Reviewer’s report

Title: A phase-II trial of combined chemotherapy with S-1, oral leucovorin, and bevacizumab in heavily pre-treated patients with metastatic colorectal cancer

Version: 3
Date: 8 June 2015

Reviewer: Andrea Evangelista

Reviewer’s report:

Dear Editor,

Yamaguchi et al reported the results of a single-arm, single-stage phase II trial of combined chemotherapy with S-1, oral leucovorin, and bevacizumab (SL/Bev) in heavily pre-treated patients with metastatic colorectal cancer (mCRC). The statistical analysis is mainly descriptive and appropriate for the design, and the supporting data are clearly presented.

Major Revisions:

There are some statistical issues arising, as follows:

- in the first sentence of “Statistical analyses” section, does not appear clear to which group (SL/Bev or historical control) the proportion “of 41%–44% reported in previous large trials” relates. According to the sample size justification described later, it would seem the expected proportion in the experimental group (SL/Bev). In general, however, it would be more clear a more explicit indication of 1) treatment administered in the historical control, 2) proportion of DCR in the historical control 3) expected improvement in the group SL / Bev (e.g. “The objective was to demonstrate a xx% improvement in DCR with the new regimen SL/Bev relative to an expected DCR of xx% with “X” treatment”).

- the authors should give a reference for the 22% DCR (assumed as proportion of DCR in the historical control) that has been used for sample size calculation (null hypothesis). Although some references to prior published data were reported in the “Discussion” section, the authors should cite prior studies also in the “Statistical analyses” section.

- the authors should explain in more detail the type of study design. The sample size proposed seems compatible with a Fleming-A’Hern single-stage design for Phase II trials. Is it correct?

- parameters to establish whether SL / Bev was a success and then to determine its activity should be described in the "Statistical Analysis" section. Generally, in a single-arm phase II trial using a dichotomous primary endpoint (as DCR), the experimental treatment is declared active on reaching of a predetermined number of successes. Or, according to sample size justification, if the lower limit of one-sided 95% confidence interval of DCR exclude the null value (22%). In the “Results” section, the authors state “this study met its primary endpoint” since “DCR was higher than the predefined expected hypothesis of 44%”. However,
according to the specified “null” (22%) and “alternative” (44%) proportion of DCR, the activity of the SL/Bev would arise even with a proportion of DCR less than 44% (e.g. DCR=12/31=38.7%, lower limit of the one-sided 95% CI=24.1%).

Minor Revisions:
- the title of the manuscript should specify that this study is a single-arm trial.
- for continuous variables described in the “Results” section (text and tables), include also the 25th and 75th percentile (IQR). The range (min-max) is sensitive to outliers and does not use all the observations (in most cases only 2 observations: the highest and lowest values).
- please add the number of patients at risk beneath the survival curves (Fig 2 and Fig 3).
- if possible, at the end of the discussion, authors may suggest the comparator arm that could be included in a future RCT designed to evaluate the efficacy of SL/Bev.

Discretionary Revisions:
- subgroup analyses are generally underpowered also in phase III trials. Thus, the authors may consider removing results of the log-rank test for comparison between wild and mutant KRAS patients, reporting only the estimates of median OS. For the same reason, the authors may consider to remove from the study limitations the fact that “the number of subjects is too small to perform significance subgroup analysis”.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
'I declare that I have no competing interests'