

28th July, 2021

Prof. Hiten R.H. Patel , MD, PhD
Editor-in-Chief
World Journal of Clinical Oncology

Dear Prof. Hiten R.H. Patel and reviewers of the manuscript,

First of all, we want to thank you for your kind comments about our **topic highlight** review about the neoadjuvant immunotherapy in NSCLC and for the acceptance to be published in **World Journal of Clinical Oncology**.

Please find enclosed our last version of the manuscript entitled "**Immunotherapy combinations and chemotherapy sparing schemes in first line non-small cell lung cancer** " which we submit for consideration as an **invited topic highlight** article for the **Topic Highlights monographic**. This is an invited manuscript to the journal editor **Felipe Couñago** (ID 03428837)

This review presents the results of the main articles reporting on immunotherapy combinations, with or without chemotherapy, focusing principally on efficacy and toxicity data. The convenience of adding shorter chemotherapy regimens versus the standard 4-cycle regimens to immunotherapy doublets is discussed.

We have disclosed our conflicts of interests in the COI form. We confirm that this work is original and has not been published previously, nor is it currently under consideration for publication elsewhere. We confirm that the manuscript has been read and approved for submission by all the named authors.

Yours sincerely,

María Sereno,

Corresponding Author

María Sereno MD, PhD; mariasereno75@gmail.com, Av de Europa 32, Hospital Infanta Sofía 28702

RESPONSE TO THE REVIEWERS

First of all, thank you for reviewing our manuscript and for thy comments. We would like to improve it according to your suggestions.

1. Introduction is simple, please also add some information about the basic information of NSCLC and the current immunotherapy for NSCLC. Two key reviews are recommended for you, PMID: 33653420 and PMID: 33643442.

Yes, we have added more information about PD-L1/CTLA-4 mechanisms and the relevant role of these type of drugs in non small cell lung cancer setting. We have read the papers that you have suggested and we have included them in references. Thank you very much for it.

2. The basic writing needs to be improved. For example, in the introduction, Anti-PD-L1/PD-1 and anti-CTLA-4 should use full name in the first time. Authors should revise it throughout the draft.

Ok, we have explained the significance of anti-PD-L1 and PD-1 as well as CTLA-4 in the first paragraph

3. "although in the d- IT the median OS of 11.9 months was shorter than that obtained with CT", why have highlight information. What is "the d- IT"? Please carefully check the manuscript.

**Sorry, the highlight is a mistake
d.-IT is double immunotherapy**

4. The authors must put the p values to all the tables describing the OS, PFS in different clinical trials.

Ok. We have added updated p value in the studies where it is missed. However, in some of them, we could not find these data in the publication

5. The challenge of current Immunotherapy combinations and chemotherapy in NSCLC should be added.

We have described this challenge in some parts of the text:

- Phase I-III studies
- What are the benefits of immunotherapy combinations together with short chemotherapy cycles?

6. A schematic diagram should be provided about how PD-1/PDL-1 interact with immune cells to combat NSCLC. This is important.

Figure 1 and 2 show the interaction PD-1/pDL-1/CTLA4 in immune system

7. The language is needed to be improved.

Professional translators have reviewed English style and grammar mistakes

8. In table 1 and table 2, the more information should be provided.
Some information has been added to table 2