Reviewer’s report

Title: Influence of complete administration of adjuvant chemotherapy cycles on overall and disease-free survival in locally advanced rectal cancer: post hoc analysis of a randomized, multicenter, non-inferiority, phase 3 trial

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Reviewer: Javier Sastre

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REVIEW OF THE ARTICLE: INFLUENCE OF COMPLETE ADMINISTRATION OF ADJUVANT CHEMOTHERAPY CYCLES ON OVERALL AND DISEASE-FREE SURVIVAL IN LOCALLY ADVANCED RECTAL CANCER: POST HOC ANALYSIS OF A RANDOMIZED, MULTICENTER, NON-INFERIORITY PHASE 3 TRIAL, by Flavius Sandra-Petrescu et al.

Reviewer: Dr. Javier Sastre

Head of the GI Tumor Unit of Medical Oncology Department at San Carlos Hospital, Madrid, Spain

Dear Editor-in-Chief,

The author report a well written manuscript about a post-hoc analysis of a previous phase III trial published in the Lancet Oncology entitled "Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial". This analysis is focused on the effect of treatment adherence in overall survival (OS) and disease-free survival (DFS), being treatment adherence defined as the total number of cycles of planned chemotherapy. Their results suggest that treatment outcomes depend on treatment adherence but that conclusion is limited but several factors:

This analysis was done over the total population of the phase III study that survived for at least 6 months, but this is not an homogeneous population since OS and DFS was different between those patients treated with capecitabine and those with 5-FU (this is the conclusion of the previous phase 3 trial). In the discussion of the phase III trial, the author indicated that the positive effect in OS and DFS of capecitabine cannot be explained by treatment adherence. Then, a multivariate analysis including, apart from the completion of chemotherapy, the planned treatment (capecitabine vs 5-FU) and other confounding factors such as age, gender, ECOG, T and N status, stage, adjuvant or neoadjuvant group, complete pathological response and tumor regression grade (Ryan) to neoadjuvant treatment, is mandatory.

The role of adjuvant chemotherapy and its duration is not completely established in locally advanced rectal cancer. In colon cancer stage III, where 6 months of oxaliplatin plus capecitabine
or 5-FU/leucovorin is the gold standard, the recent IDEA study (preliminary results presented at ASCO 2017) suggested that in a low risk population defined as T1-3N1, 3 months of treatment with oxaliplatin plus capecitabine may be enough (but not with 5-FU/LV). These new data remark the importance of prognostic subgroups (low and high-risk groups) and the effect of capecitabine over 5-FU in the adjuvant setting. Then, a separate subgroup analysis about the effect of complete adherence to chemotherapy, in the lower (N0), intermediate (T1-3 N1) and high-risk of relapse (T4 or N2) is mandatory in the current post hoc analysis.

More important than complete chemotherapy may be the influence of the total dose and dose-intensity of capecitabine or 5-FU in overall outcomes. Data about dose-reduction, % of the planned 5-FU or capecitabine received and dose-intensity of both drugs are lacking. Due to adverse events, it is common to reduce the dose of chemotherapy during the adjuvant treatment, even completing the total number of planned cycles. In the present study, it would be of interest to know if differences in OS and DFS can be found between patients that completed all planned cycles without dose reduction and those that completed all planned cycles but with dose reduction and the impact of the percentage of dose-reduction (ie 20%, 40% etc). Differences in OS and DFS according to dose-intensity of chemotherapy should have been explored.

The discussion section is too long. It should be focused on the potential effect of those variables that can have some influence on their treatment outcomes rather than explain the best neo/adjuvant approaches for locally advanced rectal cancer. The comparison between patient’s characteristics between the CoC and non-CoC groups revealed a huge difference in treatment adherence between the called adjuvant and neoadjuvant groups. 73% of patients that complete the planned chemotherapy were in the adjuvant group. 67% of patients that no complete the planned chemotherapy were in the neoadjuvant group. Risk of long adjuvant chemotherapy adherence failure after rectal radical surgery should be discussed in deep.

Spelling errors:

Line 72 und must be with

Line 155-156: 5-year OS 76% (95% CI 69.1-81-6%) vs 60-6% (95% CI 48.0-71-0%).

Line 180 The pooled analysis of 5-year disease-free survival showed a non significant (add)better outcome…

Line 181 64.9% (95% CI 57.8-71.0%)…non CoC group 58.7% (95%CI 46.7-68-8%).

Line 182 HR for non-CoC vs CoC was 1.42 (95% CI 0.98-2.07)

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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