

Peer Review File

Article information: <http://dx.doi.org/10.21037/tlcr-20-546>

Reviewer #1

This is a well-written review on a relevant topic made particularly current from recent preliminary results of the ADAURA trial reported at ASCO 2020. It well describes the state of the art of older and newer systemic treatments in the (neo)adjuvant setting of NSCLC, allowing the Reader to thoughtfully contextualize recent challenging data on the current background of established evidence. I would suggest rapid review process and publication after revision.

I have the following comments:

Major:

Comment 1: The recent results from the ADAURA trial should be adequately discussed (in the paragraph “Adjuvant TKI as a substitute of adjuvant Cht” and the “Discussion”) and reported in Table 4. Perhaps, the conclusions of the abstract should be accordingly reviewed i.e. I would suggest deleting the word “may” (page 1, line 8) in the sentence stating that TKIs and ICI are challenging the current standard of care.

Thanks for your comments, we have revised the manuscript as follows:

Reply 1:

- Added ADAURA results in page (p)17-18. Line (l) 444-467 and in Table 4.
- Added Survival data on CTONG1104 presented in ASCO 2020, p19, l: 478-494 and in Table 4.
- Abstract changed p 2, l: 9-19.

Comment 2: In the “Major pathological response as a surrogate endpoint”, I would consider adding at the end comment about the current definition of pCR and possible differences in this definition (i.e. following in the text a pCR with residual disease in hilar nodes is described for the NCT0225921 trial)

Reply 2:

Thanks for your comments , please see added paragraph on pCR definition p 7, l:144-152.

Comment 3: The paragraph “Conclusion” should be rather titled as “Discussion” and generally revised based on the ADAURA results (particularly in page 21-22, lines 327-333), but also by avoiding to repeat all the numbers already reported in the manuscript or Tables and enlightening more and more synthetically underlying concepts.

Reply 3:

Thanks for your comments, we have revised the manuscript as follows:

- Title changed to Discussion, p20, l: 521.
- ADAURA (and CTONG-1104) results added in discussion section p 23-26, l: 652-667 and l:672-757.
- Change numbers in Discussion section, p20-27

Comment 4: In Tables 1 and 3, I would suggest adding 2 columns reporting data about Grade \geq 3 toxicity and disease progression (PD) rate, respectively. In Table 4, I would suggest adding a column with data on Grade \geq 3 toxicity.

Reply 4:

Thanks for your comment. We have added columns of PD and AE \geq 3 in table, 1, 3 and 4.

Minor:

Comment 5: In the “Adjuvant chemotherapy” paragraph the sentence “Carboplatin-based Cht can be considered for patients not eligible for cisplatin” (page 4, lines 51-52) is not supported by the evidence discussed besides the stage IB (to which the reference refer), please clarify. In the same paragraph, the conclusion “although other platinum-based combinations are accepted” (page 4, line 55) screeches with the data previously discussed (i.e. the LACE meta-analysis); I would consider to delete it.

Reply 5:

Thanks for your comments. We have amended the manuscript as follows:

- In reference to “Carboplatin-based Cht.”, we have added that this refers to stage IB, p4, l:83
- In reference to “although other platinum-based combinations are accepted”. This is in line with ESMO recommendation, and we have added appropriate reference (Postmus PE, et al, Ann Oncol, 2017) p5, l:88

Comment 6: In the “Neoadjuvant chemotherapy” paragraph, I would add in the first sentence (page 4, line 60) “Vs Surgery alone”. In page 5, line 64 please check if the correct word is really “pre-operative” (as written) or likely “post-operative” or “peri-operative”. Page 6: line 80 it is already written that is an indirect meta-analysis, thus, in line 81 “indirect comparison analysis” is a repetition that could be deleted.

Reply 6:

Thanks for your comments. We have amended the manuscript as follows:

- Changed to “Vs Surgery alone” p 5, l:95
- Pre-operative has been changed to perioperative in p5, l:101

Comment 7: In the “Major pathological response as a surrogate endpoint”, please specify how many NSLC specimens were analysed by Junker et al. (page 6, line 91) and for both the studies mentioned which was the percentage of MPR observed (page 6, lines 91-95).

Reply 7:

Thanks for your comments.

We have added the number of specimens analyzed in p7, l:153-157.

-

Comment 8: In the “(Neo)adjuvant immune checkpoint inhibitors” paragraph: consider to add the following meta-analysis on the use of IO+CT as a reference in page 7 line 105 PMID: 31058078; to mention the combination of ICI doublet with Nivolumab plus Ipilimumab and limited Cht as for the recent interim analysis of the CheckMate-9LA trial (<https://news.bms.com/press-release/corporatefinancial-news/us-food-and-drug-administration-approves-opdivo-nivolumab-ye-2>); page 7, line 109 delete “(neo)” since evidence refers only to the use of adjuvant ICI in melanoma.

Reply 8

Thanks for your comments.

We have amended the manuscript as follows:

- We have added ICI meta-analyses on p8, l:192-195.
- We have added ICI doublet trials on p8, l: 188-190.
- We have Added CheckMate-9LA trial on p8, l: 190-192.

Comment 9: In the “ICI doublet” paragraph: page 11 line 162, the “t” of twenty is not capital; at the end of the paragraph, a summary sentence describing at least ongoing trials (reported in Table 1), particularly RCTs with drugs and expected date of results should be added. A similar sentence should be added at the of the “Adjuvant immune checkpoint inhibitors” paragraph (page 12, line a174).

Reply 9

Thanks for your comments. We have amended the manuscript as follows:

- “t” has been corrected on p14, l: 361.
- We have added a summary paragraph for neoadjuvant trials in Table 1. p12-13, l: 282-289, 299-346.
- Expected date of results are already present in Table 1,2,3 and 4. Please see column “completion date”
- We have added a paragraph to summarize upcoming trials in Table 2, p 13, l:322-325.

Comment 10: In the “Neoadjuvant Tyrosine Kinase Inhibitors” paragraph: page 14 line 216 please check the right percentage, i.e. 91% as reported in the text or 90% as in the Table?; page 15, line 220, I would suggest correcting the sentence in two possible ways, or “The FLAURA trial granted FDA and EMA approval of Osimertinib for the first line...” (preferred) or “The FLAURA trial set a new standard of care for the first line...”.

Reply 10:

Thanks for your comments. We have amended the manuscript as follows:

- We have corrected the percentage as 91%, amended in Table 3.
- We have amended the sentence “The FLAURA trial granted FDA and EMA approval of Osimertinib for the first line...” in p16, l:399.

Comment 11: In the “TKI as consolidation therapy following adjuvant Cht” paragraph: page 15, line 230, please rephrase the first sentence to better explain the meaning of “is hampered by the fact that EGFR status was not an inclusion criterion”.

Reply 11:

Thanks for your comment. We have amended the deleted the sentence on p 16, l: 411.

Comment 12: In the “Adjuvant TKI as a substitute of adjuvant Cht”: page17, line 263, add “absolute” to “The 3-year DFS difference” and check the percentage which should be 24% instead of 26%, as reported in the Table.

Reply 12:

Thanks for your comments. We have amended the manuscript as follows:

- We have added “absolute” on p 20, l: 505.
- The 3-year DFS absolute difference between EVAN and CTONG trials is 34%. We have amended text on page 20, l: 506.

Comment 13: In the “Conclusion” paragraph” page 20, line 312-313 the sentence should be clearer written/explained.

Reply 13:

Thanks for your comment. We have amended the sentence on p27, l:773-787.

Comment 14: In Table 1: put a footnote regarding the pCR of the first-mentioned study (NCT02259621) to specify that pCR included residual disease in hilar nodes; specify the number of cycles of Cht+ICI for the Checkmate 816 and 77T; consider to add a row with subtitles before each series of studies reported: i.e. neoadjuvant monotherapy, neoadjuvant combination, etc.. as reported in the descriptive text.

Reply 14:

Thanks for your comments. We have amended the manuscript as follows:

- We have added a footnote in table 1 in reference to pCR.
- We have not been able to find information regarding the number of cycles of Cht+ICI in the Checkmate 816 and 77T trials
- We have added a row with subtitles ICI monotherapy , ICI + Cht added to table 1

Comment 15: In Table 3: in the title the “completely resected” should be deleted since neoadjuvant studies are reported; indicate the duration of TKI before surgery for Rizvi et al (page 32)

Reply 15:

Thanks for your comments. We have amended the manuscript as follows:

- In table 3, we have deleted title: “completely resected” as requested

- We have added duration of TKI indicated in Rizvi et al ton Table 3.

Comment 16: In Table 4: consider renaming the column regarding DFS including mo. and the 2-year DFS to help the reading of data; put a footnote for the NC-T00049543 study (page 34) about the “molecular driver column” specifying that 3% of the “not EGFR selected” patients had EGFR mutations.

Reply 16:

Thanks for your comments. We have amended the manuscript as follows:

- We have added a 2-year DFS column to table 4
- We have added a footnote regarding “EGFR not selected”

Comment 17: In all Tables: check alignments of text; indicate references numbers for all the studies.

Reply 17

Thanks for your comments. We have checked the alignments and added references for studies in tables 1-4.

Reviewer #2

The aim of the review is to summarize and discuss the evolution and the potential applications of immunotherapy and target therapy in the treatment of early non small cell lung cancer. Data are clearly presented, and the topic is well developed.

Comment 1: Authors should complete their discussion including recent data from the ADAURA trial, presented at the virtual American Society of Clinical Oncology meeting.

Reply 1:

- Added ADAURA results in page (p)17-18. Line (l) 444-467 and in Table 4.
- Added Survival data on CTONG1104 presented in ASCO 2020, p19, l: 478-494 and in Table 4.

Moreover, two specific corrections are needed:

Comment 2: - in line 54 the sentence “*can be considered in stage IB > 4cm*” (according to TNM VIII edition stage IB includes tumors not more than 4 cm in greatest

dimension),

Reply 2:

Thanks for your comments. We have amended the manuscript as follows:

- We have amended “*can be considered in stage IB > 4cm*” in p 5, l:86-87.
- We have added clarification with regards to TNM 7th and 8th ediction, p3,l: 54-59.

Comment 3: - in line 70 insert the specific reference for cited systematic review (“*the addition of this results to a systematic review of N-Cht of 1507 patients resulted in an equivalent improvement of 5% in 5-years OS*”).

The correction of some typing errors and a further English language revision will certainly improve paper quality.

Reply 3:

Thanks for your comments. We have amended the manuscript as follows:

- The sentence refers to same reference previously given in the paragraph (12), we have added for clarification on p 5, l:111.
- We have extensively revised the manuscript to correct typing errors