Peer Review File

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Reviewer A

Comment 1. Lines 80-82 I would specify that the authors are talking about the chemotherapy regiments used "in the control arms"

Response 1: We wish to thank the reviewer for this comment. Our expression is not clear here, and modified it as “Additionally, the cytotoxic chemotherapy regimens combined in the two studies were also different. KEYNOTE-407 used either paclitaxel or nab-paclitaxel, while IMPower131 only used nab-paclitaxel in the analysis.”

Comment 2. Lines 101-106 Since the authors introduce the PD-L1 concept, and the editorial is about KEYNOTE-407, a brief discussion of whether PD-L1 was predictive of benefit in this trial is suggested.

Response 2: We appreciate the reviewer's comment on this point. We have added information than “PD-L1 expression is a useful biomarker, but it is not the sole determinant for the decision to use pembrolizumab. Although some patients with tumors that have low or no PD-L1 expression may still benefit from pembrolizumab in combination with chemotherapy treatment, the KEYNOTE 407 trials did not demonstrate any improvement for patients with PD-L1 <1%.” (Line 146- 149)

Comment 3. Line 111 when the authors specify four cycles here it could be misleading as pemetrexed maintenance was allowed in NSQ histology (2/3 of NSQ NSCLCs received it

Response 3: We thank the reviewer for this comment. Our expression here is not clear. We have modified our manuscript as follows: “The CheckMate 9LA trial compared first-line treatment with nivolumab plus ipilimumab and two cycles of chemotherapy to chemotherapy alone (four cycles) in patients with advanced NSCLC, including 227 cases of squamous NSCLC and 493 cases of non-squamous NSCLC.”

Comment 4. Line 124 is this nivolumab + ipilimumab + chemotherapy?

Response 4: We appreciate the reviewer's comment on this point. Our expression here is

not correct and modified as follows: “The CheckMate 9LA trial showed that nivolumab plus ipilimumab and chemotherapy significantly improved OS compared to chemotherapy alone, with a manageable safety profile.”

Reviewer B
Comment 1. May need some clarification - total up to 35 cycles instead of maintainence up to 35 cycles.

Response 1: We appreciate the reviewer's comment on this point. Our expression is not correct here and modified it as follows: “After induction treatment of 4 cycles, a pembrolizumab/placebo was prescribed total up to 35 cycles.”

Comment 2. May want to be more specific. According to the KN407 publication, "Patients were eligible to receive second-course pembrolizumab monotherapy for 17 cycles (approximately 1 year) on PD after either completing 35 cycles of pembrolizumab with a best overall response of stable disease (SD) or better or achieving a confirmed complete response (CR) per investigator assessment after receiving eight or more cycles of pembrolizumab and having received two or more cycles beyond the initial CR assessment."

Response 2: We wish to thank the reviewer for this comment. Our expression is not correct here clarified here and revised it as the reviewer suggested “Patients were eligible to receive second-course pembrolizumab monotherapy for 17 cycles (approximately 1 year) on PD after either completing 35 cycles of pembrolizumab with a best overall response of stable disease (SD) or better or achieving a confirmed complete response (CR) per investigator assessment after receiving eight or more cycles of pembrolizumab and having received two or more cycles beyond the initial CR assessment.”

Comment 3. May want to include the range here.

Response 3: We wish to thank the reviewer for this comment. We add range and modified as “After a median follow-up of 56.9 (range, 49.9-66.2) months, …”

Comment 4. Wrong numbers, should be 17.2 vs. 11.6.

Response 4: We appreciate the reviewer's comment on this point. Our expression here is

not correct, and modified it as follows: “the median OS was 17.2 months (95% confidence interval [CI], 13.8 to 23.4) in the combination therapy group compared to 11.6 months (95% CI, 6.5 to 13.7) in the chemotherapy alone group.”

Comment 5. CIs need to be expressed in percentages.

Response 5: We wish to thank the reviewer for this comment. We added percentage in each CI and modified as follows: “The 5-year OS rate was 18.4% (95% CI, 13.8% to 23.4%) in the combination therapy group versus 9.7% (95% CI, 6.5% to 13.7%) in the placebo plus chemotherapy group. The combination therapy group also had a longer median PFS of 8.0 months (95% CI, 6.3 to 8.5) compared to 5.1 months (95% CI, 4.3 to 6.0) in the chemotherapy alone group. The ORR was 62.2% (95% CI, 56.2% to 68.0%) and 38.8% (95% CI, 33.1% to 44.8%) with pembrolizumab plus chemotherapy versus placebo plus chemotherapy.”

Comment 6. At data cut off is more accurate - you do not know if they are all followed for 5 years.

Response 6: We appreciate the reviewer's comment on this point. Our expression here is not correct, and modified it as follows: “In the pembrolizumab plus chemotherapy group, 55 patients completed two years of pembrolizumab treatment, and 38 (69%) of those patients were still alive at the data cut off.”

Comment 7. Please specify these patients are from the placebo + chemo arm.

Response 7: We wish to thank the reviewer for this comment. Our expression is not clear here, and modified it as “One possible explanation for this is that 50.9% (143) of the patients from placebo with chemotherapy arm received subsequent anti-PD(L)1 therapy, with 117 patients crossing over to receive pembrolizumab and 26 patients receiving treatment outside of the study.”

Comment 8. Please specify disease stage and treatment line.

Response 8: We appreciate the reviewer's comment on this point. Our expression is not clear here, and modified it as “In addition to KEYNOTE 407, various clinical trials, such as IMPOWER131, Checkmate 227, and Checkmate 9LA (4-6), have also demonstrated

the effectiveness of ICIs as the first line chemotherapy in treating advanced stage of NSCLC.”

Comment 9. Please specify CnP.

Response 9: We appreciate the reviewer's comment regarding this point. Our expression was not clear in this section. We have made revision to our manuscript as follows:
"The IMPower131 study also presented results for the treatment of advanced squamous NSCLC using atezolizumab plus chemotherapy. The study included 1,021 patients with previously untreated advanced squamous NSCLC who were randomly assigned in a 1:1:1 ratio to receive one of the following treatments: atezolizumab plus carboplatin plus paclitaxel, atezolizumab plus carboplatin plus nab-paclitaxel (referred to as the A + CnP group), or carboplatin plus nab-paclitaxel (referred to as the CnP group). After a median follow-up of 18.1 months in the A + CnP group and 16.1 months in the CnP group, the study revealed that the A + CnP therapy led to a longer median progression-free survival (PFS) of 6.3 months (95% CI, 5.7 to 7.1) compared to 5.6 months (95% CI, 5.5 to 5.7) in the CnP group."

Comment 10. Please specify median follow-up for the final OS analysis

Response 10: We appreciate the reviewer's comment on this point. Our expression here is not clear, and modified it as follows: “However, after a median follow up of 26.8 months in the A + CnP group and 24.8 months in the CnP group, there was no significant difference in OS between the two groups, with a median OS of 14.2 months (95% CI, 12.3 to 16.8) in the A + CnP group and 13.5 months (95% CI, 12.2 to 15.1) in the CnP group (4).”

Comment 11. Please specify which chemotherapy this is.

Response 11: We appreciate the reviewer's comment on this point. Our expression here is not clear, and modified it as follows: “The KEYNOTE-407 study demonstrated a significant improvement in both OS and PFS with A + CnP compared to CnP alone”

Comment 12. Exactly speaking, the trial allows to use paclitaxel while the analysis was based on nab-paclitaxel.

Response 12: We appreciate the reviewer's comment on this point. Our expression here is not clear, and modified it as follows: “Additionally, the cytotoxic chemotherapy regimens combined in the two studies were also different. KEYNOTE-407 used either paclitaxel or nab-paclitaxel, while IMPower131 only used nab-paclitaxel in the analysis.”

Comment 13. Please specify the trial is for metastatic NSCLC

Response 13: We appreciate the reviewer's comment on this point. Our expression here is not clear, and modified it as follows: “The CheckMate 227 trial highlights the significance of ICIs in treating metastatic NSCLC.”

Comment 14. Is PFS a primary or a secondary endpoint?

Response 14: We appreciate the reviewer's comment regarding this matter. Our statement was incorrect. Previous studies have reported PFS and OS as two independent primary endpoints. We have made the following modification to our manuscript: “PFS and OS were reported as two independent primary endpoints by previous studies (7,8).”

Comment 15. Trial.

Response 15: We appreciate the reviewer's comment on this point. We modified the wrong spelling.

Comment 16. The paper also reported results by histology, why did not the authors compare SQ results with KN407?

Response 16: We appreciate the reviewer's comment regarding this matter. We have added the results of overall survival (OS) in squamous cell lung cancer from the CheckMate 227 trial. However, due to differences in study design and median follow-up period, a direct comparison is not applicable. We have modified our manuscript as follows:
"After a median follow-up of 54.8 months, the median OS was 14.8 months (95% CI 12.1, 18.7) for squamous NSCLC patients with PD-L1 $\geq$ 1% who received nivolumab and ipilimumab treatment, compared to 9.2 months (95% CI 7.6, 13.9) for those who received chemotherapy. For squamous NSCLC patients with PD-L1 < 1%, the OS was 15.9 months (95% CI 9.0, 33.9) for those treated with nivolumab and ipilimumab, compared to 8.8 months (95% CI 6.4, 13.0) for those who received chemotherapy."

Comment 17. I am not sure if "conversely" is the right word here. In addition, please specify KN407 is for SQ only.

Response 17: We appreciate the reviewer's comment regarding this matter. We have modified our manuscript as follows: "Although the KEYNOTE 407 trial specifically enrolled squamous NSCLC patients, both studies investigated the use of immunotherapy as a first-line treatment for patients with NSCLC. These studies provide valuable insights into the use of immunotherapy in NSCLC."

Comment 18. 30,7 months, 15.8 vs. 11.0, 38 vs. 26

Response 18: We appreciate the reviewer's comment regarding this matter. Our expression here in not correct. We updated the result of CheckMate 9LA and modified our manuscript and updated references as follows: “After a median follow-up of 30.7 months, the trial showed that the combination therapy led to a significant improvement in OS compared to chemotherapy alone. The median OS was 15.8 months (95% CI, 13.9-19.7) in the combination group compared to 11 months (95% CI, 9.5-12.7) in the chemotherapy group, and the 2-year OS rate was 38%in the combination group compared to 26% in the chemotherapy group (6).”

Comment 19. I don't think the two can be compared directly, 9LA include both SQ and NSQ patients. The comment also applies to other SQ & NSQ vs. KN407 comparisons authors made here.

Response 19: We appreciate the reviewer's comment on this point. As the reviewer pointed enrolled patients were different in CheckMate 9LA and KEYNOTE 407 trails. We deleted this information.

Comment 20. Please specify metastatic, EGFR/ALK-, both SQ and NSQ. The results summary is not complete.

Response 20: We appreciate the reviewer's comment on this point. We specified POSIDON study and modified our manuscript as follows: “The POSEIDON study, which enrolled metastatic NSCLC patients with EGFR/ALK wild-type status, has shown that a combination of durvalumab with or without tremelimumab in combination with

chemotherapy has significantly improved PFS. The PFS were 6.2 months (95%CI 5.0, 6.5), 5.5 months (95%CI 4.7, 6.5), and 4.8 months (95%CI 4.6, 5.8) for the tremelimumab plus durvalumab and chemotherapy group, durvalumab plus chemotherapy group, and chemotherapy alone group, respectively."

Reviewer C

Comment 1. Chen and colleagues provide a comment on the current treatment landscape of NSCLC. Overall, the manuscript is well written and highlights specific points of the respective phase III trials. However, as the comment is based on the 5y OS of KN407. I suggest only to focus on results for sqNSCLC and not the entire NSCLC population. Furthermore, outcome(s) according to PD-L1 expression should be discussed in greater detail, especially as KN407 did not show any improvement for PD-L1 negative patients.

Response 1: We appreciate the reviewer's comment on this point. We have added information that "PD-L1 expression is a useful biomarker, but it is not the sole determinant for the decision to use pembrolizumab. Although some patients with tumors that have low or no PD-L1 expression may still benefit from pembrolizumab in combination with chemotherapy treatment, the KEYNOTE 407 trials did not demonstrate any improvement for patients with PD-L1 <1%" (Lines 146-149).

Due to only a few studies having investigated the effect of immune checkpoint inhibitors (ICIs) in combination with chemotherapy for the treatment of squamous non-small cell lung cancer (NSCLC), we extracted the results of the CheckMate 227 trial for the treatment of squamous NSCLC. The findings are as follows: "After a median follow-up of 54.8 months, the median overall survival (OS) was 14.8 months (95% CI 12.1, 18.7) for squamous NSCLC patients with PD-L1 ≥ 1% who received nivolumab and ipilimumab treatment, compared to 9.2 months (95% CI 7.6, 13.9) for those who received chemotherapy. For squamous NSCLC patients with PD-L1 < 1%, the OS was 15.9 months (95% CI 9.0, 33.9) for those treated with nivolumab and ipilimumab, compared to 8.8 months (95% CI 6.4, 13.0) for those who received chemotherapy" (Lines 134-143).

In order to provide a comprehensive understanding for readers regarding the effect of ICIs in the treatment of NSCLC, we also discussed other studies that included both squamous NSCLC and non-squamous NSCLC.