Peer Review File

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Reviewer A

The authors explored the impact of patient-reported outcomes on the prognosis of patients with advanced NSCLC treated with chemoimmunotherapy, using the individual data from pivotal phase III clinical trials. I agree that PROs have potentials to be utilized in the care of advance cancer patients, and the authors' analysis has some clinical values especially in that it pointed out the limitations of ECOG-PS based assessment. In my opinion, some revisions are warranted before considering this manuscript for publication. Please see my comments below.

Major comments:
1. The authors state that PROs had higher predictive performance than ECOG-PS. Although c-statistics for PROs were numerically higher than that for ECOG-PS, it would not simply mean the difference are clinically meaningful (or statistically significant). The authors should discuss this point in the discussion section, showing the pre-defined decision criteria in comparisons of predictive performance in the method section. Also, I recommend the authors more modestly present the predictive performance of PROs based approach.

Response

Firstly, the purpose of the manuscript is not to imply that ECOG-PS needs to be replaced, but that PROs have inherent value. This conclusion is well supported by the presented results.

With regards to the c-statistic the study pre-defined superiority in discrimination performance according to the highest value; we appreciate that this does not mean the difference is clinically meaningful. Nonetheless, the modestly higher c-statistic for patient-reported physical function over ECOG-PS is indicative of a slight discrimination improvement within the large given dataset (Steyerberg, Clinical Prediction Models, 2009). These finding warrants publication and investigation in future studies.

The result text for the univariable patient-reported physical function versus ECOG-PS comparisons have been updated for clarity, particularly with regarding to the superiority being slight. The result text has also been updated to include the c-statistic of the multivariable model including both patient-reported physical function and ECOG-PS. In the case of adding patient-reported physical function to ECOG-PS, the c-statistic for OS prediction increased from 0.57 to 0.62 – transforming the prediction from poor performance to moderate performance, which is clinically meaningful (D. Révész, Decision support systems for lung cancer: a systematic review, 2017).

Changes:
The results presenting the univariable and multivariable patient-reported physical function/

ECOG-PS models have been updated to:

On univariable analysis, the OS prediction performance (c) of ECOG-PS (1+ vs. 0) was 0.57 (P <0.001; Table 1). Comparatively, the OS prediction performance of the patient-reported physical function groups were slightly higher at 0.60 (P <0.001; Table 1). Demonstrating independent prognostic information, in a multivariable model including both patient-reported physical function and physician-assessed ECOG-PS, the OS prediction performance increased to 0.62 with both variables showing statistical significance (P <0.001, Table 1). Sensitivity analysis indicated that on univariable analysis, the PFS prediction performance of the patient-reported physical function groups was also slightly higher; more importantly, multivariable analysis demonstrated both variables provide independent prognostic information (P <0.001, Supplementary Table 6).

2. As authors stated in the discussion section, this research is suffered from several limitations for future application of PROs for clinical practice. I recommend the authors discuss the weakness of PROs (e.g., times and effort for getting the data, as well as not a few missing values) in comparisons with ECG-PS.

Response

In lines 227 to 233 we added the weakness and challenges of utilizing PRO.

Reviewer B

In "predictive utility of patient-reported outcomes and performance status for survival in metastatic lung cancer patients treated with chemoimmunotherapy," Badaoui et al present PROs from three phase III RCTs and examine their associations with OS and PFS. In addition to the data coming from RCTs, study strengths include use of well-established measures of health-related quality of life, clinically well-defined sample, minimal missing data, a clinically relevant research question, and a well-written manuscript. This manuscript will be of use to the field.

Minor suggestions to improve the manuscript are as follows:
1) Discussion:
a. Recommend discussing the other PROs that were predictive of OS and which have been previously demonstrated vs. are new findings to report. For example, your finding about financial difficulties being predictive is of strong interest to researchers studying financial toxicity. Some of these PROs indicate a different intervention (e.g., financial toxicity vs. impaired physical function).

Response

We have added an extra section in the discussion lines 224 to 232

b. Related to this, I'm very curious, and suspect others will be too, which PROs predict OS after treatment has started. It may be too much for one paper, but it would be helpful to see which PROs worsened or crossed a clinical threshold during treatment and whether that was associated with OS. Again, some of these PROs suggest very different clinical interventions and it would be helpful to know who might be at risk at baseline and which factors are most prognostic once treatment begins. Perhaps a second manuscript is in order.

Response

This is a very valid point and certainly can give insight on targeted intervention focusing on the PROs effected to improve outcomes. Currently we have not investigated this aspect of PROs but we have the capacity to investigate this further for future/subsequent projects.

2) Limitations:

a. The EORTC-QLQ-C30 does not measure some of the side effects and toxicities associated with atezolizumab. It was developed when chemotherapy was the main therapy for LC. Recommend discussing this limitation and whether there might be i/o specific PROs that should be evaluated in a future trial in relation to PFS and OS.

Response

Addressed in lines 254 to 256

b. Metastatic lung cancer patients have a high comorbidity rate and many (perhaps up to a third?) have a PS of 2. Recommend noting the percentage of mLC pts estimated to have a PS2 in limitations (similarly to how you note the % of pts age 75+ in your data and their underrepresentation)

Response

Addressed in line 250 to 251