

## Peer Review File

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### Reviewer A

The authors are addressing an important topic with this review paper, specifically reviewing whether high ECOG PS, age, or cachexia are associated with worse outcomes due to immunotherapy. This paper unfortunately is not particularly novel and does not add to an already rather large body of literature that demonstrates the ECOG PS and age are associated with worse outcomes for patients treatment with immune checkpoint inhibitors (ICIs)

(Reply) Thank you for your critical comment. The objective of the current review is to provide a comprehensive summary of the effectiveness and safety of immune checkpoint inhibitors (ICIs) in vulnerable patient populations, including those with poor performance status, older individuals (aged over 75 years), and those suffering from cancer cachexia. We believe that our analysis of pivotal historical reports and up-to-date data will offer valuable insights to guide the future of immunotherapy in these susceptible patient groups.

### Reviewer B

The manuscript by Morimoto et al is a narrative review that covers a very important topic with relevance for clinical practice and implication for further clinical research. The structure is good and the analysis of the available literature is well reported. However, some points need revision and implementation.

Major comments:

1) line 332: the frequency of cachexia in lung cancer patients is even superior than 20%. Please check also other analyses.

(Reply) We have checked other analyses and revised the sentence.

(Revision in the text) “A recent study revealed that 45.6% of patients with advanced NSCLC had cancer cachexia at baseline (52).”

2) line 344: the mechanisms are more complex and involve multiple pathways related mainly to inflammation associated to cachexia. Since they are relevant please cite them (for ref see for example PMID: 36807335 or PMID: 33809200

(Reply) In accordance with the above suggestion, we have included the relevant citations.

3) line 379: please check and cite also other more recent studies (published in 2023) on this point (for example PMID: 37037511; PMID: 36831431). Ref 63 citation seem wrong or incomplete.

(Reply) In accordance with the reviewer's suggestion, we have cited additional studies published in 2023 in the revised manuscript.

4) Conclusions: please add a summary on the results about elderly: it seems that ICI monotherapy may be effective and recommended while chemoimmunotherapy seems more toxic on the basis of the data reported by you

(Reply) Thank you for your suggestion. In the revised manuscript, we have added the suggested statement in the revised conclusion.

(Revision in the text)

(Page 18, lines 366-368) "ICI monotherapy may be effective and recommended, whereas chemoimmunotherapy appears to be more toxic based on some retrospective studies."

Minor comments:

1) line110: this sentence is not clear. Is it monotherapy a poor prognostic factor or PS?

(Reply) In accordance with this statement, we have revised this statement in the revised manuscript.

(Revision in the text)

(Page 6, lines 98-99) PS of 2 could be a poor prognostic factor for ICI monotherapy (17-21).

2) line 316: the consensus group is not only an european consortium. Please check; it is an international consensus report.

(Reply) In accordance with this statement, we have revised this statement in the revised manuscript.

(Revision in the text)

(Page 14, lines 288-289) The definition and diagnostic criteria for cancer cachexia have been reported in an international consensus (50).

3) please check references data (for example ref 63 seems wrong or incomplete)

(Reply) Thank you for highlighting this discrepancy. We have checked and corrected

the cited reference.

## **Reviewer C**

I would like to congratulate the authors on this well-written review article. Some minor adjustments are needed for the following below.

This paper reviewed recent researches and trials related with vulnerable groups with treating ICIs. The manuscript was well-written and contained very informative content. Some minor adjustments are needed for the following below;

Minor points

1. I suggest to organize cited papers into tables according to each section to improve readability

(Reply) Thank you for your suggestion. We have added Table 2-4 to the revised manuscript.

2. Poor PS: I think it seems that only the results of each representative paper (CM171, PePS2, OLCSG1801, IPSOS trial) are simply described. It would be a good to mention the conclusions of each study and organize them according to the authors' intentions.

(Reply) In accordance with the reviewer's suggestion, we have stated the main conclusions of each study in the revised manuscript.

(Revision in the text)

(Page 6, lines 111-112) "Accordingly, it can be suggested that although nivolumab is well-tolerated by patients with PS of 2, treatment outcomes remain poor."

(Page 7, lines 124-126) "There were no grade 5 treatment-related AEs or early deaths due to hyperprogression. Accordingly, pembrolizumab can be safely administered to patients with NSCLC and PS of 2."

(Page 7, lines 131-132) "The findings of the trial revealed that pembrolizumab was effective and tolerable for treating patients with NSCLC with PS of 2 plus high PD-L1 expression (25)."

(Page8, lines 138-140) "The IPSOS trial revealed that first-line treatment with atezolizumab monotherapy is associated with improved OS and a favorable safety profile when compared with single-agent chemotherapy."

3. Elderly patients: The elderly criteria for each cited paper is not unified, so it feels disjointed overall. I suggest to focus on references that meet the criteria for elderly defined by the authors.

(Reply) Thank you for your suggestion. We defined the elderly as aged  $\geq 75$  years. In addition, we have focused on references that meet the criteria for elderly patients.

(Revision in the text)

(Page 3, lines 35-36) “Herein, we defined vulnerable as the group of patients with NSCLC and performance status (PS)  $\geq 2$  (poor PS), advanced age ( $\geq 75$ ), or cancer cachexia.”

(Page 11, lines 206-212) “In the IPSOS study, the median age of patients was 75 years, with more than 30% of patients being 80 years or older (26). Atezolizumab substantially improved OS in patients aged 70–79 years when compared with chemotherapy alone (HR 0.68; 95% CI: 0.49–0.94), whereas in patients aged  $\geq 80$  years, the HR for OS was 0.97 (95% CI: 0.66–1.44), with no clear difference observed between treatment modalities. In terms of safety, atezolizumab therapy was associated with a lower frequency of grade 3–4 treatment-related AEs than chemotherapy.”

(Page 11, lines 222-225) “The eNergy study found no benefit in patients with NSCLC and PS of 2, whereas in patients with NSCLC aged  $\geq 70$  years with PS 0 or 1, nivolumab plus ipilimumab substantially prolonged OS when compared with platinum combination therapy (22.6 months vs. 11.8 months  $p=0.02$ ) (29).”

4. References needs to be modified. Please check again.

(Reply) As pointed out, we have corrected and appropriately formatted the cited/listed references.

## **Reviewer D**

Overall, the review is well written and informative. My comments are detailed below and can hopefully increase the readability and user-friendliness of the review.

Major comments

- It would be very helpful to have tables summarizing key results

(Reply) Thank you for your suggestion. Accordingly, we have prepared Tables 2-4 summarizing key results.

- The sections of the manuscript are clearly delineated according to patient characteristics: poor PS, elderly, cancer cachexia. However, the order of the various studies/articles quoted is not always easy to follow. It would be helpful to group studies more clearly, or perhaps use subsections e.g. Data from RCTs, Data from observational studies, meta-analysis. An alternative could be to group studies according to treatment regimens used in various patient subgroups (IO alone, chemo-pembro etc).

(Reply) In accordance with the above suggestion, we have grouped studies according to treatment regimens.

- Surely, there is some overlap between the three subgroups examined: poor PS, elderly, and cancer cachexia... Can the authors comment on how these factors intersect?

(Reply) As highlighted by the reviewer, the impact of poor PS, advanced age, and cancer cachexia might overlap. According to the Japanese Lung Cancer Society registry database, age and PS differ significantly between patients with and without cachexia (Shukuya T, Takahashi K, Shintani Y, et al. J Cachexia Sarcopenia Muscle. 2023;14(3):1274-85.). In addition, there were substantial differences between age groups according to PS (Lichtenstein MRL, Nipp RD, Muzikansky A, et al. J Thorac Oncol. 2019;14(3):547-52.). These findings suggest that three factors were closely linked.

#### Minor comments

- In the abstract, I am not sure I understand what is meant by a “descriptive review of the literature”, particularly as the authors state “we then conducted a narrative review”...

(Reply) In accordance with the suggestion, we have altered the statement in the revised manuscript as follows:

(Revision in the text)

(Page 3, lines 36-37) “We conducted a narrative review of the literature on the efficacy and safety of ICIs in vulnerable patients with advanced NSCLC.”

- I am not sure “sociologic” background is an accurate description for the factors examined here namely poor PS, advanced age and cancer cachexia

(Reply) As suggested, we have deleted the word "sociologic backgrounds".

(Revision in the text) (Page 4, lines 61-63) “In addition, with the rapid implementation of ICI-based treatments, these therapeutics are being administered to patients with NSCLC from diverse health backgrounds.”

- It would be helpful to define “elderly” at first mention in text (or at least, the most commonly used definition, since it seems to vary)

(Reply) In the revised manuscript, we defined “elderly” as aged  $\geq 75$  years.

(Revision in the text)

(Page 3, lines 35-36) “Herein, we defined vulnerable as the group of patients with NSCLC and performance status (PS)  $\geq 2$  (poor PS), advanced age ( $\geq 75$ ), or cancer cachexia.

- At first mention of the authors’ study (line 152), it would be helpful to mention the number of patients

(Reply) As suggested, we have added the number of patients.

(Revision in the text)

(Page 8, lines 141-143) “In a prospective observational study, we previously evaluated the efficacy and safety of pembrolizumab monotherapy in 16 PD-L1-positive patients with advanced NSCLC with PS of 2, revealing a median PFS of 4.4 months and median OS of 11.6 months (27).”

- AT line 181, the mention of study #31 after #30 (“However”) is confusing, more context would be helpful to understand what #31 is referring to

(Reply) In accordance with the reviewer’s suggestion, we have revised the statements as follows:

(Revision in the text)

(Page 9, lines 171-173) “According to the ESMO Clinical Practice Guideline for managing non-oncogene-addicted metastatic NSCLC, chemoimmunotherapy has not been evaluated in clinical trials and cannot be recommended for patients with PS of 2 (30).”

- Please clarify the findings related to G8-screening, the authors present data on hospitalization and AE however the conclusion refers to treatment outcomes

(Reply) We have clarified the findings as follows:

(Revision in the text)

(Page 10, lines 197-198) “Accordingly, G8 screening could identify patients with a high risk of hospital admission and mortality (35).”

- Line 250, I think you mean real-world data on chemotherapy + IO?

(Reply) We apologize for any confusion. We have changed this to “chemoimmunotherapy”.

(Revision in the text)

(Page 12, line 230) “Real-world data on the effects of chemoimmunotherapy in the older population has been documented.”

- Would change “enhanced” to “advanced” age

(Reply): As suggested by the reviewer, we have changed “enhanced” to “advanced” in the revised manuscript.

(Revision to the text)

(Page 5, lines 87-88) “In this narrative review, we focus on poor PS, advanced age, and cancer cachexia.”