Author's response to reviews

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

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Version: 5
Date: 11 March 2015

Author's response to reviews: see over
Dear Dr. Solera:

We are grateful for the opportunity to revise our paper (MS 1508357181127685) entitled "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", as well as for the helpful comments of your reviewers.

We attach a version showing the tracked changes and our point-by-point responses are written below. We feel that the comments have allowed us to improve the paper and hope that you convey our gratitude to the reviewers.

“Our point-by-point responses”

Comments by “Referee 1”

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.

Response
In IRIS/bevacizumab study regimen, the treatment schedule for irinotecan was 100 mg/m² × 2 every 4 weeks. In the SIRB regimen, the treatment schedule for irinotecan was 150 mg/m² every 3 weeks. Therefore, the dose of irinotecan per week was the same in both studies (50 mg/m²).

Although the results of controlled studies are unavailable, in phase II studies of IRIS/bevacizumab as first-line treatment for unresectable colorectal cancer the response rate (RR) was 57.7% (95% confidence interval [CI], 43.2% to 71.3%), and the progression-free survival (PFS) was 16.7 months (95% CI, 13.1 to 18.7 months) (reference 8). In phase II studies of SIRB, the RR was 67% (95% CI, 52.1% to 79.1%), and the PFS was 12.4 months (95% CI, 10.0 to 14.7 months) (reference 9).

In Japan, the approved dose of irinotecan for the treatment of colorectal cancer is 150 mg/m² every 2 weeks, which is lower than that in Western countries. Although the dose intensity of irinotecan in the study treatment was lower than the 90 mg/m² per week in FOLFIRI, the RR and PFS were not inferior to the outcomes obtained with FOLFIRI in Western countries. The lower limit of the confidence interval
for median PFS was longer than 10 months for both the IRIS/bevacizumab and SIRB regimens. Therefore, both regimens are considered to be at least as effective as standard treatment.

The study regimens did not merely use a lower dose of irinotecan than that in FOLFIRI. In addition, irinotecan was combined with S-1, and the optimal dose of irinotecan in this combined regimen was studied and decided.

The sentences from line 22 on page 6 to line 19 on page 7 were revised. In addition, “response rate 60.0%” was revised to 72.0% (see line 12, page 7). Because the report by Kato (reference 10) included patients who received second-line treatment, the text was revised (see line 8-13, page 7).

Before revision
Phase II clinical trials evaluating a combination of S-1 plus irinotecan and bevacizumab as first-line chemotherapy have been reported by Komatsu et al., Yamada et al., and Kato et al. The response rates were 57.7%, 67.0%, and 60.0% with PFS of 16.7, 12.4, and 11.5 months, respectively, indicating good outcomes [8, 9, 10].

After revision
The results of phase II studies evaluating S-1 plus irinotecan combined with bevacizumab as first-line treatment have been reported. In a study by Komatsu et al. [8], bevacizumab (5 mg/kg) and irinotecan (100 mg/m$^2$) were given as a continuous intravenous infusion on days 1 and 15, and S-1 was given orally for 2 weeks, followed by a 2-week rest period. This 4-week regimen was regarded as 1 course. The RR was
57.7% (95% CI, 43.2% to 71.3%), and the PFS was 16.7 months (95% CI, 13.1 to 18.7 months). In a study performed by Yamada et al. [9], bevacizumab (7.5 mg/kg) and irinotecan (150 mg/m²) were given as a continuous intravenous infusion on day 1, and S-1 was given orally for 2 weeks, followed by a 1-week rest period. This 3-week regimen was regarded as 1 course. The RR was 67.0% (95% CI, 52.1% to 79.1%), and the PFS was 12.4 months (95% CI, 10.0 to 14.7 months). Kato et al. [10] evaluated S-1 plus irinotecan combined with bevacizumab as first- and second-line treatment. Bevacizumab (7.5 mg/kg) and irinotecan (150 mg/m²) were given as a continuous intravenous infusion on day 1, and S-1 was given orally for 2 weeks, starting on day 3, every 3 weeks, defined as 1 course. The RR was 72.0% (95% CI, 50.6% to 86.2%), and the PFS was 11.5 months (95% CI, 10.4 to 19.8 months).

The results of these studies demonstrated that a PFS of 10 months can be expected with either a 4-week course (IRIS/bevacizumab) or a 3-week course (SIRB) of S-1 plus irinotecan combined with bevacizumab. Although the dose of irinotecan in these regimens was 150 mg/m² every 3 weeks, which is lower than the dose in FOLFIRI (270 mg/m² every 3 weeks), we considered this dose of irinotecan to be appropriate for combination therapy with S-1, irinotecan, and bevacizumab.

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.
Response

The study regimen did not merely use a lower dose of irinotecan than that in FOLFIRI or merely substitute S-1 for capecitabine or 5-FU in FOLFOX or substitute irinotecan for oxaliplatin. The concept of our study was to compare combination therapy with irinotecan plus S-1 as the study treatment with the standard regimens of FOLFOX or CapeOX as control treatment.

We believe that this major problem has been addressed in the revision proposed in our response to the previous comment.

Minor Essential Revisions:

Why does the protocol exclude patients with a performance status of 2?

Response

In previously performed phase II studies of combination therapy with S-1, irinotecan, and bevacizumab as first-line treatment in patients with unresectable colorectal cancer (references 8 and 9), patients with a performance status (PS) of 0 to 2 were eligible, but were not enrolled. We therefore excluded patients with a PS of 2. In the study of reference 10, patients with a PS of 0 to 1 were enrolled.

We believe that it is not necessary to add the response to this comment to the text.
I would like to see evidence referenced that the two S1 regimens are equivalent in efficacy, the 2 week and 4 week regimens. I understand that they are commonly used in Japan, but are we assuming the TTP and response rate are the same. Otherwise the data may be hard to interpret in a study with four treatment regimens. I consider this to be a discretionary revision.

Response

In a phase II study of IRIS/bevacizumab as first-line treatment for unresectable colorectal cancer that had been performed before our study, the RR was 57.7% (95% CI, 43.2% to 71.3%), with a PFS of 16.7 months (95% CI, 13.1 to 18.7 months). In a phase II study of SIRB, the RR was 67% (95% CI, 52.1% to 79.1%), with a PFS of 12.4 months (95% CI, 10.0 to 14.7 months). The confidence intervals suggested that a PFS of 10 months can be expected with both the IRIS/bevacizumab and SIRB regimens.

The concept of our study was to compare a combination of irinotecan plus S-1 as the study treatment with FOLFOX or CapeOX as standard treatment. Our study was not designed to compare 4 treatment regimens.

In accordance with the major compulsory revision proposed by Referee 1, the text was revised from line 22 of page 6 to line 19 of page 7. Therefore, we believe that this revision has addressed this comment.

About the “Editorial request”

Please ensure that there are detailed authors' contributions for all of the authors. We
believe there are a few sets of initials missing from this section.

Response

We wrote the initials of all authors in the Authors’ Contribution section on page 25.

Before revision

YK, CI, KS, and YY devised the study concept and design. All authors contributed to the study protocol. SM was responsible for statistics. ST contributed to translational research. RG contributed to cost-effectiveness analysis research. YK wrote the manuscript. All authors reviewed and approved the final manuscript.

After revision

YK, CI, KS, and YY devised the study concept and design. YK, CI, KS, YY, MG, AS, TY, SY, SM, ST, RG and MK contributed to the study protocol. SM was responsible for statistics. ST contributed to translational research. RG contributed to cost-effectiveness analysis research. YK wrote the manuscript. YK, CI, KS, YY, MG, AS, TY, SY, SM, ST, RG and MK reviewed and approved the final manuscript.

Sincerely,

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