

Peer Review File

Article information: <https://dx.doi.org/10.21037/asj-23-15>

Reviewer Comments:

The article entitled “The role of immunotherapy in neoadjuvant treatment of NSCLC - a narrative review” presents an interesting review on the role of neoadjuvant immunotherapy in non-small-cell lung cancer and how this treatment is changing the paradigm of treatment of these tumours in localised and locally advanced stages. Undoubtedly, neoadjuvant treatment with immunotherapy is a highly original and highly topical subject that requires further review and study to fully understand its implications. Therefore, I believe that the authors have chosen an ideal topic for review.

In a general review, it can be said that the article is correctly written in English that does not need major modifications. Along with this, the structure is also correct and the checklist necessary for a narrative review has been followed in an orderly manner. Regarding the presence of figures and tables, one or two tables summarising the results of the article in a simple way are missing, since in this type of review it is necessary to know the results in a comparative way with each other. Another flaw in the article, which is the main one and which the authors should put more emphasis on correcting, is the lack of updating. A major clinical trial such as NADIM II is missing and the results of the clinical trials of neoadjuvant chemo-immunotherapy based on nivolumab and pembrolizumab need to be updated. The references are mostly current, although some ongoing clinical trials remain to be included in the study. To finalise the overall review, a few errors in the abstract need to be corrected and are listed below.

Changes specific to the article and necessary to assess its publication in the journal are indicated below:

Major changes

1. Methods: The fact that the search was conducted until May 2022 limits the entire article and its value. The most important results regarding neoadjuvant immunotherapy have been published precisely during the last year, so it is mandatory to correct this in order to assess the publication of the article.

[Response: The data has been updated as instructed.](#)

[Change in the text: Pages 6-8, Table 4](#)

2. Methods: Why were databases other than PubMed not included? This may be an

important limitation for the study.

Response: The data has been corrected and other databases added.

Change in the text: Page 3, Table 1

3. Results: I think section 3.1 corresponds more to the introduction than to the results.

Response: The data has been changed and the paragraph added to the introduction.

Change in the text: Page 3, line 75-82

4. Results: it would be correct to make a couple of summary tables of the results. One for results with immunotherapy alone and one for chemo-immunotherapy in neoadjuvant.

Response: Tables have been added.

Change in the text: Pages 4 (line 149), 5 (line 159) and page 7 (line 213)

5. Results: The clinical trials CheckMate-816 and KEYNOTE-671 have already been published in the New England Journal of Medicine. It is currently not possible to publish a review on this topic without including these clinical trials. The first one (CM-816) has in fact given approval to chemotherapy plus immunotherapy for stage II-III neoadjuvant treatment by the FDA and EMA. On the other hand, the NADIM II clinical trial is not mentioned directly and has also just been published in the New England Journal of Medicine. It is essential to include these three studies in the review.

Response: The data has been updated.

Change in the text: Pages 6 (149- 153, 176- 187)

6. Discussion and conclusions: once the results have been corrected, adapt these two sections to the new corrections.

Response: Data has been updated.

Change in the text: Page 8 (220-225 228-229,234-239, 249- 266)

Minor changes

1. Title: no acronyms in the title. Replace NSCLC with its full meaning.

Response: Text has been corrected as suggested.

Change in the text: Page 1, Title, row 2

2. Throughout the article immunotherapy is referred to as "checkpoint inhibitors". This should be corrected throughout the manuscript and the correct name should be "immune checkpoint inhibitors".

Response: Correction has been made as suggested.

Change in the text: Page 1 (row 12, 14,18, 22, 31), page 3 table 1

3. Correct “non-small cell lung cancer” to “non-small-cell lung cancer”.

Response: Correction has been made as suggested.

Change in the text: Page 1 - row 6, 13, 24, 30; page 2- row 57, page 3 -table 2, page 9, row 258

4. Abstract: the overall results of the main clinical trials should be included as this is too sparse in the current format.

Response: Corrections have been made.

Change in the text: Page 1, row 11-26

5. Keywords: add "immune checkpoint inhibitors".

Response: The changes have been made.

Change in the text: Keywords and table 1

6. Introduction: there is a very good overall review of adjuvant therapy in NSCLC. However, I think it would be necessary to talk about the basics of neoadjuvant therapy both with and without immunotherapy, so that the reader can better understand the nature of the review.

Response: The text has been added.

Change in the text: Row 83-92

7. Introduction, line 47-48: give specific numerical data on incidence and mortality.

Response: There are data on benefit from chemotherapy, which is the point of the paragraph.

8. Introduction, line 54-56: indicate that what we are talking about here is the PACIFIC study and give specific response or survival data.

Response: Changes have been made as suggested.

Change in the text: Row 43-44

9. Table 1: in the JBR.10 study correct "vinoreblin" to "vinorelbine".

Response: The table has been removed.

10. Introduction, line 81-82: indicate that the main combination for adjuvant is cisplatin with vinorelbine.

Response: Correction has been made.

Change in the text: Line 67-68

Editorial Comments:

Cancer immunotherapy is a hot topic. This article reviews studies related to immunotherapy in the neoadjuvant treatment of NSCLC to clarify the therapeutic promise of neoadjuvant immunotherapy, and there are still some issues that need to be addressed.

1. Abstract:

1) Please also report the language considerations in the Abstract - Methods.

Response: Changes have been made as suggested.

Change in the text: Page 1, row 14

2) Please also add in the conclusion how the review may potentially impact future researches, clinical practice and policy making.

Response: The abstract has been updated as suggested.

Change in the text: Page 1, row 19-23, 26-27

2. "... while another study compared neoadjuvant and adjuvant chemoradiotherapy in over 1700 patients (5 - year OS rate: 38.1% vs 27.0%; hazard ratio, 0.74; P <0.001) (9,10)", however, reference 9 reported that the 5-year overall survival (OS) was 26.3 for adjuvant chemoradiotherapy rather than 27%. Please correct it.

Response: Changes have been made as suggested.

Change in the text: Page 2, Row 73

3. For readers, may be confused about why authors detail adjuvant chemotherapy in the introductory section. Since the main purpose of this paper is to review and summarize the role of neoadjuvant immunotherapy in NSCLC, we support and suggest the authors introduce the following basic information about immunotherapy and neoadjuvant therapy without immunotherapy as suggested by the reviewer.

Response: The paragraph has been changed as suggested.

Change in the text: Rows 56-62, 85 -94

4. The manuscript fails to provide a persuasive justification for the publication of this review in the introduction. A cursory search reveals that many reviews have been published in this field, such as PMID: 37541935, 37532102, 37530615 and 37488229. How is this paper different compared to them? It is not clear to the reader how this study adds to the existing knowledge.

Therefore, in order to better highlight its value, we strongly recommend the authors introduce existing similar reviews and clarify what they summarize, point out current knowledge gaps, and further specify the problem that this review is intended to address.

Response: The paragraph has been added to address this topic.

Change in the text: Rows 105 - 107

5. According to author instruction (<https://asj.amegroups.org/pages/view/guidelines-for-authors#content-3-3-2>), we recommend that authors use a structured introduction to increase the readability:

a) Background

b) Rationale and knowledge gap

c) Objective

Response: The changes mentioned before should cover this issue, making the introduction more easier to read and understand.

6. "The aim of this article is to approximate the current knowledge on neoadjuvant checkpoint inhibitor therapy in non-small cell lung cancer. Here we present the article in accordance with the narrative review reporting checklist".

Given the existence of section 1.2, there is no need to re-emphasize the purpose of the study. In addition, the Checklist claim is suggested to be reported at the end of the introduction.

Response: Corrections have been made.

7. The reviewers mentioned that the search time limited the whole article and its value. The most important results on neoadjuvant immunotherapy were published precisely in the last year. Absolutely agree! In addition to the studies mentioned by the reviewer, other several heavyweight clinical trials also need to be included, for your reference: PMID37272513, 36928818, 36870519, 36794455, 37379158 and 37535377. In this way, readers can really get a more comprehensive picture of the trends in neoadjuvant immunotherapy in NSCLC.

Response: Data have been updated.

Change in the text: Pages 6, Tables 2-4

8. For the authors' kind reference, we prefer any point based on a more objective judge on the quality of cited literatures in the manuscript.

Response: Corrections have been made.

9. The title of Table 3 should be corrected- "Table 3: Ongoing trials on perioperative checkpoint inhibitor therapy". More importantly, we found this table is almost similar to a published article, i.e., 34083418 (Table 2), written permissions from the copyright holder (usually the publisher) are required.

Response: The table has been replaced with tables 3 and 4.

10. Please define all the abbreviations mentioned for the first time, such as MPR (line 33), NSCLC (line 53), and OS (line 69), et al.

Response: Corrections have been made.

Change in the text: Line 41, line 59, line 76, line 77

11. Line 61, please correct "limited" to "limited".

Response: Corrections have been made.

12. Please correct "PDL-1" to "PD-L1".

Response: Corrections have been made.

13. Line 116, "stage I-III NSCLC received 2 cycles of adjuvant nivolumab", whether

it should be neoadjuvant?

Response: The corrections have been made.

Change in the text: Line 166.

14. “several preclinical models were constructed, where the results showed a significantly higher survival rate in animals receiving PD-1 and CTLA-4 inhibitor neoadjuvant, compared to adjuvant and single agent treatment, respectively (24)”, please provide more references to support “several preclinical models”.

Response: The text has been changed.

Change in the text: Row 95