Peer Review File

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Reviewer A

The authors provide a robust discussion of perioperative treatment options for non-small cell lung cancer based on the results of the KN671 trial. This paper should be published in TLCR and is worthy of acceptance.

Reviewer B

Overall, this is a very well-done piece on an important trial and treatment paradigm.

Thank you.

Comment 1
I do think this would be a well-received publication. Please see the following feedback:

"However, there remained equipoise whether a combination of neoadjuvant with adjuvant ICI-based therapy would drive additional benefits for patients with localized NSCLC."

I do not think this is accurate. Although the trial was designed before the results of CM-816 and the adjuvant ICI studies were resulted, equipoise still remains for whether the additional benefits are related to perioperative use of ICI compared to neoadjuvant or adjuvant ICI. I would restructure this sentence because there is still equipoise here.

Response 1
The authors would like to thank the reviewer for their kind words, and for reviewing our paper. We agree with the reviewer that the wording can be confusing. As such, we've clarified this in the revised editorial as the following.

Changes in text:
"However, there remains equipoise whether a combination of neoadjuvant with adjuvant ICI-based therapy would drive additional benefits for patients with localized NSCLC compared to neoadjuvant or adjuvant ICI-based therapy alone." Lines 22-25.

Comment 2
"Although the lack of OS benefit across these trials could be due to immature follow up, the OS can also be confounded by the inter-patient heterogeneity with a considerable proportion of patients may not be cured by ICI and the possibility that recurrent NSCLC can be successfully salvaged"

This sentence is unclear and i don't think accurate. The OS results are surely immature, but randomization is the gold standard for addressing heterogeneity of patients and we cannot assume the groups are imbalanced with regards to benefitting from ICI or eligibility for receipt of salvage treatment. Immature results are a product of power of the study and number of events occurring at a specific analysis time point. Likely. not enough time yet for the results to be significant based on the apparent effect size of the intervention and size of the study. This is why the OS results are not positive and we should not harp on

that until more time goes by- hence, results are immature. This is characteristic for a perioperative study in which it takes time for OS results to mature.

Response 2
Thank you for this comment. We revised it accordingly as the following.

Changes in text:
The trend toward better OS in ICI group was also observed in multiple perioperative trials, but none of these has reached statistical significance, which could be due to immature follow up. Line 43-45.

Comment 3
"These results indicate that with neoadjuvant chemo-ICI, surgical resection may become a new option for patients who are not traditionally treated by surgical resection."

The discussion around stage IIIB and C patients and neoadjuvant ICI-based therapy is interesting. It should be mentioned that the PACIFIC trial has established the current standard of care for these patients in chemoRT followed by durvalumab, and any deviation from that regimen should be compared head-to-head in a randomized trial. That is the gold standard for establishing superior efficacy to a current standard of care.

Response 3:
Thank you for this thoughtful suggestion. We revised the manuscript as the following.

Changes in text:
These results indicate that with neoadjuvant chemo-ICI and surgical resection could be revisited as a new option for patients who are not traditionally treated by surgical resection. Of course, this option has to be compared in randomized trials to the current standard of care concurrent chemoradiation followed by adjuvant durvalumab established in the PACIFIC trial. Lines 72-77

Comment 4
The discussion about RIOT is excellent.
The inclusion of liquid biopsy as a potential biomarker is important, as you have included.
The discussion behind the pathologic response as a potential predictive biomarker for the patients who may benefit from additional therapy is also well formulated.

Reply 4
Thank you.

Changes in Text:
None

Reviewer C

I applaud the authors for presenting an outline for needed critical thinking and data with neoadjuvant chemoIO RX.

Comment 1
Timing can be everything, but the recent NADIM II trial (Provencio et al) published in the NEJM August 10, 2023 is missing from the overall discussion. Although a randomized phase 2 trial, it did show an improved PFS and OS with neoadjuvant chemoIO then followed by 6 months of IO (similar to KN671). This study strengthens their discussion and merits inclusion in the editorial commentary.

Response 1
The authors would like to thank the reviewer for their kind words and for this suggestion. We have addended the editorial to include the results from the NADIM II trial.

Changes in text:
Results from the Phase II trial (NADIM II) evaluating the effect of perioperative nivolumab and chemotherapy have demonstrated significantly increased pathological complete response in patients who received combination therapy compared to chemotherapy alone. Lines 15-18

Comment 2
Additionally, the discussion of ctDNA in neoadjuvant chemoIO studies lacked any discussion of the known ctDNA data from CheckMate 816 where a lack of ctDNA clearance with chemoIO associated with a 0% pCR (Forde et al NEJM 2022 appendix) and thus OS. Nor was there discussion regarding ctDNA from the single-arm NADIM trial (Provencio et al JCO 2022) with baseline ctDNA associated with a much poorer OS but if ctDNA shedding clearance was achieved with the neoadjuvant chemoIO RX was associated with a remarkably high OS. Extending the ctDNA discussion to include this data would also be of value to the readers.

Response 2
This is another excellent suggestion. We added relevant discussion as the following.

Changes in text:
For example, In the CheckMate 816 trial, it was observed that no patients achieved a pathological complete response (pCR) if ctDNA remained positive after neoadjuvant therapy. Similarly, the NADIM trial also demonstrated that patients with positive baseline ctDNA had a shorter OS, while patients who achieved clearance of ctDNA shedding after neoadjuvant chemoimmunotherapy experienced a remarkably high OS. Line 151-155..

Comment 3
Plus, a simple spell check typo...unprecedented came through as unpresented.

Reply 3
Thank you for bringing this to our attention.

Changes in text:
Line 12

Reviewer D

I would like to thank the handling editor for offering me the opportunity to review the manuscript entitled "The opportunities and challenges of perioperative therapy of localized non-small cell lung cancer - thoughts from the Keynote-671 trial" by Deboever and Zhang and, which is currently under consideration for publication in the Translational Lung Cancer Research. I would also like to commend the authors for their scholarly work, which presents a commentary on KEYNOTE-671.

The manuscript reviews the opportunities and challenges of perioperative therapy, specifically immune checkpoint inhibitors (ICIs), for the treatment of early-stage and locally advanced non-small cell lung cancer (NSCLC). Recent clinical trials, including KEYNOTE-671, have shown that addition of ICIs, such as pembrolizumab, to platinum-based chemotherapy in the neoadjuvant and adjuvant settings can improve outcomes, including event-free survival, for patients with stage IB-IIIA NSCLC. However, KEYNOTE-671 and other trials have not yet demonstrated an overall survival benefit. The authors discuss considerations for selecting neoadjuvant, adjuvant, or combined perioperative ICI therapy based on disease stage, ability to resume therapy after surgery, and response to neoadjuvant treatment. They highlight the need for continued research to optimize treatment protocols, identify patients most likely to benefit, and integrate emerging biomarkers and radiomic data to further personalize lung cancer care while minimizing toxicity and cost. The commentary summarizes the current evidence for perioperative ICI therapy in NSCLC and important open questions remaining in this rapidly evolving therapeutic landscape.

The manuscript under review provides a thoughtful and timely analysis of the evolving role of perioperative ICI therapy for resectable NSCLC. The authors summarize recent landmark clinical trials in this area, mostly KEYNOTE-671, in a scientifically and technically sound manner. The data and conclusions of the commentary are presented accurately and ethically.

A key strength of this manuscript is placing the KEYNOTE-671 findings into the broader context of other perioperative immunotherapy trials, including CheckMate-816 and IMpower010. By comparing and contrasting the data across these studies, the authors provide a comprehensive overview at the current evidence base supporting the use of ICIs, such as pembrolizumab, nivolumab, and atezolizumab, in the neoadjuvant and adjuvant settings. The commentary is further strengthened by the clinically focused critical analysis of the results. The authors thoughtfully consider nuances such as the lack of proven overall survival benefit, challenges with patients completing adjuvant therapy after surgery, and the need to better understand which patients stand to benefit the most from added immunotherapy. Their balanced perspective emphasizes that while adding ICIs shows promise for improving outcomes like recurrence rates, many open questions remain regarding optimal patient selection, treatment protocols, and integration of emerging biomarkers.

Overall, this is a high-quality commentary that makes a meaningful contribution to the current discourse surrounding perioperative immunotherapy for NSCLC. It offers valuable new synthesis and commentary regarding the state of the evidence and key next steps for moving this research forward. The balanced analysis of the opportunities and lingering uncertainties with this evolving treatment approach will be of substantial interest to the thoracic oncology community.

While the manuscript provides valuable insights, there are a few areas that could be refined to further augment the quality and impact of the work. Here are some respectful suggestions that could potentially improve the manuscript if the authors choose to implement them:

Comment 1

When discussing ICI treatment limitations, such as patients not proceeding to surgery or not completing adjuvant therapy, consider citing available data on specific reasons (e.g., treatment toxicity, disease progression, patient preference). This context could help readers better understand the scope of the problem.

Response 1

Thank you for these favorable comments and constructive advice. We agree discussion of these specific reasons are important to inform future research. We have revised the manuscript to discuss these important points.

Changes in Text

In addition to disease progression, other factors that may have impacted this metric included adverse effects from systemic treatment, logistic reasons such as lodging and travel to receive these treatment, and patient preference. However, details of these factors are difficult to capture. Lines 118-121

Comment 2

Consider expanding the discussion of genomic characteristics to highlight emerging biomarkers beyond PD-L1 that may predict immunotherapy response (e.g., tumour mutational burden, interferon-gamma signatures). This would showcase the growing potential for personalized decision-making.

Response 2

We thank the reviewer for this constructive advice and we agree this is critically important. There are many reviews in the literature on this important topic. On the other hand, this topic is broad and complicated, which may not be well discussed in this editorial with word limit and the reference constraints. We appreciate the reviewer's suggestion and added this as one of important open questions in the field of perioperative research.

Changes in Text

The completion and continuation of perioperative immune checkpoint inhibitor (ICI)-based therapies have indeed transformed the landscape of lung cancer treatment. However, despite the significant progress, numerous unanswered questions persist, extending beyond those previously discussed. …. Moreover, there is a pressing need to establish effective methods for selecting patients for perioperative ICI-based therapies, moving beyond the current biomarker-based approaches such as PD-L1 expression and tumor mutation burden. Line 171-179.

As personalized medicine continues to evolve, comprehensive integration of molecular, clinical, radiomics characteristics and other treatment modalities will undoubtedly aid in refining treatment strategies, allowing for more tailored and effective therapeutic approaches. Line 180-183.

Comment 3

It could be useful for readers to briefly compare/contrast perioperative immunotherapy toxicities versus cytotoxic chemotherapy. Are ICI side effects reduced in the perioperative space?

Response 3

This is an excellent suggestion; we have added a section relating to toxicities.

Changes in Text

In addition to assessing efficacy, the consideration of treatment-associated toxicity is a crucial element in the decision-making process for choosing the appropriate perioperative regimens. In the context of neoadjuvant and adjuvant trials employing agents targeting anti-PD1/PD-L1, the occurrence of adverse events, particularly immune-mediated, remains consistent across various studies. However, it is essential to highlight that the incidence of grade 3 or above toxicities was notably elevated in the perioperative

Keynote-671 trial in comparison to other neoadjuvant or adjuvant trials. Specifically, the percentage of patients in the treatment group experiencing grade 3 or above toxicities was 44.9% compared to 37.3% in the control group in the Keynote-671 trial, while it stood at 35% versus 25% in the Keynote-091 trial, 22% versus 13% in the Impower010 trial, and 33.5% versus 36.9% in the Checkmate-8161-4. It is important to acknowledge that direct comparisons across trials might not be entirely equitable due to variances in patient characteristics among these studies. Nevertheless, the higher rate of toxicities observed in the Keynote-671 trial suggests a correlation between the intensity of treatment and the incidence of adverse effects. This observation underscores the necessity of carefully weighing the balance between treatment efficacy and associated toxicity when making informed decisions regarding cancer treatment strategies. Lines 122-137.

Comment 4

Consider adding a comment on whether there are open questions regarding the optimal duration of perioperative immunotherapy.

Response 4

This is an excellent suggestion. Once again, we are limited by the word limit and the reference constraints with this editorial. We therefor added this as one of important open questions in the field of perioperative research and discussed in the following.

Changes in Text

A robust neoadjuvant protocol incorporating dual systemic therapy (chemotherapy plus immunotherapy) may be a viable option aiming to optimize tumor response before proceeding to surgery although the optimal duration of treatment remains as an open question. Line 61-64

The completion and continuation of perioperative immune checkpoint inhibitor (ICI)-based therapies have indeed transformed the landscape of lung cancer treatment. However, despite the significant progress, numerous unanswered questions persist, extending beyond those previously discussed. For instance, the optimal duration of neoadjuvant and adjuvant treatments remains uncertain. Line 171-175.

Comment 5

When discussing optimal neoadjuvant regimens, consider briefly commenting on the potential role of radiation therapy as well based on emerging data. This could provide a more comprehensive look at the available toolkit for clinicians.

Response 5

Again, this is an excellent suggestion. But we are limited by the word limit and the reference constraints with this editorial. We therefore added this as one of important open questions in the field of perioperative research.

Changes in text

The completion and continuation of perioperative immune checkpoint inhibitor (ICI)-based therapies have indeed transformed the landscape of lung cancer treatment. However, despite the significant progress, numerous unanswered questions persist, extending beyond those previously discussed. … Additionally, the role of radiation, both with and without immunotherapy, in the neoadjuvant setting needs further clarification. Line 171-175.

As personalized medicine continues to evolve, comprehensive integration of molecular, clinical, radiomics characteristics and other treatment modalities will undoubtedly aid in refining treatment strategies, allowing for more tailored and effective therapeutic approaches. Line 180-183

Comment 6
The discussion of financial toxicity and quality of life is impactful. Consider slightly expanding on approaches to assess and mitigate these issues in future trials. This could further highlight the importance of your work.

Response 6
We appreciate the reviewer's comments and agree with reviewer regarding this important point. We have added to this discussion in the revised editorial.

Changes in Text
Fast-tracked access to financial advisors, or nurse navigators and social work may mitigate economic complications associated with cancer diagnosis. Lines 168-170.

In conclusion, I would like to reiterate my appreciation to both the editor and the authors for the opportunity to review this interesting and informative commentary.

Overall, this is a strong manuscript. The above minor suggestions aim to highlight some important nuances in the data and point to future directions for this exciting area of research.