Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-22-146

Reviewer A

This study by Choi et al addresses the potential impact of gender on immunotherapy outcome for NSCLC. Despite the single-center nature, the study is well-performed and the manuscript well-written, so that the conclusions are convicing and clearly formulated. The credibility is increased by the fact that other established parameters, like PD-L1 expression and EGFR status, did show an association with outcome in this patient population. I have a couple of minor only comments:
1. some minor inguistic issues, e.g. higher smoking habits in line 59, understudied line 162

Reply: Thank you for pointing this out. We revised the linguistic expression to convey the meaning clearly.

Changes in the text:
(Page 3, line 64) "Male patients also showed higher smoking rates, programmed death-ligand 1 (PD-L1) expression, and expression of wild-type epidermal growth factor receptor (EGFR), known as favorable prognostic factors."
(Page 8, line 161) "The median PFS in all patients was 2.1 months (interquartile range [IQR]: 1.4–5.7). It was 2.2 months (IQR: 1.4–6.1) in males and 2.1 months (IQR: 1.4–4.5) in females."

2. One could add in the discussion that - in accordance to the results of this study - the rate of oligoprogression under immunotherapy in NSCLC also does not differ by gender (e.g. PMID 32340408) and also that the rate of irAE (which are associated with better prognosis) also does not differ by gender (several publications).

Reply: Thank you for your valuable comments. The findings in these studies supported our results, and we have cited them with our current findings in the discussion of revised manuscript.

Changes in the text:
(Page 10, line 209 – line 213) "Moreover, in previous real-world studies, the incidence of immune-related adverse events–which could be a predictor of better response to immunotherapy(23,24)– or oligoprogression was not different between genders.(25-27) One

previous study showed that gender played no role in the occurrence of severe immune-related adverse events in multivariate analysis (OR 1.07, p = 0.45).(26) Our findings supported this evidence."

Reviewer B

The study is well done and I would have only minor comments. Nevertheless, this clinical question has been already addressed in several trials and studies, and immunotherapy in 2nd or later lines of treatment is no longer used in clinical practice due to their implementation in the first-line setting. Globally, I do not think that such a study deserves to be published in a journal with an IF of 7.

Reply: Thank you for your valuable comments.
Several studies have shown that males with NSCLC responded better to immunotherapy in clinical trials or meta-analysis, which did not adjust for various factors affecting responses. However, so far, no real-world studies have considered the confounding factors contributing the response. The strength of our study is that we adjusted the confounding factors using the individual patient data rather than published results of the clinical trials, and we could also infer the reason why responses in males appeared better in previous studies.
Additionally, at a time of the recent increase in the use of immunotherapy as the first-line treatment worldwide, first-line immunotherapy – which were mainly conducted as clinical trials because of its inapplicable insurance coverage in Korea during the study period–was excluded from this study. Nevertheless, there was no difference in response to immunotherapy according to gender between the first-line and the subsequent-line treatment in the previous study.(18) Moreover, gender played no role in response to immunotherapy by different treatment line in this study. Therefore, the impact of gender would not depend on the line of therapy, and the results of this study could be applicable in clinical practice regardless of the line of therapy. We added this limitation to the discussion.
Changes in the text:
(Page 12, line 262 – line 270) "Finally, at a time of the recent increase in the use of immunotherapy as the first-line treatment worldwide, first-line immunotherapy – which were mainly conducted as clinical trials because of its inapplicable insurance coverage in Korea during the study period–was excluded from this study. Nevertheless, there was no difference in response to immunotherapy according to gender between the first-line and the subsequent-line treatment in the previous study.(18) Moreover, gender played no role in response to immunotherapy by different treatment line in this study. Therefore, the impact of gender would not depend on the line of therapy, and the results of this study could be applicable in clinical practice regardless of the line of therapy."