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Reviewer A

The manuscript based on the protocol design, study to be carried out in neoadjuvant camreluzimab, plus nab-paclitaxel and carboplatin in early-stage non-small cell lung cancer looks very efficiently designed and feasible and optimizing molecular and immune landscape testing. Perhaps it could be better specified the correlates with potential assessment of the tumor microenvironment, any consideration to classify the resected tumors according to the predominant sub-class of macrophages?

For your perusal, see the recent review Krishnamoorthy et al. Neoadjuvant immunotherapy for high-risk, resectable malignancies: scientific rationale and clinical challenges. JNCI J Natl Cancer Inst 2021.

Comment 1: Perhaps it could be better specified the correlates with potential assessment of the tumor microenvironment, any consideration to classify the resected tumors according to the predominant sub-class of macrophages?

Reply: Thank you very much for your constructive suggestion on our study, which have helped our study improve to a higher scientific level. The references you mentioned was greatly help us to further understand the possible changes of cellular mechanisms that occur during neoadjuvant immunotherapy. Macrophages not only play a role in chronic inflammation by secreting various factors and influencing other immune cells, but also can initiate, promote or inhibit the development of cancer. As we mentioned in our manuscript, we will collect the patients' tumor tissue samples and blood samples for whole genome sequencing, whole transcriptome resequencing, and single-cell sequencing (See Page 9, line 152-155), which will include the patient's macrophages data information. In future data analysis, we would like to consider the correlation analysis between the predominant sub-class of macrophages and the immunotherapy benefit of patients. If it could be used to further classify the resected tumors, that would be great significance. We appreciate your insightful suggestion.

Reviewer B

It is an interesting approach - and for example due to personal studies radiomics of PDL1 is linked to enhanced CT data much better than to PETCT data. It is a little bit surprising that 40 patients seem to be enough to show significance with the predicted AI model. For me unclear is why you expect an MPR of >42% in the defined triple-therapy - could you include a comment on this question? Furthermore, you do not exclude smokers - and it is well known that there is quite interference of PDL1 expression and smoking habit. I would fear that with 40 patients only there will be a non-predictable bias due to smoking habits. Please include a comment on this.

Comment 1 : For me unclear is why you expect an MPR of >42% in the defined triple-therapy - could you include a comment on this question?

Reply: We appreciate your insightful question, and we are glad to answer this question in detail. In the NATCH trial (1), patients receiving neoadjuvant chemotherapy achieved an MPR of 22.8%. And studies show that in patients receiving neoadjuvant ICI monotherapy, the MPR was 17% in Neostar trial (2), and 19% in LCMC3 trial (3). We believe that the MPR of patients receiving neoadjuvant immunization monotherapy can achieved about 20%. Therefore, the MPR is expected to be> 42.8% in this study. we hope our explanation can satisfy you.

Comment 2 : Furthermore, you do not exclude smokers - and it is well known that there is quite interference of PDL1 expression and smoking habit. I would fear that with 40 patients only there will be a non-predictable bias due to smoking habits. Please include a comment on this.

Reply: We appreciate your insightful question, and we are glad to answer this question in detail. There are studies have discussed on this question. Recent subgroup analysis of KEYNOTE-042 study (4) showed no significant OS benefit in both never smoking subgroup of patients for PD-L1 positive expression, regardless of PD-L1 TPS≥1%, ≥20%, or ≥50%. While, subgroup analysis of the KEYNOTE-189 study (5) showed a better OS benefit in never smoking NSCLC patients than current or former smoking patients that treated with Pembrolizumab in combination with first-line chemotherapy. In a recent study (6), researchers retrospectively analyzed the association between smoking and ICIs activity in 315 NSCLC patients with PD-L1

TPS≥50% ， and results show that the effect of smoking history was found to be smaller than expected, with a significant number of never smokers and light smokers benefiting from immunotherapy. In addition, Heavy smokers benefited more from immunotherapy, although there was no significant difference in clinical efficacy. Although higher TMB levels in heavy smokers may make the benefits of immunotherapy more significant, smoking status alone does not fully explain the complexity of neoantigen production and presentation. Therefore, there was no inclusion restriction on patients' smoking status and look forward to further discussion by subgroup analysis of smoking status in our study. Here, we thank you for raising such a meaningful question.

Reference:

1. Felip E, Rosell R, Maestre J, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010;28(19):3138-3145.
2. Cascone T, William W, Weissferdt A, et al. Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study. J Clin Oncol 2019;37 (suppl; abstr 8504).
3. Rusch V, Chaft J, Johnson B, et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): interim analysis and biomarker data from a multicenter study (LCMC3). J Clin Oncol 2019;37(15_suppl):8503-8503.
4. Wu Y, Zhang L, Fan Y, et al. Randomized clinical trial of pembrolizumab vs chemotherapy for previously untreated Chinese patients with PD-L1-positive locally advanced or metastatic non-small-cell lung cancer: KEYNOTE-042 China Study. Int J Cancer 2021;148(9):2313-2320.
5. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378(22):2078-2092.
6. Gainor J, Rizvi H, Jimenez A, et al. Clinical activity of programmed cell death 1 (PD-1) blockade in never, light, and heavy smokers with non-small-cell lung cancer and PD-L1 expression ≥50. Ann Oncol 2020;31(3):404-411.

Reviewer C

In this study, the authors planned to evaluate the clinical utility of neoadjuvant therapy with camrelizumab, nab-paclitaxel and carboplatin for resectable NSCLC. Although their procedure may provide the new strategy for neoadjuvant therapy in Stage IB-IIIA NSCLC. there are several questions about their clinical trial.

Comment 1 : On page6, line 83, the authors cited KEYNOTE-001 as a reference, is it correct?

Reply: We were sorry about this mistake in our text and sincerely thank you for your kindly correction. This reference has been checked and revised. And the correct reference "Shu C, Gainor J, Awad M, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21(6):786-795." was used to replace the wrong one.

Changes in the text: See Page 6, line 85; Page 16, line 299-301.

Comment 2 : In this study, CTCAE ver4.0 is used to evaluate the adverse events. Why is old version used?

Reply: We appreciate your insightful question, this is exactly what we found in our first manuscript submission. After careful consideration, we think that the latest CTCAE version should be used, and then we have submitted an application for scheme modification to the ethics committee of our hospital. Recently, the modification has been passed. We will incorporate this change into our manuscript.

Changes in the text: See Page 10, line 179.

Reviewer D

This article is protocol concept article. Only minor comments.

Comment 1: In line 83, The content of the text does not match the reference. Please correct.

Reply: We were sorry about this mistake in our text and sincerely thank you for your kindly correction. This reference has been checked and revised. And the correct reference "Shu C, Gainor J, Awad M, et al. Neoadjuvant atezolizumab and

chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21(6):786-795." was used to replace the wrong one.

Changes in the text: See Page 6, line 85; Page 16, line 299-301.

Comment 2: Please add when this study starts and how long study plan to register clearly.

Reply: We appreciate your insightful suggestion and agree that it would be better to show our studies 'time plan to the readers who were interest in this study. We have added that "Study status This study was opened to recruitment in August 2020. We're going to finish enrolling patients in the study over the next two years." in our text.

Changes in the text: See Page 13, line 228-230.

Comment 3: Please describe in a little more detail how to analyze artificial intelligence.

Reply: We appreciate your insightful question, and we glad to further describe our artificial intelligence (AI) analysis process. In the process of AI analysis, convolutional neural network (CNN) deep learning will be used to train images, and a variety of algorithms, including GoogLeNet, RetinaNet, ResNet, RCNN, fast-rCNN, fath-rCNN, VGGNet and other network algorithms will be used to carry out feature extraction, screening, modeling and verification. At the same time, transfer learning algorithm will be used, which refers to the method of transferring the pre-trained CNN model to other dataset and relearning the characteristics of the target dataset. Data augmentation will be adopted to increase the size of the training dataset and expand the existing samples by iterations of random translational shift, rotation, and horizontal and vertical flips. The effectiveness of the model was evaluated by mapping the diagnostic specificity curve (ROC) of the predictive model and calculating the corresponding area under the curve (AUC), diagnostic accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and 95% confidence interval. Based on the deep survival /Cox proportional risk regression /logistic regression model, the image omics characteristics, tumor microenvironment indicators, clinical pathology and other factors were included in the model as

alternative factors, and the artificial intelligence accurate prediction system was established. We have made additional description in the statistical analysis section.
Changes in the text: See Page 11, line 195-203.

Reviewer E

I think that this paper is worth publishing.

Reply: We are very pleased that this manuscript has been recognized by you, which greatly encourages us! We sincerely appreciate your affirmation.