Peer Review File

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Reviewer A

The paper contributes valuable perspectives on integrating immune checkpoint inhibitors (ICIs) in managing non-small cell lung cancer (NSCLC). However, several areas could benefit from revision to enhance the manuscript's overall quality and impact.

1. Title and Running Title:
The current and running titles may mislead the readers as they do not accurately reflect the focus on early-stage and/or operable NSCLC in the manuscript. A revision specifying this focus in the title and running title is recommended.

The title and running titles have been changed as recommended.

2. Table-1: Phase III Trials on Peri-operative ICI-Chemotherapy in NSCLC:
The table could be significantly enriched by incorporating the following elements:
Use the full names of the medications instead of abbreviations or trade names to ensure comprehensibility.
Include metrics of clinical efficacy such as pathological complete response (pCR), event-free/progression-free survival (EF/PFS), and overall survival (OS) to provide a comprehensive overview.
The PD-L1 marker should be categorized under the "Biomarker" section to align with the standard classifications in oncological research.
More specific of the medicine in the chemotherapy regimen.

Changes have been made in Table-1, as recommended: with the addition of metric of clinical efficacy (addition of the primary outcome); PD-L1 marker has been changed for “biomarker”; and specific details on chemotherapy regimen have been added.

3. More References:
The manuscript may benefit from referencing the following papers, which provide current and future perspectives on precision neoadjuvant systemic therapy in resectable NSCLC:

Godoy LA, et al. "Emerging precision neoadjuvant systemic therapy for patients with resectable non-small cell lung cancer: current status and perspectives." Biomarker Research, 2023 Jan 18;11(1):7.
Lee JM, et al. "Neoadjuvant Targeted Therapy in Resectable Non-Small Cell Lung Cancer: Current and Future Perspectives." Journal of Thoracic Oncology, 2023 Jul 13.

The references have been added, as well as two new sentences in that regard, in line 135: *"On the question of biomarkers, the presence of an oncogenic mutation should probably discourage the use of an ICI-based perioperative strategy, as it is well described that these patients respond poorly to immunotherapy (19). For these patients, several perioperative strategies using targeted therapies are being developed."*

4. A section discussing the adverse effects would add valuable information or add information to the table if word limits.

In Line 89 was added the following sentence regarding safety in the KN trial: *"and 82.1% and 79.4% of patient underwent surgery in the pembrolizumab and placebo group respectively"*

The following paragraph was added, beginning in line 112:
"In terms of safety, as in Keynote-671, the addition of ICI to chemotherapy did not lead to a major increase in toxicity in these phase III studies. Grade 3 or 4 treatment-related adverse events did not differ between the two groups in checkmate-816: 33.5% versus 36.9%. In AEGEAN study the all-cause grade 3 or 4 adverse events were similar with durvalumab or placebo: 42.3% vs 43.4%, during the whole treatment-period. In the NEOTORCH trial, the incidence of grade 3 or more all-causel adverse events was slightly increased with toripalimab compared to placebo: 63.4% vs 54.0%, as was the rate of immune-related adverse event: 42.1% vs 22.8%). It is also worth mentioning that in all these trials, the addition of ICI did not negatively affect the feasibility of surgery, with around 80% of patient undergoing surgery in the AEGEAN trial, and even a slight increase in the surgery rate in patients treated with ICIs and chemotherapy in the NEOTORCH (83% vs 73.3%) and Checkmate-816 trials (83.2% vs 75.4%)."

By addressing these comments, the authors can elevate their manuscript's academic rigor and clinical applicability.

Reviewer B

This is a nice review of the role of immunotherapy in early-stage lung cancer. The authors have covered the key studies and addressed some of the remaining questions in the field. I have a few suggestions for the authors:

1. Regarding question 3, inconsistencies between pCR or image-based responses and PFS/OS have been observed in other studies, such as Tebentafusp in uveal melanoma. This discordance is partially attributed to the delayed effects of immunotherapy (IO). We are aware that the IO curve intersects with the chemo-only curve at around 3 months, coinciding with the time of surgery. It is challenging to clarify that this discordance is not solely a result of potential adjuvant therapy impacts, but can also arise within the context of the delayed effects of neoadjuvant treatment."

We recognize the relevance of this comment, and therefore added (line 142): *"A discrepancy between image-based response assessment and progression-free survival or OS has also been described for immunotherapy in other settings (22), possibly due to the delayed impact of immunotherapy, highlighting the fact that neoadjuvant ICI may have a prolonged or delayed impact."*

2. Do all patients who receive adjuvant therapy need to undergo the full year of therapy? ctDNA detection can serve as a surrogate marker for high-risk patients. It can also aid in defining the appropriate duration of adjuvant therapy.

The following sentence has been added (line 144): *"New prospective data will be needed to answer these questionsdetermine if some patients could undergo less than a full year of adjuvant treatment or even totally avoid adjuvant treatment".*

3. In relation to your final points, I would recommend adding this reference PMID: 37188597, which investigated the impact of pembrolizumab on relapse/refractory stage III after chemoRT

The reference has been added

4. I suggest to expand your table and add all other newly published studies:
-Nivolumab (2 cycles) (Forde et al., 2018)
-Sintilimab (2 cycles) (Gao et al., 2020)
-Pembrolizumab (2 cycles)) (Eichhorn
et al., 2019)
-Pembrolizumab (1 or 2 cycles) (Bar et al.,
2019)
-Atezolizumab (2 cycles) (Chaft et al.,
2022)
-Durvalumab (3 cycles) (Wislez et al.,
2022)

-Nivolumab and Ipilumumab (2 cycles) (Cascone et al., 2021)
-Nivolumab + paclitaxel + carboplatin (3 cycles) (Provencio et al., 2022 May 1)
-Toripalimab + platinum-doublet chemotherapy (4 cycles) with 14 cycles postoperative toripalimab (Lu, 2023)

While we appreciate the proposition and we acknowledge the importance of these phases II studies, we voluntarily chose to include in the table only phase III trials that are the most clinically pertinent. Adding more studies could result in an overload of information.

Reviewer C

This is an editorial on the use of pembrolizumab (or ICIs in general) in a neoadjuvant setting for NSCLC.

- Line 52: this sentence is very unclear, please adjust because the message remains unclear for the reader.
The sentence "*Since the results of the PACIFIC trial and practice changes it heralded",* has been modified for: *"Since the results of the PACIFIC trial and the subsequent shifts in clinical practices it introduced"*

- Line 64: please add "of" between administration and ICI
Corrected.

- You are not referring to Table 1 in the text, please do so and make clear what the added value of this table is for your editorial.
We referred to table-1 by adding this sentence (line 90): "*The different characteristics of these trials are summarized in Table-1, for better comparison*"

- Line 75: patients instead of patient
Corrected.

- I would change the running title to "preoperative immunotherapy in NSCLC"
Corrected as suggested.