ANSWERING REVIEWERS

Subject: Revision of manuscript "*Phase II study of Docetaxel, Cisplatin and Capecitabine as preoperative chemotherapy in resectable gastric cance*"

Dear Editor,

Hereby, we present to you our revised manuscript "*Phase II study of Docetaxel, Cisplatin and Capecitabine as preoperative chemotherapy in resectable gastric cancer*" according to the reviewers' suggestions:

Reviewer 1

1) The authors did not present the statistical methods. It is impossible to analyse the results without informations related to patients sample size calculation.

In the *Patients and methods* section the statistical methods are described. As this is a one armed Phase II feasibility study no sample size calculations were made.

2) The authors should discuss the disadvantages to not use HER2 status and anti-HER2 therapy in preoperative chemotherapy, based on trials already available evaluating trastuzumab, T-DM1 and lapatinib in gastric cancer.

At the time of the trial design (2007) not many results were known about the treatment of gastric cancer with anti-Her2 therapy, especially not in the (neo)adjuvant setting. Moreover, only a small percentage (7-34%) patients have overexpression of Her2 receptor. In this feasibility study in 50 patients it was therefore not considered to add anti-Her2 therapy.

3) Why did the authors perform D1-extra lymphadenectomy instead of D2 lymphadenectomy? D2 procedure is the most adopted modality worldwide.

At the start of the study design, a D2 lymphadenectomy was not standard treatment due to earlier results comparing D1 vs D2 lymphadenectomy (Bonenkamp, Lancet 1995, Cuschieri, Br J Cancer 1999). In order to improve lymph node retrieval and to possibly prevent morbidity and mortality due to a D2 lymphadenectomy we designed a modified lymphadenectomy.

4) The paper has a well-written discussion. The reasons for the choice of a three-drug regimen were well explained. Treatment-related mortality of 5.9% is prohibitive. Almost 6% of treatment-mortality deaths is unacceptable in a potential curable resectable disease. There is no agreement that three-drug regimens are superior than two-drug regimens in gastric cancer. The authors should explore this point. ECF and ECF-like regimens were not compared to two-drug regimens in preoperative setting. Superiority of DCF over CF in V325 trial was too small. After comparison between FOLFIRI vs ECX by Guimbaud et al (J Clin Oncol 2014), in which FOLFIRI had better TTF, the potential superiority of three-drug regimens is more debatable than before. I believe that DCC should be recommended against its use in preoperative gastric cancer after a 5.9% treatment-related mortality and a high rate of febrile neutropenia.

We agree with the remarks of the reviewer and used them, in general, for revising the manuscript. The 5.9% treatment-related mortality was to some extent nuanced by the fact that one of these three patients refused further treatment.

5) The correct number of febrile neutropenia is 31%, and not 10%. Thirty one percent of patients presented febrile neutropenia in this study, and the authors should discuss and compare with correlate studies based on this number.

In table 3 the rate of febrile neutropenia is pointed out. 31% of patients suffered from this complication, occurring in 10% of all cycles, as depicted in the paper.

Reviewer 2

1) The study patients including wide range of disease stage (stage Ia-IVb) which may affect the results of resectability.

We agree with the reviewer, but it is not easy to assess the exact stage of gastric cancer using CT- and PET-scanning. Based on other studies it is likely that most patients in this study did have stage 2 and 3 disease.

2) In study was included one patient with a performance status 2, which was initially exclusion criterion

The comment of the reviewer is correct, but because of an intention-to-treat protocol we did not exclude this patient.

3) References are not the most recent and do not completely reflect the current views on this topic.

As far as we know we included the most important studies on this subject, especially on the use of this specific regimen.

Reviewer 3

This is the study of preoperative chemotherapy with 53 resectable gastric cancer patients. I think it may be some helpful to other's further studies. But sample size is small and just single arm study. The feasibility of preoperative DCC regimen is questionable because of high toxicity with low pCR rate. There were some minor points of revision.

We agree with the reviewer that this study may be very helpful to other's further studies.

Sincerely yours,
On behalf of all authors,
Anneriet Dassen