Peer Review File

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Comments from the reviewers and author responses:

1. ***In the discussion the authors should indicate that CROSS now has 10 year follow up with a survival benefit still maintained. The impact seemed to be driven largely by reducing local recurrence.***
    a. Reply: 10 year outcomes data from CROSS has been added to the discussion

2. ***Mentioning OEO2 instead of OEO5***
    a. Reply: further information regarding OEO2 and INT-113 have been added to the section "trials before FLOT". We chose to kept the OEO5 study to provide the readers the information on the spectrum of studies done in this space.

3. ***In discussion of CHECKMATE 577 the authors should indicate better benefit for CPS PDL-1 positive patients. Some comment that TPS was also factored in, but likely not a reliable marker as over 80% of the patients were TPS negative.***
    a. Reply: added to paragraph regarding Checkmate 577 – improvement in OS for patients with a CPS ≥5 has now been mentioned.

4. ***In the discussion of CALGB 8083 the authors when reviewing the path CR rate in the induction therapy PET non responders, these patients likely responded because their chemotherapy was changed during radiation, directed by the PET scan. What was the nonsignificant difference between patients who responded to and continued either FOLFOX or carboplatin/paclitaxel, do they mean the number of patients responding? This needs clarification.***
    a. Reply: This has been clarified

5. ***What did the comparison show? I think the mention of pulmonary embolism is an error here, this should be corrected. At the end of this section the multiple ongoing trials should be cited, including ESOPEC, TOPGEAR, and CROSS2.***
    a. Reply: We double checked the slides from the presentation and poster and indeed pulmonary embolism has been listed as a complication. We listed some other studies in addition to KEYNOTE-585 and MATTERHORN that the authors feel hold relevance in today's standard practice.

DISCUSSION:

6. ***What is the evidence that more chemotherapy offers benefit? If anything, the studies the authors present argue that more chemotherapy does NOT benefit. OEO5 makes the argument that 4 cycles or adding another agent, epirubicin, adds no benefit over 2 cycles. Another interpretation of NEOAEGIS is that a mere 5 weeks of carboplatin/paclitaxel plus radiotherapy yielded the same survival as 4 months of EOX. Neither of these studies argue that more cycles of chemotherapy add any benefit. The authors correctly state that we finally have an active systemic therapy after chemoradiotherapy and surgery, nivolumab. We do not know yet if the same benefit will be seen with immunotherapy added to chemotherapy alone, and the ongoing trials are mentioned. However, one recent negative trial of adjuvant nivolumab added to adjuvant chemotherapy given after up front surgery for GEJ and gastric cancers was just reported in a press release.***
    a. Reply: We appreciate the comment. We included a statement about ATTRACTION 5 study.

7. ***Another issue not raised by the authors in comparing FLOT versus CROSS is that stage for stage, esophageal cancers have worse survival compared to gastric cancer. Arguably therefore the FLOT trial may have treated a more favorable population than the CROSS trial.***
    a. Reply: The authors appreciate this comment. Yes, esophageal cancers are considered more aggressive than gastric cancers. However, in the Western part of the world, it yet remains unclear if GEJ cancers are biologically more like gastric cancers or esophageal cancers. The FLOT study had more than twice the percentage if GEJ tumors than the CROSS study. The CROSS study also had a quarter of patients that were SCC histology which are inherently more chemo and radiation sensitive. Therefore, the authors feel that these 2 factors balance out the FLOT and CROSS studies in terms of unfavorable subgroups.