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Reviewer A

The paper by Riano and colleagues seeks to provide a summary and some commentary about the rapidly growing collection of data on immunotherapy in the pre-operative and post-operative settings for resectable NSCLC. I have several suggestions for the paper.

Comment 1: 1) I feel it would be helpful to add structure to the paper by dividing it into sections after an introduction, covering adjuvant therapy, neoadjuvant therapy, perioperative therapy (both neoadjuvant and adjuvant), implications for surgery, then perhaps biomarkers/subgroups if that isn't covered in each of the preceding sections by individual paper (I think it would make the most sense to discuss individual subgroup findings with the discussion of each individual study). As it is, you have a large amount of data that seems to flow more as stream of consciousness than in a clearly designed narrative.

Reply 1: Thank you very to the Reviewer for the thoughtful comments. Considering that this is an *Editorial Commentary* type, we initially wrote the article with an *unstructured* style, as indicated in the author's guidelines for this journal. However, we agreed to divide the Editorial into sections for ease of reading. Thank you for this important comment.

Changes in the text: As suggested by the Reviewer, we have divided the Editorial into *adjuvant*, *neoadjuvant*, and *perioperative immunotherapy* sections, followed by *surgical considerations* and *biomarkers*. This certainly provides more organization to the editorial structure.

Comment 2: 2) Similarly, I would advise that the authors use a format of dedicating a separate paragraph to the summary of each trial if the trial is worth discussing. As it is, there is a very long paragraph that covers not just IMpower010 and PEARLS but then continues to cover the early neoadjuvant work from Forde and colleagues, while KEYNOTE-671 is covered in 2 separate paragraphs.

Reply 1: Thanks for bringing this to our attention. We agreed to separate each trial into its own paragraph as recommended by the Reviewer. Adopting this style will definitely make the article more organized. We dedicated more coverage to the KEYNOTE-671 trial considering that the Editorial Office asked us to focus on this one. Consequently, we summarized other relevant phase 3 trials to contextualize the KEYNOTE-671 trial and what questions were sought to be answered.

Changes in the text: We have divided the long paragraph covering IMpower 010 and PEARLS to summarize the trials in its own paragraph. We have also made own paragraphs for other trials including the AEGEAN, and Neotorch trials.

Comment 3: 3) The IMpower010 OS data have now been published online in Annals of Oncology. There should be discussion of the OS data with the articulated finding that the benefits of adjuvant atezolizumab appear to be limited to patients with high tumor PD-L1, and implications for clinical practice.

Reply 1: Thank you very much for point this out. Certainly, it is important to include the updated OS results from the prespecified interim analysis in the Editorial, and more importantly, to discuss clinical benefit.

Changes in the text: We have written a paragraph with the update highlighting those recent results of the IMpower010 for the first pre-specified interim analysis of OS, which indicate a positive trend favoring atezolizumab in PD-L1 subgroup analyses, primarily driven by the PD-

L1 tumor cell (TC) ≥ 50% stage II-IIIA subgroup. We highlighted the clinical implications of this finding.

Comment 4: 4) The value of the paper would be greater if there was more commentary provided beyond just summarizing data. What is the value of the PEARLS data relative to IMpower010? How valuable is a statistically significant DFS benefit if there is no OS benefit, nor a strong promise of one from the early data from PEARLS? How should we weigh the importance of the various peri-operative trials beyond "careful discussion is indicated"?
Reply 1: Thank you very much for this important suggestion. We have made several changes in the manuscript to avoid a 'summarize data' format and adopt a more commentary type. We have included a more critical way to present the results from the different trials.
Changes in the text: The questions made by the Reviewer significantly expanded the value of our Editorial. We, therefore, included the main differences between PEARLS and IMpower010 trials including the heterogenicity results in high PD-L1 levels, *EGFR* mutation/*ALK* translocation, and how those interplay to carefully make decision for our patients. We have added the following paragraph to give more clarity to the reader:
"Notably, all these approvals were based on surrogate endpoints, with varying levels of OS data, some more promising than others. PEARLS/KEYNOTE-091 and IMpower010 trials provided valuable contributions into the field of adjuvant treatment of early-stage NSCLC. In contrast to IMpower010, PEARLS/KEYNOTE-091 showed no statistical benefit of pembrolizumab inpatients with high PD-L1 expression (HR=0.82; 95%CI=0.57-1.18;p=0.14), neither benefit in patients with squamous NSCLC (HR=1.04) vs. nonsquamous NSCLC (HR=0.67). Moreover, PEARLS/KEYNOTE-091 trial showed no benefit for patient with ALK translocation or EGFR mutations regardless of the PD-L1 expression, whereas IMpower010 showed a benefitfor patients with EGFR mutations if they had high PD-L1 levels. Certainly, there is no clear pattern of best benefitfor those with higher tumor PD-L1 expression, as we have seen in many other trials ofadjuvant therapy, and current adjuvant data are not sufficient to support these conclusions. Thus, to determine whether adjuvant immunotherapy is beneficial, andfor which patients, mature overall survival data is needed. In the meantime, the question remains as to how we can prioritize these available treatment optionsfor the patients. We must therefore carefully discuss with our patients whether the benefits of immunotherapyjustify the additional costs and risks. "

Comment 5: 5) KEYNOTE-671 has now been published in NEJM, so this should be updated.
Reply 1: We have updated the reference number 1 which refers to the KEYNOTE-671, as the article was published in NEJM. Thank you for noticing this.
Changes in the text: Updated the following reference: Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. *N Engl J Med. 2023;389(6):491-503.*

Comment 6: 6) I would recommend that there be a section on "surgical implications" that include not only discussion of whether immunotherapy or chemoimmunotherapy is safe to give preoperatively without complications, but also discussion of the implications of patients with stage IIIB disease being included on these trials. How should resectability be defined, and specifically, should it change if a surgeon speculates that someone who does not have resectable disease at presentation could have a response that renders their disease resectable later?
Reply 1: Thank you very much for this recommendation. We have added a *surgical implications* section to provide more information. Since we are limited to 2,500 words (Editorial Commentary), we have addressed the questions of the Reviewer in a concise manner.
Changes in the text: We added a 'surgical implications' section where we mentioned not only the safety of immunotherapy, but also the implications of including patients with stage IIIB N2 node stage in the KEYNOTE-671 trial. We also mentioned about definition of 'resectability',

which is mainly provided by thoracic surgeons. Please refer to this section of the manuscript for more details.

Reviewer B

It's commendable to see a comprehensive summary of trials, yet I'd like to offer several insights and suggestions to provide a broader perspective.

Comment 1: Incorporation of Adjuvant Trials: While the review includes an extensive array of trials, the mention of the IMPOWER010 and PEARLS trials is curiously absent from table, especially given their relevance and the subsequent discussions surrounding them. It would be beneficial to readers to see these integrated into the table, providing a holistic view of the landscape.

Reply 1: Thank you very much for the suggestions of the reviewer to our Editorial. Our table was initially designed to include only the most relevant published trials with neoadjuvant *and* adjuvant component in NSCLC. However, we consider important to add these 2 trials to the table as mentioned by the Reviewer.

Changes in the text: We incorporated the IMpower010 and PEARLS trials in the table to provide a more holistic view under the subtitle "Key trial with adjuvant component" . I have also changed the title of the table. Please refer to table 1 for more detailed changes.

Comment 2: Reconciliation with Findings: The conclusion drawn in the summary paragraph regarding the superiority of perioperative regimens warrants further elucidation. Given that the CM816 trial showcased impressive results, in tandem with the mentioned adjuvant trials, it becomes crucial to explain the rationale behind this conclusion. Providing a clearer comparison or deeper analysis might help the readers navigate this landscape.

Reply 1: Thank you very much for the comments on our Editorial. The summary paragraph concludes that the 3 key trials (KEYNOTE-761, AEGEN, and Neotorch) that included neoadjuvant *and* adjuvant component showed perioperative immunotherapy benefits. We did not mention that any of these regimens is superior to the other. Certainly, we stated that neoadjuvant pembrolizumab has not been approved in resectable NSCLC and that we need more solid evidence to define if the neoadjuvant component is, in fact, beneficial. Along the Editorial, we highlighted that approvals in this topic were based on surrogate endpoints, with varying levels of OS data, some more promising than others. We have made several changes to the Editorial to address a more critical overview of the CheckMate-916.

Changes in the text: In the *conclusion* section, we eliminate the sentence "This study lays the foundation for developing new combination regimens" to avoid any confusion regarding the superiority of perioperative regimens. We also emphasized that more solid evidence is needed to make a definitive conclusion, especially maturity of overall survival data. Please refer to the *conclusion* section for detailed changes.

Comment 3: Incorporating a Multidisciplinary Perspective: Any discussion about neoadjuvant and adjuvant treatments isn't complete without shedding light on the surgical and radiation oncology dimensions. The review could greatly benefit from addressing questions such as: How does the choice between neoadjuvant and adjuvant treatments influence the feasibility of surgical resection? Are there potential cytoreductive benefits to be considered? Which specific cancer stages are most impacted by these choices? What role does radiation therapy play in this matrix of decisions? Understanding these intersections might lead to a more enriched and clinically relevant review.

Reply 1: Thank you very much for the critical comment in our Editorial. We will answer the questions in a consecutive manner. We included a *surgical implications* section where we discussed how neoadjuvant treatment can influence the feasibility of surgical resection. We cited 3 different trials that concluded that although unique side effects may occur during neoadjuvant immunotherapy, those are generally manageable and do not exclude patients from

surgery. In the table 1, we included a column that clarify which cancer stages were included in each clinical trial. Since this approach is being described in early disease, most of them included patient from stage IB to IIIA. We also discussed the fact that patients with stage IIIB were

included in the KEYNOTE-671, and how this affected the results and surgical implications. Further, we certainly agree with the Reviewer about importance of radiation therapy as a multidisciplinary step in the making-decision process. For purpose of this Editorial, we have focused only discussing about in resectable, early-stage NSCLC and key *phase 3* trials with neoadjuvant *and* adjuvant components. We certainly mentioned the importance of concurrent chemoradiation in locally advanced NSCLC followed by adjuvant durvalumab, in the introduction section, however this Editorial does not focus on it.

Changes in the text: As commented above. In summary, we dedicated an especial section to *surgical feasibility* and implications in early stages NSCLC when we commented about 'resectability' and outcomes. We specify which NSCLC stages are more suitable for this option through the Editorial and within the table 1.

Comment 4: Expanding on Biomarkers: It's imperative to address emerging biomarkers, especially cfDNA, amongst others. By doing so, the review would be more comprehensive .

Reply 1: Thank you very much for your comments in our Editorial. We agreed with the importance of addressing biomarkers, therefore we included a section about this topic. Considering that our Editorial is focused on key *phase 3* trials of perioperative approaches in resectable NSCLC, we have discussed the biomarkers included in these trials. It would be very interesting to discuss about cfDNA, however none of the trial included this biomarker. Since we are limited to 2,500 words, per author's guidelines for Editorial Comments, we will not discuss in a comprehensive manner about biomarkers, but we did recognize in the manuscript the unmet need for biomarkers to identify patients who might benefit ofneoadjuvant or adjuvant immunotherapy.

Changes in the text: We have added a section about *biomarker* addressing those reported in the key clinical trials discussed in this Editorial. We mentioned about the lack of uniform biomarkers in resectable NSCLC. We added data about EGFR murations/ALK translocation as per KEYNOTE-671, as well as ctDNA as per CheckMate816, although none of those have a predictive value.

Comment 5: Distinguishing this Review: There are multiple published reviews addressing this topic, some of which delve deeper into mechanisms, other biomarkers, and others aggregate data to form treatment strategies. Thus, it becomes pivotal for this review to distinguish itself. What is its unique perspective or contribution? How does it advance the conversation or offer something that hasn't been discussed previously?

Reply 1: Thank you very much for this insightful reflection. We agree that every medical article, including an Editorial, Review, or Original Research, should contribute to science in a variety of ways. Considering that the perioperative immunotherapy in resectable NSCLC is rapidly evolving, there are emergent data every day that provide new topics of discussion or different perspectives. We think that our *Editorial Commentary* is different from other Editorials because we aim to provide a critical review of the main trials assessing the role of perioperative immunotherapy. This includes the latest published KEYNOTE-671 trial. This study was presented at the 2023 ASCO Annual Meeting with simultaneous publication in NEJM this past June. Therefore, our Editorial will discuss unique aspects with the *most updated available data* that allows oncologists to have a deeper discussion about how to prioritize their patients when selecting perioperative immunotherapy (neoadjuvant and adjuvant setting). We summarized other relevant trials to contextualize the KEYNOTE-671 trial and what questions were sought to be answered. We presented a timeline ofkey trials and how the KEYNOTE-671 trial provides more relevant clinical information.

Changes in the text: N/A

Reviewer C

In this editorial comment they have reviewed the latest advances in perioperative immunotherapy in a well written and concise manner. However, there are some issues I would like to discuss:

Comment 1: 1. As from I understand reading the manuscript, the authors' purpose is to give an overview of current status and future perspectives of immunotherapy in the neoadjuvant and adjuvant setting. However, they only seem to focus in the USA, when in Europe, for example, the European Medicines Agency stablishes different criteria and thresholds for approval. Territorial disparities and heterogeneous approval criteria and access are some challenges immunotherapy faces and I think should be reflected in the manuscript.
Reply 1: Thank you very much to the Reviewer for this thoughtful comment. This is a great point. Sometimes we focused a lot on understanding trial endpoints and forget important things such as regulatory approvals and accessibility of immunotherapy worldwide. We apologize for had not comment about the European approval.
Changes in the text: We added comments about the heterogeneous regulatory approvals worldwide in the *conclusion* section. We also mentioned that EMA approved adjuvant atezolizumab in resectable NSCLC with a PD-L1 cutoff ≥ 50% for the selection of patients and who do not have a molecular alteration of driver genes, while FDA approved it for NSCLC with less restriction PD-L1 level of ≥ 1%.

Comment 2: 2. The authors refer to surgical feasibility, but there are some publications showing worrisome conversion to open and morbidity (for example: NADIM study) that should at least be taken into account.
Reply 1: Thank you very much for this comment. We included a *surgery* section where we discussed about feasibility as well as morbidity and mortality related to surgery. We included data from the NADIM study as the Reviewer recommended, however, this data showed a greater percentage of patients in the experimental group than in the control group underwent surgery (93% vs. 69%; relative risk, 1.35; 95% CI, 1.05 to 1.74).
Changes in the text: We included a dedicated section named *surgical implication* where we discussed current data regarding this topic, and included some consideration from the NADIM study, as per Reviewer suggestions.

Comment 3: 3. It is not clear to me whether the authors' have focused only in phase three studies, but phase II NADIM results, with 6 months of postoperative immunotherapy are also promising to be included.
Reply 1: Thank you very much for this comment. We certainly focused only on key *phase 3*

trials that included both a neoadjuvant *and* adjuvant component such as KEYNOTE-671, AEGEAN and Neotorch. However, we provided an overview of previous key *phase 3* with separate adjuvant and neoadjuvant components that led to regulatory approvals such as IMpower010 and CheckMate-816. Considering that our Editorial is limited to 2,500 words, we would not have room to discuss results from this important phase 2 trial.
Changes in the text: We have added some surgical considerations from the phase 2 NADIM.

Comment 4: 4. Although the authors' mention the importance of multidisciplinary teams, I think more emphasis, especially given the scope of the manuscript should be given. There are references assessing survival after multidisciplinary and even tumor board discussion that support authors affirmations.
Reply 1: Thank you very much for this insightful reflection. We emphasized more about the importance of having multidisciplinary teams along the Editorial. Unfortunately, per 'author guidelines', we are limited to 25 references for this Editorial, therefore we will not be able to add further references. Certainly, data supporting tumor board discussion is an excellent topic to address in the future.
Changes in the text: Throughout our Editorial, we stressed the importance of multidisciplinary discussion in the *introduction*, *surgical considerations*, and *conclusions* sections, as well as when we concluded findings from the KEYNOTE-671.

Comment 5: 5. Furthermore, there is a lack of multidisciplinary participation in designing this type of trials, and that should warrant a discussion too.
Reply 1: Thank you for commenting about this point. We agree that multidisciplinary participation, particularly thoracic surgeons, should be involved in the design and implementation of these trials.
Changes in the text: We added a paragraph in the *surgical consideration* section as follows: "*Importantly, thoracic surgeons should be actively involved in trial design considering that clinical outcomes will be heavily influenced by patient selection and surgical expertise. Therefore, a multidisciplinary participation in designing this type oftrials is encouraged.* "

Comment 6: 6. Finally, I suggest reviewing the references, as the style is not homogeneous and reference 17 and 20 are duplicated.
Reply 1: Thank you for bringing this up to our attention. We have eliminated the reference 20 since this was duplicated, as mentioned by the Reviewer. We are using an EndNote tool as a reference manager. Our selected style is Vancouver. We have also updated all reference to make them homogenous. Please let us know if the editors prefer a different bibliography style, we are happy to adopt it.
Changes in the text: Several changes were made to the reference section. Please refer to this part of the manuscript.