**Reviewer's report**

**Title:** Randomized controlled trial of S-1 maintenance therapy in metastatic esophagogastric cancer - the multinational MATEO study

**Version:** 1  **Date:** 27 Feb 2017

**Reviewer:** Matthew T. Seymour

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It is welcome that the investigators of the ongoing MATEO study wish to place the rationale and design of their study into the public arena.

MATEO takes as its starting point the assumption that, in the participating countries, patients with advanced gastroesophageal cancer are treated with platinum-based combination chemotherapy schedule without breaks, until either disease progression or unacceptable toxicity intervenes. This practice is by no means universal, and many oncologists would argue that a more relevant standard comparison would be with intermittent chemotherapy. However, that notwithstanding, MATEO compares indefinite combination chemotherapy vs de-escalation to S1 after 12 weeks of combination chemotherapy. It is designed as a phase II non-inferiority trial based on overall survival. The stated intention is that, if non-inferiority is satisfied and the S1 maintenance approach gives improved QoL/toxicity, a future phase III would be undertaken.

This choice of design for phase II is debatable. The relatively small sample size means that a very permissive non-inferiority boundary has been set: overall survival HR≤1.33. Overall survival, whilst a conservative endpoint for a superiority trial, is a non-conservative endpoint for non-inferiority. Many effects may conspire to iron out differences between the treatment arms: most obviously, patients on the control arm (B) may have agents dropped from their combination regimen for toxicity and so end up on single-agent fluoropyrimidine; and patients on the investigational arm (A) may be restarted on a platinum combination after progression on S1.

One might reasonably speculate that a policy of treatment break with no maintenance therapy could satisfy the non-inferiority criteria set in this trial. In colorectal cancer, phase III trials comparing complete treatment break (a.k.a. "stop-and-go") vs continuing chemotherapy have produced HRs well within this range (e.g. COIN, 1600 patients, HR 1.084 (90% CI 1.008-1.165), Lancet Oncol 2011, 12:642-53). Arguably therefore, even if S1 were completely inactive, the non-inferiority criteria may still be met.
For this reason, for this phase II trial it might have been more appropriate to set time to treatment failure (progression or toxicity) as the primary endpoint, reserving OS for the future phase III with larger sample size and more stringent criteria.

With this reservation, the authors are to be congratulated on addressing the important issue of treatment duration/de-intensification in this disease.

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If not, please specify what is required in your comments to the authors.

Yes

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