT THE RELEVANT DATA FROM THESE CITED REPORTS - WHAT EXACTLY WAS REPORTED IN THESE INDIVIDUAL REPORTS - NUMBERS AND PERCENTAGES ALONG WITH THE NUMBER OF PATIENTS EVALUATED. ONLY, THEN A MEANINGFUL CONCLUSION COULD BE DRAWN ESPECIALLY WITH REGARDS TO A) IF THERE IS INDEED A CASE TO BE MADE FOR PROGNOSTIC ROLE OF RASHES IN PDAC AND B) IF THE SAMPLE SIZE IN CURRENT STUDY IS TO BE BLAMED.

While, we did not find a statistical difference in OS between rash-positive and rash-negative patients (primary endpoint), we observed a trend towards better median OS in patients with rash grade ≥2 vs. patients with rash grade 1 and patients without rash. This is in line with previous observations, that described a grade-dependent benefit from erlotinib with the greatest benefit in patients with rash grade ≥2 [References 7, 8, 9, 10]. With regards to effectiveness, PFS could be considered as another relevant endpoint. In the cohort presented here, patients with higher grade rash and elderly patients indeed derived a significant benefit in progression-free survival.

Importantly, it has to be taken into account that the studies cited [7-10] were interventional studies in the first line setting. Furthermore, these trials included up to 25% of patients with locally advanced disease. Patients with locally advanced pancreatic cancer tend to have a better outcome than patients with metastatic disease. In contrast, the non-interventional study reported here included a purely metastatic population and 21.5% of patients had received previous palliative chemotherapy (indicating more advanced disease). Accordingly, the underlying differences in study design and patient population might explain part of the differences observed. We have updated the discussion accordingly (Discussion, para 3, p.14).

6. **IN CONTINUATION OF MY ABOVE COMMENT, I AM CURIOUS THAT IF THE OVERARCHING AIM OF THE STUDY WAS TO CHECK IF EARLIER ASSERTIONS WERE CORRECT, WHY WOULD THE AUTHORS NOT PLAN TO INCLUDE ENOUGH CASES TO MAKE THIS EXERCISE WORTHWHILE!**

We had carefully planned the study from a statistics point of view (for details on the sample size calculation see Methods, para 2, p.6). The overarching aim of showing a survival benefit for all patients with rash was diluted by the fact that mainly patients with rash grade 2 contributed to this effect. Simply continuing recruitment until attaining 309 FAS cases would not have substantially changed the overall outcome. As the study design was not adaptive, over-recruitment was not an option.

In accordance with ICH E9 statistical principles, a confirmatory claim for the subgroup of rash grade 2 population (in the absence of an overall effect) would require a new study. The current rather exploratory finding (subgroup effect) is nevertheless of high interest.

7. **DID THE TUMOR GRADES DIFFER IN THEIR CORRELATIONS WITH SKIN RASHES?** Unfortunately, histologic tumor grading was not documented as part of the study.

8. **FINALLY, THE AUTHORS HAVE PERFORMED FAR MORE ANALYSES THAN WHAT IS CONVEYED IN THE RESULTS SECTION OF THE ABSTRACT. PLEASE RE-WRITE THIS SECTION OF ABSTRACT TO ACCURATELY REFLECT THE ANALYSES AND INCREASE THE IMPACT OF THE WORK.**
As suggested by the reviewer, we have extended the results and conclusions section of the abstract (p.4).