TLCR TRANSLATIONAL LUNG CANCER RESEARCH
AN OPEN ACCESS JOURNAL FOCUSING ON CLOSING THE GAP BETWEEN "BENCH AND BEDSIDE"
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Peer Review File

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Reviewer A

The authors performed a systematic review and meta-analysis to explore the safety and efficacy of ICI retreatment, either as re-administration after PD or discontinuation due to irAE. I felt the theme itself was interesting and can have certain value, because preceding reports were mainly case series which included relatively small number of patients. However, several revisions are warranted before considering this manuscript for publication. Please see my comments below.

Major comments:

1. The authors failed to clearly show the novelty of this study. They should present what is already known (or publish) and what is not yet not just showing "little is known about safety and efficacy of ICIs retreatment in NSCLC". Is this the first systematic review and meta-analysis explored the clinical utility of ICI retreatment? What if in other types of cancer? Please include this point either in introduction and discussion section.

We have summarized some studies about ICIs retreatment in other types of cancers such as melanoma and renal cell carcinoma (see Page 3, line 22-31). We have tried to elaborate our novelty of this study further (see Page 7, line30-32 and Page 8, line 1-8).

2. Inclusion and Exclusion Criteria: The authors more clearly present the eligibility criteria for participants, especially on "stage" (Were those received durvalumab for stage 3 included?) and "ICI regimen" (Were those received chemo+IO included?).

We have modified the inclusion and exclusion criteria more accurately according to your advice (see Page 4, line 22 and 26)**.**

3. Discussion: Now chemo+IO or anti-PD-1+anti-CTLA-4 regimens are available for advanced NSCLC. The discussion on this point can improve the comprehensibility of this research for readers in line with current clinical practice.

We researched some studies about ICIs giving in combination with chemotherapy for advanced NSCLC as first-line regimen which showed the potential benefit from immunotherapy combined with chemotherapy. We think more attention could be paid to the efficacy and safety of ICI retreatment in combination with chemotherapy concurrently. (see Page 11, line 19 to 30)**.**

Minor comments:

1. Page 3, Line 2-8: This part should be explained in MATERIAL AND METHODS section, not in intro.

We have adjusted this part from introduction to MATERIAL AND METHODS. (See Page 5, line14-21)

2. Page 6, line 42, "Koji et al. (44)": Koji is first name, not family name. Please check again this point for all the references.

We have corrected the negligence and checked this point for all the references. (See Page 10, line 1)

3. Table 2: The authors should provide more specific title, not just as "results". Also, "high-grade irAEs" should more specifically explained (>= Grade 3?).

We have added more specifical explanation to the "Results" and "High-grade irAEs" in the table2. (See Table, Table 2)

Reviewer B

The review article entitled, "Safety and Efficacy of Retreatment with Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis "by Cai Z, et al. showed that the efficacy and safety of re-administration of ICIs compared to initial ICI administration in patients with non-small cell lung cancer through meta-analysis. While the content is interesting, there are some concerns. The reviewer respectfully provides the following comments:

Major comments:

1. In page 2, line 39, the authors demonstrated that little is known about safety and efficacy of ICIs retreatment in NSCLC. However, there were multiple reports evaluating the safety and efficacy of ICI re-administration in NSCLC. They should revise the description of the introduction to begin the study.

We have pointed that the characteristic of previous studies about ICIs retreatment in NSCLC and searched for ICIs retreatment in other types of cancers such as melanoma and renal cell carcinoma to enrich our article (see Page 3, line 22-31).

2. In Figure S5, what does the ICIs retreatment mean? ORR? DCR? Please clarify. Furthermore, in page 5, line 16-20, please indicate 95% confidence intervals, Odds ratios, and p-values.

We have clarified the definition of these words and phrases (see supplementary material 1). The relevant information about ORR and DCR for subgroup analysis has been added. (See Page 7, line 6-10)

3. Reference 13 differs from the other studies because it uses a combination of anti-TIGIT antibody and pembrolizumab. Reference 13 should be excluded from the analysis.

We have reviewed the reference 13 more carefully and discussed with each other. Considering that the regimen of ICI retreatment in other studies were immunotherapy alone without combined with any other treatment concurrently, we have excluded it from the analysis. Meanwhile, we have modified the inclusion and exclusion criteria to make the article more scientific. We have reanalyzed these include studies and some data have changed accordingly but not influence the conclusion greatly. (See Page 6, line 12 and Table 1)

4. Cases with ICI switching were related to a decrease of ORR when ICI re-administration, but not cases with the same types of ICI re-administration. The authors speculated that the reasons were incidences of poor PS with multiple lines-treatment and that of progression by first line ICI treatment. This is one of the critical points in this article. The authors should check the difference between PS status and/or the incidence of PD in both the same types and different types of ICIs.

To further elaborate the possible reasons for the difference in clinical benefit from the regimen of ICIs retreatment, we have tried to take the PS and reason for discontinuation of prior ICIs in the included studies for example. Among people who retreated with different types of ICIs, almost 93% discontinued prior ICIs treatment due to progressive disease, while only 44% in the subgroup with the same type of ICIs. Meanwhile, when searching for relevant studies, we found there were also opinions that retreat with the same type of ICI as before was of limited benefit. Therefore, which regimen of ICIs retreatment to choose is still controversial and there is clearly a need for multicenter, large-scale trials to aid ICIs retreatment in the future regarding the regimen of retreatment. (See Page 11, line 3-17)

5. In reference 14, Patients randomized to pembro who completed 2 years of therapy or who stopped pembro after achieving CR and then had PD were eligible for a second course of pembro monotherapy. These patients do not fit the definition of retreatment after PD.

We have checked the reference 14 again and found these patients fit the definition of resumption after a fixed course of ICIs treatment. We have reanalyzed these studies and the pooled ORR and DCR of ICI rechallenge and resumption have experienced a little adjustment which do not influence the total conclusion greatly. After adjusting reference 14 from rechallenged group to resumed group, the I^2 in the analysis of ORR and DCR of ICIs rechallenge is 0%. (See Page 6, line 25-33)

Minor comments:

1. **In Figure S3B, "Favours [Retreat]" and "Favours [Initial] are inverse. In**

addition, because the 95% confidence interval is 0.28-0.99, it appears to be p<0.05.

We have corrected the error in Figure S3B (see supplementary material 1). The conclusion has been fine-tuned based on the $p < 0.05$. (See Page 6, line 19-22)

2. The numbering of the supplemental and main Figures is mixed.

We have adjusted the number of the supplemental and main Figures. (See supplementary material 1 and main figures)

3. In the footnote of table 1 and table 2, the explanations of "PD-1, programmed cell protein-1", "PD-L1, programmed cell protein-ligand 1" and "PD, progression disease" were wrong. The authors should correct these explanations.

We have corrected those explanations according to the proper definition of PD-1, PD-L1 and PD. (see Table 1 and Table 2)

Reviewer C

Comments:

Abstract – results

1. **In methods section you indicate outcomes include ORR and DCR for efficacy and irAEs for safety, in this order. Therefore, in results section would also present findings related to efficacy first, then safety**

   We have adjusted the sequence of the parts for efficacy and safety. (See Page 1, line 29-30, Page 2, line 1-11 and Section of Results)

Introduction

2. **Page 2, Line 23: programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1)**

   We have corrected those explanations according to the proper definition of PD-1 and PD-L1. (See Page 2, line 25-26)

3. **Lines 23-24: "have witnessed the exciting progress" -> these drugs are not witnessing progress – consider rephrasing this. Perhaps "have contributed to the progress"**

   We have replaced "have witnessed the exciting progress" with "have contributed to the progress". (See Page 2, line 25-26)

4. **Line 29: remove "encounter with" and consider require discontinuation**

   We have replaced the expression that "encounter with" with the phrase "consider require discontinuation". (See Page 2, line 31)

5. **Lines 31-32: mention conventional chemotherapy may be used sequentially, but often times now it is in combination with immunotherapies as well upfront, so may be worth mentioning**
   We have illustrated the choices about next regimen of treatment after patients discontinue the prior ICIs for progressive disease are various. Compared with conventional chemotherapy used sequentially, there are no established strategies to overcome acquired resistance. The clinical benefit of chemotherapy or targeted therapy in combination with immunotherapy have been presented in clinical trials. Considering the dynamic nature of the immune response and long-term benefit of ICI, ICIs retreatment could also be a potential therapeutic option. Meanwhile, we have presented briefly the research status of ICI retreatments in patients who discontinued prior ICIs because of irAEs and completion of a fixed course. (See Page 3, line 2-21)

6. **Line 34: "what allowed them" not proper grammar**
   We have corrected the grammar. (See Page 3, line 22-23)

7. **Page 3, Line 2 - definitions here do not necessarily align with common terminology used, as "re-challenges" often is term used for treating a patient after experiencing irAE. Therefore, this may cause confusion for audience throughout manuscript – the reference cited "Metro" specifies that "re-challenge" is a term used but not always clearly defined WHY ICI was stopped and even goes on to state "In one case, ICI rechallenge may refer to retreatment of a patient who previously discontinued immunotherapy because of an irAE." I do not feel this citation or definitions are appropriate.**
   Metro defined rechallenge as retreatment with ICIs after the discontinuation of prior ICIs in general instead of explaining the definition of ICI retreatment, rechallenge and resumption which may confuse readers. While our study is the first time to define what is ICIs rechallenge and ICIs resumption according to the reason for the discontinuation of prior ICI treatment in patients with NSCLC rather than ambiguously refer as ICIs rechallenge in general regardless of heterogeneity. Our definitions of ICIs rechallenge was quite different from Metro's, but three situations in clinical practice were noticed in this article. We cited it as reference for intention to help readers recognize the three situations in ICIs retreatment to understand the definition of ICIs retreatment, rechallenge and resumption. If readers are going to be confused with the definition of retreatment, rechallenge and resumption in our study due to this reference, we could exclude it.

Material and methods, search strategy

8. **Line 15: last search date missing exact day**

The exact day was November 21st，2021. (See Page 4, line 10)

9. **Line 19: Term you had used was "resumption" so was this search inclusive of "resumption" [not just resume] for specific terminology?**
   When we searched at begin, "resumption" and "resume" were both used for specific terminology. And the results were not great different. But we have replaced "resume" with "resumption" according to your thoughtful advice considering the scientific character of our study.

Inclusion and exclusion criteria

10. **Line 25: why limit inclusion to at least 10 patients with NSCLC? Were there many publications including <10 patients?**
    We referred to same already published meta-analysis which recommend limit inclusion to at least 10 patients. In fact all of case reports included < 10 patients almost and lots of case reports only included one patient.

11. **Line 28: similar to above, why exclude case reports? I see in Figure 1 that 25 case reports were identified and these may hold valuable information relevant to these findings**
    Case reports lack systematic study design and retrospectively report the diagnosis and treatment information of a single or a few cases, which often fails to meet the need of quantitative pooled analysis. If the case reports could be used properly, the information from them would be valuable because they were informative cases.

Discussion

12. **Page 5, line 24: "what cohered" -> when using term "what" I think you may mean "which" and same in line 26 "what is comparable" should read as "which is comparable"**
    We have corrected the grammar mentioned above. (See Page 7, line 22 and 24)

13. **Line 29: "any reason" is very broad statement – perhaps more appropriate to say "for a variety of reasons"**
    We have replaced the statement that "any reason" with "for a variety of reasons". (See Page 7, line 27)

14. **Line 31: what "different reasons" are you taking about – this is unclear**
    We have clarified what "different reasons" mean. (See Page 7, line 30-31)

15. **Line 31: "as we all know" is not phrase that should be used in formal manuscript, do not use this expression/assumption**

We have abandoned the expression of "as we all know". (See Page 7, line 31-32)

16. **Page 6, line 13: may be useful to include trial names to provide more context/background about these ongoing studies**

We have listed trial names instead of ID alone. (See Page 7, line 27-33)

17. **Overall, great discussion/conclusion here that although ORR may have been less on retreatment, DCR was not significantly different which shows ongoing disease control. Although the outcomes in this trial did not assess progression free survival or overall survival, similar DCR may be indicative that even a lower ORR on retreatment still prolongs PFS/OS. However, in next paragraph it's mentioned that PFS/OS in select retrospective reviews were not seen to be prolonged – I would be interested to hear more elaboration on these findings**

Our study tries to define what is ICIs rechallenge and ICIs resumption according to the reason for the discontinuation of prior ICI treatment in patients with NSCLC rather than ambiguously refer as ICIs rechallenge in general regardless of heterogeneity.

Reference 14 in fact fits the definition of resumption after a fixed course of ICIs treatment, while we divided it to ICIs rechallenge group. We have reanalyzed these studies and the pooled ORR and DCR of ICI rechallenge and resumption have experienced a little adjustment which do not influence the total conclusion greatly.

After adjustment, ICIs rechallenge was associated with a decrease in ORR and DCR compared with initial treatment which may indicate that the clinical benefit from ICIs rechallenge is limited. As for those who discontinued prior ICIs due to PD, nearly forty percent of patients can still regain control of disease, what was comparable to the survival data of third-line standard chemotherapy for advanced NSCLC and mono-chemotherapy after ICIs progression.

In the next paragraph, the patients we are talking about were those who discontinued prior ICIs because of irAEs. Reference 38 and 39 also enrolled patients. Among these patients, some researchers found that the resumed and non-resumed group did not differ statistically significantly regarding median PFS. Santini et.al also reported that for patients who achieved an objective response and developed an irAE that requires holding immunotherapy, resumption upon improvement/recovery of the irAE should not be encouraged.

Therefore, there are two types of targeted patients under discussion in these two paragraphs. Patients who discontinued prior ICI because of PD shows a decreased ORR and DCR compared with initial ICIs, but 40% of

them can still regain control of NSCLC. As for those who discontinued prior ICI due to irARs, although they show a similar ORR and DCR compared with initial ICIs, whether to resume with ICIs or not is still on debate. It is the seemingly contradictory conclusion that illustrates the heterogeneity more strongly between ICIs rechallenge and ICIs resumption.

18. **Page 6, line 36 ? could this be new paragraph to focus on discussion of resumption of treatment after irAE**
We have broken this section into a new paragraph. (See Page 9, line 26-33)

19. **Line 38: "most guidelines" – please specify which guidelines you're referring to**
We have included these guidelines as reference 53 and 54. (see Page 9, line 30)

20. **Line 47: typo - potion ? option?**
We have corrected the spelling mistake. (See Page 10, line 4)

21. **Do you have specific information from included studies regarding incidence of re-current irAEs in patients who resumed ICI after irAE? Discontinuation rates, elaboration of re-treatments after toxicity had previously been observed, etc.**
We have tried to summarize the occurrence and recurrence of irAEs among patients with NSCLC who discontinued prior ICIs due to irAEs. The occurrence and recurrence of irAEs is 41.5% and 27.5%, while only five studies reported relevant information. We can only calculate a pooled occurrence or recurrence of irAEs instead of a relatively clear conclusion. Otherwise, it is also difficult for us to summarize the common irAEs or most life-threatening irAEs because of the limited information obtained from these studies. We have also searched previous observation about re-treatments after toxicity.
(See Page 10, line 5-21)

22. **Why do you believe the ORR decreased when switching ICI versus resuming therapy previously given?**
Patients who were retreated with the same type of ICI as before showed no difference for ORR and DCR (ORR: OR, 0.37; 95%CI, 0.09-1.52; $p > 0.05$; I^2=78%) (DCR: OR, 0.76; 95%CI, 0.20-2.92; $p > 0.05$; I^2=60%). As to those retreated with different ICIs, such as switching from anti-PD-1 to anti-PD-L1, displayed a decrease in ORR and DCR in contrast to initial treatment (ORR: OR, 0.09; 95%CI, 0.02-0.34; $p < 0.05$; I^2=0%) (DCR: OR, 0.35; 95%CI,

0.18-0.67; $p < 0.05$; $I^2=0\%$). It indicates that retreatment was of limited benefit among patients who switched from anti-PD-1/PD-L1 to anti-PD-L1/PD-1. It may have its root in poor PS and discontinuation for disease progression. However, the sample size of our subgroup is quite small, and more attention should be paid to the reliability when interpreting the results. After all, there are inverse conclusions drawn from other studies. (see Page 11, line 1-15)

23. **Page 7 line 9-10: "PD-L1 as a later-line therapeutic regimen after multiple anti-cancer treatment including cytotoxic chemotherapy and radiotherapy" -> comment on treatment has changed in recent years with ICI now being more commonly giving in combination with chemotherapy for initial treatment in metastatic and even earlier stages of NSCLC [Nivo now approved in this setting and recently approved as neo-adjuvent therapy in resectable disease] – how does this change the way subsequent lines/re-treatment and resumption of ICI may be important to consider for the future?**

    We have further elaborated development in treatment in patients with NSCLC to make the study more scientific and practical. Based on the improved efficacy in ICIs plus chemotherapy as first-line treatment, we have raised the question that whether it is feasible to add chemotherapy to ICIs retreatment at the same time which deserves further exploration in the future. (See Page 11, line 17-28)

24. **Great inclusion of limitations to the study**

    We must admit the limitations to our study, but readers can still obtain information about ICI retreatment from our study. Our study is the first meta-analysis to define what is ICIs rechallenge and ICIs resumption according to the reason for the discontinuation of prior ICI treatment in patients with NSCLC rather than ambiguously refer as ICIs rechallenge in general regardless of heterogeneity. Meanwhile, we try to explore the mechanism for difference in efficacy in ICIs rechallenge and resumption based on previous studies. Immune checkpoint inhibitors retreatment could constitute a feasible therapeutic option in selected NSCLC patients who have ceased the previous ICIs treatment for different reasons, especially in those who discontinued for irAEs or finished given course of treatment. Considering the improved efficacy in ICIs plus chemotherapy as first-line treatment, we propose that it will be meaningful to explore the efficacy and safety of concurrently with ICIs and other treatment such as chemotherapy, radiotherapy and targeted therapy in the future.(see Page 11, line30-33, Page 12, line 1-7, Page 8, line 1-6)

25. **Please include future directions or additional hypothesis for future studies based on your findings**

Concluded from our study, ICIs retreatment should be mulled over on a case-by-case basis in consideration of possible factors linked to the efficacy, such as reason for termination, performance status, interval treatment regimens, the type of ICI in retreatment and the type and severity of irAEs. More large-scale prospective studies are warranted to confirm our discoveries and explore the biomarkers that predict the efficacy and safety of ICIs retreatment in patients with NSCLC. Moreover, we should pay more attention to the topic on retreatment concurrently with ICIs and other treatment such as chemotherapy, radiotherapy and targeted therapy in the future. (see Page 12, line 13-20)

Acknowledgements

26. Funding – any conflicts of interests that need to be disclosed?

We have declared the conflicts of interests in the FOOTNOTE. (See Page 12, line 25-26)

Figure 1:

27. What constituted an "irrelevant record" to exclude the 107 articles?

Animal experiments, abstract of clinical trials without results and studies not focused on ICIs retreatment, rechallenge and resumption etc.

Figure 2:

28. Include "all-grade irAEs" vs. "high-grade irAEs" in titles of 2 forest plots, otherwise it is difficult to distinguish what the difference is between A vs B

We have added the title to the forest plots to make a difference from A and B. (see Figure, Figure 4)

29. How did you determine which studies were included in these forest plots? Those that included all of the necessary information regarding retreatment and incidence or occurrence of irAEs?

Yes. We have tried to include all informative retreatment to analyze the incidence of all-grade and high-grade irAEs.

Figure S3:

30. Again differentiate what each of these forest plots represent – ORR vs DCR in title

We have added the title to the forest plots to distinguish from A and B.(see supplementary materials, Figure S3)

Figure 4-S5:

31. I'd be interested to see details regarding irAEs that occurred – what type of irAEs? Was there pattern and did incidence align with irAEs reported

in literature and real world data to date?

We have discussed this part in Page 10, line 5-21. The occurrence and recurrence of irAEs is 41.5% and 27.5%, while only five studies reported relevant information. We can only calculate a pooled occurrence or recurrence of irAEs instead of a relatively clear conclusion. Otherwise, it is also difficult for us to summarize the common irAEs or most life-threatening irAEs and confirm the consistency in pattern between literature and real world data to date because of the limited information obtained from these studies.