

Peer Review File

Article information: <https://dx.doi.org/10.21037/tlcr-23-245>

Reviewer A

Congratulations for such a clear and thorough work.

I have only one minor comment:

1. Page 2, line 54: “With the advent of immunotherapy, median overall survival lengthened to 18-24 months (Table 1).” I suggest to provide a wider context from this sentence (i.e. mentioning the introduction of immunotherapy in the first line setting of NSCLC, a setting to which Authors refer to in Table 1), because the following sentence is on the pretreated setting, where the outcomes are not that good (and hardly predictable if measured from diagnosis).

Reply 1: Thank you for taking the time to carefully review our work and providing us with valuable feedback. We edited the text as advised (see page 2, line 60)

Reviewer B

This review focuses on long-term benefit of immunotherapy in metastatic NSCLC. The authors give a description of the trials leading to approved regimen in this setting. In addition, they focus on PD-L1 as a main biomarker for treatment decision. The paper is written clearly and the reader can follow even when he is not an expert in the field.

However, there are some points:

1. The paper is written with lots of enthusiastic terms (e.g., magic word cure; feeds the excitement of the field) which puts the review in a kind of advertisement rather a critical review. Side effects leading to discontinuation and even to death and a tremendous decrease in survival in the first months are not mentioned. The whole manuscript has to be written more scientifically and critical to be accepted.

Reply 1: Thank you for your thorough review which allowed us to refine our work. We deleted the sentence with the magical word cure (see page 5, line 175) and the sentence with “feeds the excitement” (see page 6, line 229).

Side effect profile (see page 3, line 95-99) and increased mortality in the initial months was added to the text (see page 4, line 155-159 and page 5, line 202-203). The select group of patients who benefit from immunotherapy and the increased mortality in the initial course were also mentioned in the concluding paragraphs (see page 6, line 226-230)

2. The main focus of this review is on KEYNOTE 42. However, it is not clear to the reviewer whether this review is an editorial commentary to this study or not. If so, it has to be made more clear both in the introduction and in the additional notes at the end of the manuscript. In addition, it should be mentioned that this trial did not

receive approval by the EMA (in contrast to the FDA). If not, other trials with a long-term survival have to be described in more details. Especially, there are data on 5y OS from the KEYNOTE 189 and KEYNOTE 407 trials [Garassino et al., ESMO 2022; Novello et al., ESMO 2022]. In addition, there are more 5y OS data from the Checkmate 017 and Checkmate 057 trials (Borghaei et al., JCO 2020) and 4y OS data from OAK and POPLAR. All these have then to be mentioned and discussed.

Reply 2: Thank you for your helpful feedback. We have added sentences to clarify the focus of the editorial (see page 2, line 52-54 and page 6, line 254). The text was modified to reflect that EMA did not grant approval for this indication (see page 3, line 101-102)

3. KEYNOTE 024, 189 and 407 have data on patients treated by pembrolizumab after reaching 32 cycles and having PD. Those data are most relevant and have to be described here.

Reply 3: We appreciate your valuable suggestions. We added the reported outcomes of this group from KEYNOTE-024 and the number of patients who received a second course of pembrolizumab on KEYNOTE 189 and KEYNOTE 407 (see page 5 line 186-194).

4. The authors assert, that there are missing data on the course of treatment and that this remains unanswered (lines 153-155). However, this is not completely true as there are two published trials with randomizing patients with stop of ICI after 1 y vs continuous treatment (Checkmate 153 trial) (Waterhouse et al., JCO 2020) or 6 months vs continuous treatment (DICIPLE trial) (Zalcman et al., ESMO 2022), respectively.

Reply 4: Thanks for pointing this out. We added the results of these two trials (see page 5 line 181-186)

5. Figure 1 is incomplete and approved regimen are missing (e.g. atezolizumab and cemiplimab mono therapy, combination therapy with platinum Ctx plus cemiplimab (EMPOWER Lung 3), platinum CTx plus bevacizumab plus atezolizumab (ImPower 150).

Reply 5: Thanks for your helpful suggestions. We have changed the title of the figure to suggested treatment algorithms. We changed most of drug names to drug classes to be more comprehensive. We also added the IMpower150 regimen.

Reviewer C

Clear editorial. I have only suggestions on the captions of table and figure.

1. Table 1 I would rather specify that these are select trials and randomized ones.

Reply 1: We appreciate your helpful comments and feedback. We modified the title of the table as suggested.

2. Figure 1 As the authors explain in the text novo-ipi-CT and dura-treme-CT are FDA approved irrespective of PD-L1 but the marginal benefit in PD-L1 > 1% may not be cost-effective; also, this algorithm is very US oriented; therefore I suggest that the authors use the term suggested or proposed algorithm in the caption.

Reply 2: Thank you for your comprehensive review and suggestions. We modified the title of our figure accordingly.