Peer Review File

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Review Comments

Reviewer A

This manuscript reported the potential differences in outcomes between males and females patients with oncogene-addicted non-small-cell lung cancer treated with targeted agents by a narrative review of published manuscripts. The findings in this paper would be useful information to make a prospective studies in the future.

Comment 1: Section 5. of ROS-1, BRAF, KRAS, HER-2, RET, MET, tyrosine-kinase inhibitors have only a little information. I recommend the deletion or shortening of Section 5.

Reply 1: As suggested, we deleted Section 5 of the text (lines 305-347) and the related references (from 49 to 63) (lines 543-577).

Reviewer B

Comment 2: This review addresses an important and timely topic: the role of gender in the treatment of lung cancer with molecular drivers. The format of the review is meant to be a narrative review that summarizes relevant trials; it is not meant to be exhaustive. The table of relevant trials, which the treatment arms, gender breakdown, and associated hazard ratio is particularly helpful.

However, the narrative section of the review could use some revision to be more useful to the reader. In particular, it reads like an unordered listing of trials, without a clear sense of why the trials are being presented in the order they are,

nor how they compare to one another. Having transitions between the paragraphs and summary paragraphs at the end of each section, summarizing the takeaways from each section, instead of all at the end at the conclusion, would help with readability.

Reply 2: As suggested we added the following sentences at the end of each section:

Lines 245-254: "In conclusion, all studies showed a consistent advantage in PFS of EGFR-TKIs over chemotherapy in first or subsequent lines, regardless of gender. Again, the two studies that compared second/third generation of EGFR-ITKs versus first generation EGFR-ITKs showed advantage in PFS of new generation of EGFR-ITKs regardless of gender. Notably, in all but one studies reported above, the risk reduction for PFS was greater in women than in men. EURTAC was the only study that reported a similar HR for PFS between gender.

In two phase 3 trials, anti-antiangiogenetic antibody (ramucirumab or bevacizumab) were associated with an EGFR TKI and compared to EGFR TKI alone. Although both studies showed a greater benefit from the combination arm, the HRs for PFS by sex resulted contradictory. "

Lines 316-321: "In conclusion, all studies that compared ALK inhibitors versus chemotherapy or that compared new generation ALK inhibitors versus crizotinib showed a PFS advantage for experimental arms compared to standard arms regardless of gender. Similarly to the studies with EGFR TKis also in those with ALK inhibitors the risk reduction for PFS was greater in women than in men. The ASCEND-4 study, that compared ceritinib to chemotherapy in untreated patients, was the only study that reported a better HR in PFS for men than for women."

Minor comments:

Comment 3: line 39: "molecules" should be "treatments"

Reply 3: we have replaced the word "molecules" with the word "treatments".

Comment 4: line 60: "may partly explain the epidemiological changes..." -what changes?

Reply 4: to better clarify the concept we have added the following sentence: ".. in terms of increased incidence of lung cancer in women". Lines 59-60.

Comment 5: line 62-64: "gender should always be an important stratification factor." This is opinion, should be backed with a reference or removed.

Reply 5: We have removed this sentence.

Comment 6: line 72: "using PubMed" - using what search terms? Search methodology not as critical to a narrative review, should either spell out methods or remove the mention of Pubmed, as by itself that tells me little.

Reply 6: The mention of PubMed was removed and replaced by the sentence "extended literature data collection". Lines 72-73.

Comment 7: Line 94-96: "some authors have speculated...It is well known..." should have a reference.

Reply 7: We added the following reference: 16) Kong A, Gudbjartsson DF, Sainz J, et al. A high-resolution recombination map of the human genome. Nat genet 2002; 31:241-247.

Comment 8: line 317: "Marchetti and coll" - coll[eagues]?

Reply 8: We removed this sentence

Reviewer C

Authors demonstrated the sex difference regarding oncogene-related NSCLC.

This review only listed the results of well-known clinical trials and did not provide any new findings. In current clinical practices for unresectable non-small cell lung cancer, the prognosis is greatly improved by changing the treatment depending on the type of genetic mutation, and the treatment is the same regardless of gender. In addition, since sex cannot be changed by treatment, this discussion seems meaningless.

Reply: Most of the reported studies demonstrate a consistent greater benefit in PFS, with the use of EGFR-TKis or ALK inhibitors, for women than for men. Sometimes this benefit also translates into an advantage in OS. The causes of this difference are not really known and, for this reason, it would be interesting to investigate them prospectively.

Reviewer D

Please see all the comments and suggestions added in the manuscript as attached. But please do not make revisions on this version of manuscript.

Some major points are listed as below but minor corrections are not included.

Comment 9: 1. Line 156. "A difference in PFS and OS was also observed between type of EGFR rearrangement: exon 19 deletions vs L858R point mutation (HR 1.92 [1.19–158 3.10]; p=0.02) and (2.98 [1.48–6.04]; p= 0.002) respectively."

This is somewhat confusing. What is the HR for PFS for exon 19 deletion and L858R mutation respectively?

What is the HR for Death for exon 19 deletion and L858R mutation respectively?

Reply 9: we changed the sentence as follows: "considering exon 19 deletions vs L858R point mutation the PFS HR was 1.92 [1.19–3.10]; p=0.02 and OS HR was 2.98 [1.48–6.04]; p= 0.002". Lines 157-158.

Comment 10: 2. Line 242. "These interesting but very preliminary data would suggest that the addition of an antiangiogenic drug (ramucirumab or bevacizumab) to erlotinib may be effective only in women and not in men. Unfortunately, no subsequent prospective studies have been conducted to confirm this finding which could have led to gender-based differential treatment."

In the RELAY trial, the HR for PFS was 0.51 for men, and 0.73 for women. In the **NEJ026** trial, the HR for PFS was 0.45 for women, and 1.06 for men.

Reply 10: we deleted the sentence. Lines 242-244.

Comment 11: Line 270. "However, you concluded that the combination of antiangiogenic drug and erlotinib may be effective only in women. This is not an appropriate conclusion from the results above. You should reframe this conclusion."

Reply 11: see reply 10

Comment 12: Again, what is the HR for PFS with ceritinib for men and women, respectively?

What is the HR for Death with ceritinib for men and women, respectively?

Reply 12: we changed the sentence as follows: "the HRs for PFS of ceritinib vs chemotherapy was 0.41 [95% C.I.: 0.27 to 0.63] in men and 0.63 [95% C.I.: 0.43 to 0.93] in women (Table 2). Unfortunately, Os data according to sex were not reported. " Lines 280-282.

Comment 13: Line 280. "Un update analysis of the ALEX trial demonstrated an overall survival advantage of Alectinib over Crizotinib with a HR 0.67 [95% C.I.: 0.46 to 0.98]; interestingly the figures were 0.76 for female, [95% C.I.: 0.45 to 1.28] and 0.66 for male [95% C.I.: 0.39 to 1.11] (40)."

Can you attempt to explain the discrepancy between the initial outcome of the ALEX trial and the outcome from the updated analysis?

Reply 13: we added the following sentence: " the discrepancy between the initial outcome of the ALEX trial and the outcome from the updated analysis is unclear. However, the difference in OS HRs according to sex was not significant". Lines 292-294.

Comment 14: Line 375. “It is interesting to note that when an anti-antiangiogenic monoclonal antibody (bevacizumab in particular) is associated with an EGFR TKI in order to boost up inhibition and clinical results the benefit in efficacy appears to be due to women only. As a matter of fact in the subgroup analysisof the NEJ026 trial women seemed to be the ones who benefited from the combination with a HR of 0.45 (0.28-0.73) versus 1.06 (0.58-1.94) in men.”

This is not an accurate conclusion.

Please, see my comment to this same conclusion on page 11.

The outcome of the RELAY trial favored men more than women, and the converse was true for the outcome of the NEJ026 trial.

You must state the actual findings of these studies and you may explain the discrepancies between them.

Reply 14: see reply 10

Comment 15: 6. Line 391. Conclusion

The data you presented above do not consistently favor the female gender. Therefore, this conclusion must be reframed.

Reply 15: as suggested we reframed the conclusion:

line 385-387: the sentence "Despite this, looking in detail the retrospective subgroup analyses, most of them reported a HR for PFS and/or OS consistently in favour of female patients over male." **was changed as follows**:

"Despite this, looking in detail the retrospective subgroup analyses, most of them reported a HR for PFS consistently in favour of female patients over male. The ASCEND-4 trial was the only one that reported a HR for PFS that favoured male patients over female."

line 377-381: the sentence "It is interesting to note that when an anti-antiangiogenic monoclonal antibody (bevacizumab in particular) is associated with an EGFR TKI in order to boost up inhibition and clinical results the benefit in efficacy appears to be due to women only. As a matter of fact in the subgroup analysis of the NEJ026 trial women seemed to be the ones who benefited from the combination with a HR of 0.45 (0.28-0.73) versus 1.06 (0.58-1.94) in men."

was changed as follows lines 396-400: " In order to boost up inhibition of EGFR receptor and clinical results, an anti-antiangiogenetic antibody (ramucirumab or bevacizumab) were associated with an EGFR TKI. Although both studies were stratified by sex, only the NEJ026 showed a greater benefit from the combination in favour of women. On the contrary, the RELAY trial gave opposite results. The reasons of these opposite results are unclear and should be clarified. "