Peer Review File

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Reviewer A

Comment 1: I recommend consistency with decimals throughout the manuscript. Currently some are to the tenth, some to the hundredth of a month - I recommend consistently reporting outcomes to the tenth (XX.X)

Reply 1: Thank you for your feedback. We have revised the text as suggested.
Changes in the text:
page 2, line 54,59
page 3, line 72
page 5, line 173
page 6, line 182, 183, 206

Comment 2: Please update the "XXX" within the ethical consideration section.

Reply 2: Any items containing the author's information in the manuscript have been erased by the editor and marked as 'XXX'

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Comment 3: Line 101 - for clarification, were the 10 relapsed patients including in the stage IV cohort? If so, you might call this cohort "stage IV or metastatic recurrence" for clarity

Reply 3: Thank you for your question. The cohort of 10 relapsed patients was not named "stage IV or metastatic recurrence" because it includes cases that do not fully fit this classification. Specifically, 2 out of these 10 patients had a supraclavicular recurrence that was non-irradiable. Therefore, for clarity, we modified the text of the revised manuscript as follows:
"Thirteen centers agreed to participate in the study, with eight of them collectively enrolling a total of 34 patients (see Table 1). They were all non-irradiable stage III or stage IV. Among them, ten patients (29.4%) underwent surgery, and histological diagnosis was available for these patients on complete surgical specimens." Line 134-137

Comment 4: Lines 191 - 193 - this is a misleading sentence, I would recommend deleting.

Reply 4: Thank you for your feedback. We have revised the text as suggested and deleted the misleading sentence.
Changes in the text: page 7 line 227-229.

Comment 5: Table 1SA - were STK11 and / or KEAP1 co-alterations examined? If they were not, it would be important to discuss this limitation in understanding outcomes for the KRAS positive patients.

Reply 5: Thank you for your comment. No co-alterations of KEAP1 or STK11 were identified. The routine panels used have limited sensitivity for detecting STK11 (covering only 30% of anomalies) and do not include KEAP1. This limitation has been added to the revised manuscript.
Changes in the text : No co-alterations of KEAP1 or STK11 were identified. Line 95. The routine panels used have limited sensitivity for detecting STK11 (covering only 30% of anomalies) and do not include KEAP1. Line 94-96 and 154.

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Comment 6: Table 1SA - I suggest breaking out the KRAS cohort into G12C and non-G12C subsets

Reply 6: Thank you for your suggestion. We have updated Table 1SA to break out the KRAS cohort into G12C and non-G12C subsets as advised.

Comment 7: Lines 212 - 215 - I suggest restructuring the conclusion to say something like this: "Our retrospective study of advanced or metastatic PSC patients treated with IO alone or in combination with chemotherapy demonstrated an improvement in clinical outcomes with a trend toward prolonged PFS and OS in patients treated with the combination of IO and chemotherapy. Prospective studies are needed to determine the optimal treatment modality for these patients."

Reply 7: Thank you for your suggestion. We have modified our text as advised.
Changes in the text: page 8, line 248 – 252.

Reviewer B

Comment 1: Please include waterfall plots for best response.

Reply 1: Thank you for your suggestion. Unfortunately, we were unable to provide waterfall plots as the percentage change from baseline scans was not collected; only the type of response was recorded as mentioned in material and methods Line 104.

Comment 2. Since stage III and stage IV patients are mixed, it would be valuable to assess if there are differences in efficacy between these stages.

Reply 2: Thank you for your comment. All stage III patients were non-irradiable/non-resectable and were treated as stage IV. We did not find any statistical difference in overall survival (OS) and progression-free survival (PFS) between these stages. This information has been added to the revised manuscript.

Changes in the text: We did not find any statistical difference in OS and PFS between stage III and stage IV patients line 197

Comment 3. Detailed information about the chemotherapy regimen and immune checkpoint inhibitor (ICI) regimen should be provided.

Reply 3: Thank you for your comment. The chemotherapy regimens are already described in the manuscript at lines 156-159. For additional clarity, patients in the IO-CT group received Pembrolizumab combined with either Paclitaxel (n = 4) or Pemetrexed (n = 7). Patients in the IO group received Pembrolizumab (n = 21) or dual immunotherapy with Nivolumab and Ipilimumab (n = 2). Line 157-159

Comment 4. Please clarify the criteria used to choose between ICI monotherapy and ICI + chemotherapy.

Thank you for your query. The criteria for selecting between ICI monotherapy and ICI combined with chemotherapy were based on the prevailing guidelines at the time of patient treatment. Specifically, monotherapy with Pembrolizumab was chosen for patients with a PD-L1 tumor proportion score (TPS) of ≥ 50% starting from January 2017, while the combination of immunotherapy and chemotherapy was indicated regardless of PD-L1 TPS starting from November 2019. It is also noteworthy that the two patients who received dual immunotherapy were enrolled in a clinical trial.
For additional clarity, we have added to the revised manuscript that the criteria for selecting between ICI monotherapy and ICI combined with chemotherapy were based on the prevailing guidelines at the time of patient treatment (lines 159-161).

Comment 5. Many patients have KRAS and MET mutations, but targeted agents were used in only one

patient. It would be interesting to know the response of this patient.

Reply 5: Thank you for your interest. Among the patients, only one received treatment with crizotinib. This individual exhibited a partial response; however, unfortunately, he died due to peritonitis complicating a perforated ulcer. This specific case is detailed in Table 2 SA with patients with MET exon 14 mutated patients.

Comment 6. Regarding Table 1, there seems to be a typo with "0 (45.5%)" and "0 (26.1%)"; please correct this.

Reply 6: Thank you for bringing this to our attention. We have duly corrected the error in Table 1 as per your observation.