Peer Review File

Article Information: Available at http://dx.doi.org/10.21037/tlcr-20-824

Reviewer A

This was a straightforward phase 1b of bevacizumab at recommended dose in NSCLC combined with escalating doses of afatinib. The design, conduct and conclusions from the study are sound.

The reader has some comments and questions:

Comment 1: What EGFR TKI were the previously treated pts exposed to? Did the previously treated pts carry the EGFR exon 20 T790M mutation?

Reply 1: Thank you for your comment. Of the 5 previously treated patients, 4 had been treated with first-generation EGFR-TKIs (gefitinib or erlotinib) and 1 with third-generation EGFR-TKI (investigational new drug). There was no patient whose tumor had been shown to have exon 20 T790M mutation prior to treatment in this study.

Changes in the text: We added the information of previously administered EGFR-TKIs to the table 1 (see Table 1).

Comment 2: What was the median number of cycles for the pts enrolled on the RP2D of this combination?

Reply 2: Thank you for your comment. The median number of treatment cycles for the patients enrolled on the RP2D is 12.5 (range; 4–28) cycles.

Changes in the text: We added these data to the revised manuscript (see page 15, line 8).

Comment 3: Were there differences seen in depth of response and duration of response between exon 21 and exon 19 del pts? The pre-treated single pt with CR in the study should be further detailed - how long did the CR last, what was the underlying pt/tumor characteristics.

Reply 3: Thank you for your interesting comment. In accordance with your comment, we made supplemental figures to show the difference in depth of response and progression-free survival between exon 21 and exon 19 del. Progression-free survival tended to be longer in exon 19 del, although the difference is not clear due to the small number of cases.

We apologize for the error in Figure 1. Actually, the patient with CR was an EGFR-TKI naïve case. Thank you for pointing that out. We had rectified figure 1 in the revised version. The patient with CR was a 65-year-old male. The patient with postoperative recurrence of lung adenocarcinoma harboring *EGFR* exon 21 L858R mutation was treated with afatinib plus bevacizumab as first-line

treatment. After 6 months of treatment, the study treatment was discontinued due to skin rash, and second-line treatment was started before the disease progression.
Changes in the text: We made supplemental figure S1, S2, S3, and S4 (see supplemental files), and we added a sentence to the revised manuscript (see page 16, line 14). In addition, we rectified figure 1 (see figure 1 file).

Comment 4: The rebiopsy tumor T790M rate is lower than expected. What other resistance mechanisms were present at this rebiopsy in the 62% who did not carry T790M mutation?
Reply 4: Thank you for your important comment. In this study, 8 patients underwent re-biopsy, and T790M mutations were identified in 3 of 8 patients (38%). As you pointed out, the T790M rate is lower than expected. However, due to the small sample size, the positive rate of T790M mutation could be variable by chance. All 8 patients were tested for resistant mechanism only using the cobas® EGFR Mutation Test v2. Unfortunately, we had not examined other genetic mechanisms.
Changes in the text: We added a sentence to the revised manuscript (see page 17, line 6).

Comment 5: There are spelling errors found which need to be corrected e.g.Pg 15, Line 9.
Reply 5: Thank you for your comment. We had corrected the spelling errors.
Changes in the text: We had corrected the spelling errors (see page 18, line 15; page 19, line 2 in the revised manuscript).

Reviewer B

Comment 1: The study is well conducted, but phase I studies on combinations of old drugs are uninteresting if not supported by subsequent studies.
Basically, the paper has a logic and clear structure. The title is appropriate for the content of the article. The abstract is concise and accurately summarizes the essential information of the paper, including principal findings and endpoints of the study. There is a sufficient background chapter and the design of the study is simple but clearly comprehensible. The results reported are effective. The discussion is coherent according to authors' purpose and conclusions are consistent with the results presented. References are correct and updated. Finally tables and figures are clear and aid understanding. The paper is pretty well written even if it may require english language editing in some points. The language is quite fluent and the article results understandable and easy to read.
Unfortunately, the topic of the article is no longer current after the publication of phase II and III studies on the association of EGFR-TKIs and angiogenesis inhibitors (bevacizumab and ramucirumab).

Reply 1: Thank you for your valuable comment. As noted in the discussion section, a randomized phase II trial to compare the efficacies of afatinib and afatinib plus bevacizumab in patients with treatment-naïve NSCLC harboring *EGFR* mutations is ongoing (CRB6180001). Subject enrollment of this trial had already been completed and the results are expected to be published in the near future. The data from our study may be useful in evaluating the results of this randomized phase II trial and considering development plans of this combination therapy. As you said, the results of phase II and III trials of EGFR-TKIs in combination with angiogenesis inhibitors are being reported. However, first-generation EGFR-TKIs have been used in most of them, and there are few reports of second-generation EGFR-TKIs in combination with angiogenesis inhibitors. We have already described it in the introduction section (page 8, line 5 – page 8, line 13 in the revised manuscript). There is a difference in mode of action between first-generation and second-generation EGFR-TKIs, and also superiority of survival has been shown in a clinical trial (Mok TS, et al. J Clin Oncol 2018; 36: 2244-2250). Therefore, we still believe that our study will provide helpful information to readers of *translational lung cancer research*, even after the results of the trials on first-generation EGFR-TKIs are published.

Changes in the text: No changes.