Peer Review File

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Comment 1: Page 3, Lines 10-13 – The first sentence should be reworded, as the intent is not clear.
Reply 1: Thank you for the reviewer's comments. We have revised the text for clarity.
Changes in the text on Page 4, lines 2-6:
The discovery of driver genes and the development of molecular targeted drugs against them have gradually improved the course of poor prognosis lung cancer. (1-7) KRAS mutations were first reported in 1985 as driver mutations on the human chromosome (8, 9). Various drugs targeting KRAS mutations have been developed over the past few decades but have failed to achieve sufficient efficacy (10).).

Comment 2: Throughout the manuscript, consider using "molecular targeted therapies" rather than "molecularly."
Reply 2: Thank you for the reviewer's comments. We have made the changes as the reviewer indicated.
Changes in the text:
We have modified our text as advised, on page 2, line 5, and page 4, line 7,8,30.

Comment 3: Correct the spelling of Sotorasib throughout - Page 1, Line 39; Page 2, Line 35; Page 3, Line 14, Line 43, Line 47.
Reply 3: Thank you for the reviewer's comments. We have corrected all spellings of Sotorasib in the text.
Changes in the text:
We corrected the spells on page 2, line 2, and page 3, line 6, page 4, line 7,32,35.

Comment 4: There are multiple grammatical errors and run-on sentences throughout the manuscript that should be reviewed and addressed.
Reply 4: Thank you for the reviewer's comments. We reviewed the entire manuscript and made corrections. In addition, a spelling error of Itaru Fujimura, one of the authors, has been corrected.
Changes in the text:
We highlighted the corrections in light blue.

Comment 5: Page 3, Lines 46-49 and Page 4, Lines 1-2 - This paragraph is not clear. The PNA-LNA PCR clamp method has been compared to therascreen in this study, not to Guardant360 CDx. If the PNA-LNA PCR clamp method has been replaced by NGS and other panel tests, what is the advantage of using it for KRAS mutation detection in this setting?
Reply 5: Thank you for the reviewer's comments. The paragraph has been changed to clarify the purpose of this study.
Changes in the text on page 5, lines 1-9:

The QIAGEN therascreen KRAS RGQ PCR kit (for tissue) and Guardant360 CDX (for plasma) are approved as companion diagnostics for sotorasib (26). However, Guardant360 CDX is not covered by health insurance in many countries, including Japan, especially due to its cost and long turnaround time. On the other hand, although the therascreen PCR kit has the potential to overcome the two drawbacks of the Guardant360 CDX, a more sensitive test method is needed to detect KRAS gene mutations in plasma in the future. In this regard, the PNA-LNA PCR clamp has been used to measure EGFR mutations in plasma as well as tumor tissue with high sensitivity (27). A comparison between the QIAGEN therascreen KRAS RGQ PCR kit and the PNA-LNA clamp method for KRAS, which is considered more sensitive, is needed.

Comment 6: An argument is made for improved sensitivity of KRAS mutation detection with the PNA-LNA clamp method over NGS and/or therascreen in the discussion section, but this should be clarified in the introduction.
Reply 6: The high sensitivity of the PNA-LNA clamp method is described lines 3-8. This paragraph is a description based on the data from the current study. Therefore, we believe that this description should be placed in the Discussion section and not moved to the Introduction.

Comment 7: Perhaps a more robust description of the methodology in the manuscript would also be helpful.
Reply 7: Thank you for the reviewer's comments. We added a sentence and a reference in the method section.
Changes in the text on page 6, lines 2-6:
Although this PCR system is as well established as the method used for EGFR gene mutations (34).

Comment 8: It would be helpful if the p values obtained for statistical significance were added to the results section.
Reply 8: Thank you for the reviewer's comments. We have added HR, P-values, and 95% CI in the result section and in Tables 4 and 5.
We also added a sentence on page 8, lines 7-9.

Comment 9: Additionally, an abundance of data is presented in the figures and tables included in this manuscript; however, there is minimal discussion of the results. A thorough discussion of each of the figures and tables included in the manuscript would improve the clarity and readability.
Reply 9: Thank you for the reviewer's comments. We have added a discussion of our results in the text.
Changes in the text:
In the discussion section, we highlighted the sentences we added and modified in green.

Comment 10: It is not clear how PD-L1 expression was assessed in this study. Which antibody was used and how was this evaluated?

Reply 10: Thank you for the reviewer's comments. We have added a note in the text regarding the antibodies used for PD-L1 staining and the evaluation method.
Changes in the text on page 6, lines 15-18:
PD-L1 expression was assessed in formalin-fixed, paraffin-embedded specimens at the department of pathology in our hospital, using the commercially available PD-L1 IHC 22C3 pharmDx assay (Dako North America).