Reviewer's report

Title: Study protocol of the TRICOLORE trial: A randomized phase III study of oxaliplatin-based chemotherapy versus combination chemotherapy with S-1, irinotecan, and bevacizumab as first-line therapy for metastatic colorectal cancer

Version: 2 Date: 1 December 2014

Reviewer: Halfdan Sorbye

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Study protocol of the TRICOLORE trial: A randomized phase III study of oxaliplatin-based chemotherapy versus combination chemotherapy with S-1, irinotecan, and bevacizumab as first-line therapy for metastatic colorectal cancer

Yoshito Komatsu, et al.

This study compares in a randomized phase III study two novel Japanese chemotherapy schedules (SIRB and IRIS/Bev) to the standard Japanese schedules (FOLFOX/bev or CapeOx/bev) for metastatic colorectal cancer patients.

The primary endpoint is progression-free survival (PFS), and the secondary endpoints are overall survival, response rate, time to treatment failure, the incidence and severity of adverse events, quality of life, quality, adjusted life years and health care costs. The target sample size is 450 patients.

Major Compulsory Revisions:

My major concern is the use of two different experimental schedules as one arm. These two schedules (SIRB and IRIS/Bev) have not been compared to each other directly and might be different. The dose intensity of irinotecan is different: 150mg/m2 vs 200mg/m2 every 3rd week, and especially the 150/mg/m2 every 3rd week is much lower than the standard FOLFIRI with 180 mg/m2 every 2nd week (= 270 mg/m2 per 3 weeks).

Possible solutions would be to do a run-in phase III with 3 arms and/or do an interim analyses after 200-300 stratified patients comparing the experimental schedules. If they are different, the inferior arm should be terminated and the number of patients increased.

Another major problem is that this phase III study compares 3 different substitutions and any differences in the endpoints can be due to any of the 3 reasons:

1. The effect of lowering the standard irinotecan dose compared to the established FOLFIRI dose which has been shown to be similar to FOLFOX.
2. Substitutes S1 for capecitabine or 5FU component in FOLFOX.
3. Substitutes irinotecan for oxaliplatin.
Minor Essential Revisions:
1. Why does the protocol exclude patients with a performance status of 2?

Otherwise the protocol seems well planned.

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.