Peer Review File

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Reviewer A: Minor Revision

Comments:

This manuscript describes nicely the role of different kinds of induction treatments in patients with the very heterogeneously stage III NSCLC. The overview looks complete. However, the role of the surgeon and their diversity in skills have not been mentioned. There are differences between surgical centers who do T4 surgery for example. What do we call resectable? Different criteria have been mentioned by different authors. For the selection of neoadjuvant setting this is an important issue to mention.

Reply: We fully agree with the reviewer that the role of surgery is highly relevant in this clinical setting. However, we considered that this would be an extensive topic in itself and will already be covered in greater detail in other articles in this Focused Issue on "Multimodal management of locally advanced N2 non-small and cell lung cancer":

- *Robotic-assisted lobectomy for locally advanced N2 non-small cell lung cancer Harvey Pass (USA)*
- *Surgery after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer Stephen R. Broderick (USA)*
- *Salvage surgery after definitive chemo-radiotherapy for patients with Non-Small Cell Lung Cancer Tetsuya Mitsudomi (Japan)*

For this reason, and for the sake of brevity, we focused our review on induction treatment and emerging data on immunotherapy as part of the induction regimens.

Another point is that none of the studies show a better treatment arm but only subpopulation that fare better.

Reply: We fully agree with the reviewer and it is extensively discussed in the Induction with chemotherapy versus CRT before surgery in stage IIIA-N2 NSCLC section.

The role of biomarkers is important for selecting better patients who do well on a certain regimen. Should we incorporate them in new trials? There is a controversial role for TMB. pCR and mediastinal downstaging are considered as surrogate markers for a better outcome but the techniques used are different. Does that influence the outcome of both markers?

Reply: As suggested, we added the following sentence in the discussion:

"Identifying biomarkers for neoadjuvant ICI (alone or in combination with chemotherapy) is crucial to provide patients with the best therapeutic approaches and avoid induction therapy in patients at risk of progression and who may benefit from definitive concurrent CRT. Although neoadjuvant trials provide an ideal platform for biomarker assessment, the association of PD-L1 and TMB with response to induction with immunotherapy has not been consistent in phase

I/II clinical trials. This might be explained not only due to differences in the study population or in the methods used, but also to their limited statistical power for validating the predictive value of those markers".

In the discussion one could make some recommendations of today most optimal treatment for which selected subgroups.

Reply: As the reviewer suggested, we added the following sentence in the Discussion: "Although we anticipate a paradigm shift in the preoperative treatment of patients with stage III resectable NSCLC, we should wait for the results from randomized clinical trials evaluating induction with chemotherapy plus ICI before incorporating this treatment into the clinical practice. We consider that allowing patients to participate in ongoing clinical trials is currently the most suitable strategy in this clinical setting".

Smaller remarks:

Line 41: T4N0M0 belongs also to stage III NSCLC, it N-status ranges from N0 to N3.

Reply: We agree that this sentence was misleading and it was modified as follows: "According to the 8th Edition of the TNM lung cancer staging manual, locally advanced NSCLC comprises a wide range of clinical presentations including primary tumor extension into extrapulmonary structures (T3 or T4) or mediastinal lymph node involvement (N2 or N3), without presence of distant metastases (M0)".

Line 45: "..chemoradiotherapy (CRT) followed by durvalumab if the tumor has positive PD-L1 expression.". The original study and in the manuscript does not take PD-L1 expression into account. It was the EMA who wanted to take this up into the label after a subgroup analysis which should scientifically been considered as exploratory. But PD-L1 expression was not performed on all patients in a systematic way.

Reply: We remove part of this sentence ("if the tumor has positive PD-L1 expression"). It was initially included because the European Medicines Agency approved durvalumab as consolidative therapy following concurrent chemoradiotherapy only in patients with PD-L1 positive tumors.

Reviewer B: Minor Revision

Comments:

Overall nicely done review. My main criticism is that there are a number of reviews on this topic already (PMID: 29410947, 29255697, 29136212, 29116951, 28225501) and a timely review of this topic in 2-3 years may be relevant as we start to see more data coming from trials evaluating neoadjuvant immunotherapy or targeted therapies. But overall a well-done review

paper which I have no major edits/comments to report other than minor ones below.

Reply: We appreciate the reviewer's comments and we agree that several reviews have been published already about neoadjuvant treatment in stage III NSCLC in the past years. Some of these papers discussed some preliminary results from neoadjuvant immunotherapy. However, they were published in 2017 and 2018 and did not review the most updated results of clinical trials evaluating immunotherapy alone or combined with chemotherapy in the neoadjuvant setting.

Introduction

Line 45: technically all stage 3 patients currently get durva after chemoradiation irrespective of PD-L1 expression so I would remove that statement

Reply: We remove part of this sentence ("if the tumor has positive PD-L1 expression"). It was initially included because the European Medicines Agency approved durvalumab as consolidative therapy following concurrent chemoradiotherapy only in patients with PD-L1 positive tumors.

Line 61: the statement that induction chemotherapy allows to treat micrometastatic disease needs to be cited – I am unaware of good randomized data suggesting induction chemo reduces micrometastatic disease

Reply: We agree with the reviewer that this sentence is not well supported by data currently available and is somehow speculative. We modified this sentence as it follows: "Induction therapy allows to start systemic treatment earlier and may increase compliance and tolerability of systemic therapy compared with adjuvant treatment".

We modified the abstract accordingly: "Neoadjuvant chemotherapy has yielded comparable survival benefit to adjuvant chemotherapy in patients with stage II-III disease and may allow for downstaging the tumor or the lymph nodes, an earlier delivery of systemic treatment, and better compliance to systemic therapy.

Metanalysis should be meta-analysis. Write out MPR the first time it is used

NEOSTAR trial – change the word tested to testing

Reply: Thanks for those corrections. We made all these changes in the manuscript following the reviewer's suggestions. MPR is spelled out the first time used in the line 192.