Author's response to reviews

Title: Phase II Study of Weekly Paclitaxel and Capecitabine in Patients with Metastatic or Recurrent Esophageal Squamous Cell Carcinoma

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Author's response to reviews: see over
Reply to Reviewer’s comments

Reviewer: (Florian Lordick)

1. This is clearly a study on squamous cell cancer of the esophagus. Many readers may be working in regions where adenocarcinoma is the predominating histological type of esophageal cancer. In my view it should be clarified already in the title of this paper that this study has been performed in the squamous cell type.

- We corrected the title of manuscript as “Phase II Study of Weekly Paclitaxel and Capecitabine in Patients with Metastatic or Recurrent Esophageal Squamous Cell Carcinoma

2. The reported response rates are higher than expected and that seen with comparable regimens in comparable patient populations. The authors do not clarify how they assessed response. Did all patients get CT scans? What were the intervals that were proposed in the study protocol for response assessment and were these intervals respected by the investigators. Were RECIST criteria applied? Do the authors report on confirmed responses? If not, what was the confirmed response rate (it may differ considerably from the reported rate in this paper). Were responses evaluated by the investigators or was an independent central response review board/radiologist involved?

- The response was evaluated using RECIST v. 1.0 and CT scans were performed every two cycles in all patients. The response was evaluated by radiologist (Hyae Young Kim, MD) blinding to clinical information. However, we did not report the confirmed response rate.

Minor point:
1. The use of two decimal numbers for the survival durations (abstract and results) are uncommon.

- We corrected the manuscript with the use of one decimal number for the survival duration in abstract and results

2. Discussion: The authors speculate on different capecitabine doses explaining the differences in the observed rate of hand-foot syndrome in another study investigating a taxane-capecitabine combination. There may be two other reasons to be considered. First, Lorenzen at al. investigated docetaxel-capecitabine, and not paclitaxel. Moreover, Lorenzen et al. investigated a Caucasian patient population, while Tak Yun et al. investigated a Korean population. Recent results suggest that the rate of hand-foot-syndrome in Americans and non-American Caucasians is higher than in East Asians.
We added the possible explanation for the differences in the observed rate of hand-foot syndrome in another study investigating a taxane-capecitabine – combination. (page 12-13)

3. Table 5 is not very informative. The information is already given in the text. In my view table 5 could be skipped.

Table 5 was removed in the manuscript.

4. Reference 25 and 29 are on the same study (one abstract and one full publication). In my view the full publication should cover everything and there is no need to cite this study

Reference of full publication will be used and abstract was removed.

Reviewer (Hugo Ford)

1. There needs to be a more detailed section in the discussion about the decision to change the patient population (from 2nd line to 1st and 2nd line) part way through the study, and particularly on the impact that this change has, if any, on the sample size calculation. The reasons for this change (seeing strong evidence of efficacy in the first 7 patients treated) do not make an especially good case for the change. I assume there may have been an element of slow recruitment as well, though this is not stated.

At the first stage, we observed a remarkably high response rate of 71% (5 partial responses among 7 patients). The protocol was therefore amended to estimate the response rate in patients with metastatic or recurrent esophageal cancer not only in the second-line setting, but also in the first-line setting.

Because the incidence of esophageal cancer is relatively low and patients recruitment was slow, we enrolled the patients in the first-line setting. With regard to protocol amendment, we did not consider statistical correction. (page 14; third paragraph)

Discretionary Revisions
1. It would be useful to have a wider review of existing data in the discussion, especially data from phase 3 trials to put the phase 2 data in perspective. For instance the authors cite reference 14 (a multicentre RCT), but then state in the text that response rate is 20-45% (and incidentally make no mention of the fact that this study was a study carried out in a largely adjuvant population in which response rates are meaningless, and in fact showed no benefit for chemotherapy over no chemotherapy). A fuller review of the (admittedly limited) phase III data
for first line therapy would be helpful

➔ To our knowledge, there is no phase 3 trials comparing different chemotherapy regimens in esophageal squamous cell carcinoma. We corrected list of references you pointed out. (Deletion of above mentioned reference)

2. It might also be interesting to comment on the more recent data reported at ASCO using paclitaxel plus carboplatin and radiotherapy preoperatively and showing a survival benefit, reinforcing the evidence for paclitaxel in this disease

➔ We described the result in the discussion section (page 13; second paragraph).

Briefly, it reads
Similar to metastatic disease, in unresectable locally advanced esophageal cancer (squamous/adenocarcinoma; 36/14), definitive concurrent chemoradiation with weekly paclitaxel and carboplatin also showed promising efficacy with OS of 17 months and median time to local progression of 14 months, which demonstrated high clinical activity of paclitaxel-based regimen.

3. The group comment that "this regimen deserves further evaluation as front-line treatment for oesophageal cancer" and "Ultimately randomized clinical trials are needed to determine the efficacy and safety of paclitaxel and capecitabine for oesophageal cancer patients". They should state whether they feel this regimen is appropriate in first or second line therapy (or both) and whether they have plans to take it into phase III trials

➔ We strongly recommend this non-platinum based regimen as first-line therapy in esophageal squamous cell carcinoma. However, we did not have any specific plans to conduct phase III trial at this time. This regimen will be compared with platinum-based regimen as comparator in phase III trial in the future.
Reviewer (Laurent Bedenne)

Major compulsory revisions:

- The patients are insufficiently described: indicate the frequency of locoregional/metastatic recurrences, the location of the metastases, the number of metastatic sites, the degree of dysphagia. The last point is important with an oral treatment like capecitabine, which entails taking several large tablets twice a day. Did all the patients with dysphagia need a stent?

  ➤ We indicated the frequency of locoregional/metastatic recurrences, the location of the metastases, the number of metastatic sites in Table 1. However, the patients who could not take oral capecitabine due to dysphagia were excluded and patients who had stent and could take oral drug were included in this study.

- The authors should define what is first line and second line. In the case of first line one can suppose that patients never had any treatment for their disease. But does “second line” mean second line CT after failure of a first line CT or second treatment after recurrence of a patient having had a previous treatment with curative intent? This question is raised by the fact that 6/20 “second line patients” had surgery or radiotherapy, and that 7/20 of those had a treatment free interval of more than 3 months.

  The twenty patients were treated as second-line chemotherapy after failure of first-line chemotherapy. All patients who performed surgery did not receive adjuvant chemotherapy, so after recurrence, patients were given first-line chemotherapy. The surgery and radiotherapy was not counted as therapy-line, only number of palliative chemotherapy was counted. (Statistical Analysis; first paragraph)

- There has been a methodological change during the trial, with the inclusion of first line patients, which was not originally planned. It would have been more correct to start a new trial with first line patients, or keep the initially calculated number of second line patients. At least, the response rate for second line patients should indicate the confidence interval, to verify that it does not include 10% (page 10). If it does, the main endpoint will not be fulfilled and it should be taken into account in the discussion and the conclusion.

  ➤ We calculated the 95% confidence interval of response rate of second-line PACE: 45% (95% CI, 23.2 to 66.8), which was added to manuscript on page 10. We agree with reviewer’s opinion with regard to sample size calculation. At the first stage, we observed a remarkably high response rate of 71% (5 partial responses among 7 patients). The protocol was therefore amended to estimate the response rate in patients with metastatic or recurrent esophageal cancer not only in the second-line setting, but also in the first-line setting given high efficacy. Because the incidence of esophageal cancer is relatively low and patients recruitment was slow, we enrolled the patients in the first-line setting. With regard to protocol amendment, we did not consider statistical correction for sample size calculation.
The authors should take into account in the discussion the randomised phase II trial by Tebbutt et al (Br J Cancer 2010;102:475-81). The results with weekly docetaxel-capecitabine are less favourable than those reported here, particularly in terms of response rate (26%).

We described the result of ATTAX study in the discussion section (page 12-13). Briefly, it reads, “Randomized phase II study of weekly docetaxel (30mg/m2) on days 1 and 8 and capecitabine (1600mg/m2 per day) on days 1-14 showed a response rate of 26%, median PFS of 4.6 months, and OS of 10.1 months in patients with esophagogastric cancer…”

Minor essential revisions:

- Results: lines 3-8 of “Patient characteristics” should be deleted, as the inclusion of first line patients was already signalled in the Methods

We deleted the above-mentioned sentences in “Patient characteristics”

- In § “Efficacy”, it is difficult to conclude to a similar efficacy for patients having received docetaxel-platinum, with 1 PR out of 6, versus 4 PR out of 7 after irinotecan-platinum. Possible cross resistance between docetaxel and paclitaxel should be discussed.

The following sentences are added to lines 12-17 of “Efficacy”

“With respect to prior chemotherapy received for patients treated in the second-line, two patients treated with prior 5-FU/cisplatin and one patient treated with docetaxel/cisplatin achieved partial responses to PACE. The clinical efficacy of PACE was slightly lower in patients previously treated with docetaxel, which suggest that paclitaxel may have cross resistance to docetaxel (Table 4). However, any definitive conclusions can not be made due to small sample size”

- In § “Efficacy”, and elsewhere, for survival, one figure after the dot should be enough (0.01 month is 7.2 hours!)
- We corrected figure for survival as reviewer commented.

- In § “Safety”, give the exact number and not percentages on such a small effective. It is generally accepted to give percentages above 50 patients. This remark applies elsewhere (page 13, 6.3% of patients are 2 patients)

- We indicated the exact number of patients as reviewer commented.

- Ref 25 is not complete and is the same as ref 29 (to be replaced in table 7 by ref 25)

- We corrected the reference number as indicated.