

Peer Review File

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Reviewer A

The original article, entitled “Immunotherapy for non-small cell lung cancer with EGFR or HER2 exon 20 insertion mutations: a real-world analysis” by Mai Zhang, et al. showed that that first-line ICI treatment might be beneficial for NSCLC patients with EGFR or HER2 ex20ins mutations. The reviewer respectfully provides the following comments:

Comment 1: PD-L1 is an important biomarker for immunotherapy. Please indicate the number of patients with PD-L1 \geq 50% in Table1.

Reply 1: we added some data in Table1 (see Page 17, line 520).

Changes in the text: Table 1.

Comment 2: The authors need to consider whether PD-L1 expression is a biomarker for immunotherapy in patients with EGFR or HER2 exon20ins.

Reply 2: We have considered your concerns and do not believe that our data are sufficient to support PD-L1 expression as a predictive biomarker for immunotherapy in patients with EGFR or HER2 exon20ins.

Changes in the text: we added some data in Paper (see Page 12, line 372).

Comment 3: PD-L1 should be added to the stratification factor for propensity score matching.

Reply 3: The expression of PD-L1 was included in the PSM matching score and 10 pairs were re-matched. The mPFS numbers of PSM before and after matching were the same, but the confidence intervals were different.

Changes in the text: we added some data in Paper (see Page 9, line 261), (see Page 2, line 56), we added some data in Table3 (see Page 18, line 528), we change the in Figure1/2/3 (see Page 20-21, line 538)

Comment 4: Please show the number of patients who received single-agent immunotherapy and the number of patients who received combination chemotherapy respectively in Table1. These patient groups should be analyzed separately in comparison with chemotherapy.

Reply 4: We have added this part of the data, but only the mPFS comparison, mOS do not reached.

Changes in the text: we added some data in Table1 (see Page 17, line 520), and in Paper (see Page 7,line 196) (see Page 8, line 217) (see Page 8, line 248).

Comment 5: Please provide analysis of overall survival (OS), if available.

Reply 5: We added mOS for all chemotherapy and all immunotherapy, but mOS for first-line, second-line and postline immunotherapy was not reached.

Changes in the text: we added some data in Table2 (see Page 18, line 524), and in Paper (see Page 7,line 201) (see Page 8, line 223) (see Page 8, line 241).

Reviewer B

This is an interesting real-world analysis of a cohort of 72 patients with EGFR/HER2 exon 20 insertion mutations according to the type of treatment received. The authors conclude that,

indirectly compared, regimens incorporating immunotherapy with chemotherapy in the 1st line setting seem to add clinical benefit and suggest a role for immunotherapy in these patients. Although the study is clinically relevant and merits to be published, it harbors some drawbacks that need to be addressed before publication:

Major points:

1. In the discussion part, the limitations of the study are not clearly stated. The authors should devote at least one paragraph instead of 2-3 lines, mentioning the following:

a. The study was retrospective, single -centered. All response evaluations were performed at timepoints that were arbitrary according to the Treating-physician's discretion and not in pre-defined intervals, as in prospective trials. Therefore, PFS is not a real PFS but rather a time-on-treatment.

**Reply: Your comments are very insightful and useful, and we have modified our text as advised.
Changes in the text: (see Page 13, line 395)**

b. All comparisons are made between not balanced, randomized subgroups and are therefore subjective to bias.

**Reply: We have modified our text as advised.
Changes in the text: (see Page 13, line 397)**

c. The numbers are too small to derive any definite conclusions.

**Reply: We have modified our relevant language to express it in text as advised.
Changes in the text: (see Page 13, line 393)**

2. All comparisons between trials mentioned in the discussion are indirect, comparing RWD with randomized trials and this should be interpreted with caution.

The authors should compare their findings to other RWD studies, like the IMMUNOTARGET study (Mazieres et al. Annals of Oncology 2019) and the EXOTIC registry (Mountzios et al, JTO-CRR 2022).

**Reply: Thank you very much for your offer. We carefully read the relevant literature suggested and added a discussion analysis of the conclusions of this and two articles.
Changes in the text: (see Page 11, line 344). (see Page 12, line 350).**

MINOR COMMENTS

1. "A recent study 321 reported that CUR-DOX/cRGD-M combination therapy promoted apoptosis in lung 322 cancer cells, which may have potential clinical value for the combined ICI treatment 323 of lung cancer (25)." Please clarify the acronyms.

**Reply: We explained the acronyms for this part in more detail and modified our text as advised.
Changes in the text: (see Page 12, line 368)**

2. The whole manuscript needs linguistic and syntactic improvements and should be revised by a native English speaker.

**Reply: We haven't found the right person to edit the article yet.
Changes in the text: None**

Reviewer C

Comment 1: Please defined ICIs and CI in the abstract.

Reply: ICIs stands for immune checkpoint inhibitor, and CI stands for confidence interval. Changes in the text: see Page 2, line 43 and 50.

Comment 2: Figure 1 and 2

a) Please check whether this is figure 1 with 2 parts (A and B), or they are figure 1 and figure 2? In the main text, you've cited them as figure 1 and figure 2.

Figure 1 Progression-free survival. (A) First-line PFS for the total immunotherapy and chemotherapy cohorts;

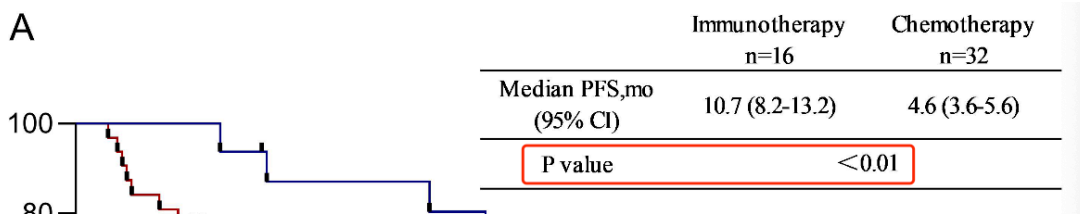
Figure 2(B) PFS for the propensity score-matched immunotherapy and chemotherapy cohorts. PFS, progression-free survival; mo, months.

276 (10.7 vs 4.6, P=0.001). (Figure 1). There was a trend for an increased ORR in patients

285 PSM cohort (P=0.028) (Figure 2). The ORR of immunotherapy was close to that of
286 chemotherapy (50% vs. 40%, P=1.000).

b) Please check if the p value matches with the figure.

276 (10.7 vs 4.6, P=0.001). (Figure 1). There was a trend for an increased ORR in patients



Reply:

a) Previously, figure 1 with 2 parts (A and B). But now we split one image into two separate figures (figure 1 and figure 2)

b) We calculated the p value again and found that the p value was indeed < 0.001, and we changed the place where the expression was incorrect.

Changes in the text: see Page 9, line 256. The corrected picture have been resented to you.

Comment 3: Please explain EGFR and HER2 in the table footnote.

Reply: We added the content in Table 1.

Changes in the text: see Page 18, line 531.

Comment 4: Please explain PD-L1 in the table footnote.

Reply: We added the content in Table 3.
Changes in the text: see Page 19, line 541.

Comment 5: Please add the description to the table footnote that how the data are presented in table. Should here be “n (%)”?

Reply: We added the content in Table 4.
Changes in the text: see Page 19, line 545.