Peer Review File

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Comment 1:

Another option was also available to investigators; after 6 months of therapy in either arm, patients were permitted to receive chemotherapy with radiation (conformational or stereotactic).” It is not clear here what another option was referred to. I believe the clinical trial protocol allowed the further treatments at the discretion of primary oncologist after the patients completed 6 months of therapy on protocol. In addition, I guess the authors wanted to say “conventional or stereotactic). Conformational is not a term. Conformal is a term, but not used for pancreatic cancer. Moreover, patients wouldn’t typically receive chemotherapy with stereotactic body radiation.

Reply 1:

Thank you for your comment, this section has been updated with a more concise overview of the options open to investigators after 6 months on therapy.

Comment 2:

“treatment-related deaths were fewer in the FOLFIRINOX cohort (1 vs. 7).” This warrants some discussion.

Reply 2:

Thank you for this comment, we agree. The difference in the number of treatment-related is now updated in our editorial. The higher rate of deaths in the gemcitabine arm is unexpected. Our editorial provide commentary on this now.

Comment 3:

“All 9 patients received chemoradiation prior to surgery and all achieved a R0 resection.” Please double check if all 9 patients received chemoradiation instead of stereotactic body radiation.

Reply 3:

. On review of the paper again – it is unclear the number of patients who received either type of radiation and the numbers in the paper do not correspond with the numbers in the table in the appendix. This element of the sentence has been deleted from the editorial.

Comment 4:

"The recently published randomized PANOVA-3 study, is the first positive study demonstrating a modest survival benefit with a novel approach: investigating tumor treating fields in addition to gemcitabine and nab-paclitaxel, in the first-line setting in unresectable locally advanced PDAC." Please brief explain what is "Tumor Treating Fields". In addition, it should be called the tumor treating fields therapy.

Reply 4:

Thank you for this comment. Tumor treating fields therapy has been defined in the paper and correctly named.

Comment 5:

"The Alliance A021501 trial, which compared overall survival after neoadjuvant-modified FOLFIRINOX versus modified FOLFIRINOX plus chemoradiation in patients with borderline resectable disease,". I believe Alliance trial tested Hypofractionated Radiotherapy (stereotactic body radiation), not chemoradiation.

Reply 5:

Thank you for this comment, this has been corrected as you state in the paper.

Comment 6:

"LAPC therefore may demonstrate less genomic instability and with classical RNA subtype, which in itself infers for improved survival when treated with FOLFIRINOX combination therapy over gemcitabine-based therapies". This sentence is not clear and would need to be rephrased. In addition, I wouldn't think the PDAC at certain stage, such as the LAPC

stage, would be less genomic instable and becomes more genomic instable when it develops metastasis.

Reply 6:

We have updated this section and rephrased the commentary. Based on the published COMPASS study –WGST on perc bx of true LAPC, a significantly lower burden of single nucleotide variants (SNVs), insertions/deletions (indels), and structural variants (SVs) than metastatic PDAC was observed and all of the COMPASS LAPC cases were classical subtype, not basal-like. There is little other data in the field to add to this but it is intriguing as to why a LAPD can obtain significant relative size to other PDAC primaries and not initially declare metastatic disease.