Peer Review File

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Reviewer A

The manuscript investigates the biological characteristics of early-stage non-squamous non-small cell lung cancer (Ns-NSCLC) patients, particularly in the Chinese population. Employing multi-omics interrogation, including whole-exome sequencing, RNA sequencing, and T-cell receptor sequencing, the study explores genomic alterations, cytoband amplifications, and immune-related gene expression. The findings reveal significant associations with disease-free survival (DFS) and provide insights into the unique biology of early-stage Ns-NSCLC.

1) The overall writing has some formatting issues, like wording, spacing, and some redundancy. I suggest the authors check the grammar and avoid any typos. More importantly, the writing needs improvement for readers to understand more easily.

Reply: Thank you very much for your valuable comments. We have checked throughout the text and revised accordingly.

2) The analysis methods are lack of details. The authors need to provide more descriptions on the analysis methods. Moreover, I would recommend the authors to make figures with high resolution, as well as consistent font styles with the manuscript.

Reply: Thank you very much for your valuable comments. We have revised accordingly.

Changes in the main text: Page 16, line 317~321: "The genomic profiles, mRNA expression, and clinical characteristics data of lung adenocarcinoma samples from the TCGA-LUAD cohort were downloaded from the UCSC Xena (https://xena.ucsc.edu/) database (acquisition date, 2023/1/11)."

Page 10, line 191~194: "The cancer cell fraction of mutations was calculated by PyClone, with the tumor purity computed by All-FIT. The proportions of subclone mutations to all mutations were defined as ITH."

Page 13, line 258~261: "MCP-counter, a versatile computational approach which robustly quantifies the absolute abundance of two stromal and eight immune cell populations from bulk transcriptomic data, was also exploited (1)."

3) I recommend the authors to include some discussions on related studies using different omics data (PMID: 33461059; PMID: 35284940), which helps expand the scope of the study.

Reply: Thank you very much for your valuable comments. We have revised accordingly.

Changes in the main text: Page 33, line 703~711: Studies using other different omics also succeeded in predicting the prognosis and immunotherapy response of cancers. For instance, Triozzi and colleagues developed a metabolomic signature that correlated with glycolysis to characterize the ICI responders of melanoma (2). Moreover, they also found that higher extracellular acidification rate and lactate-to-

pyruvate ratio were prognostic of superior outcomes. Proteomics narrows the gap between cancer genotypes and phenotypes and has paved the way for precision oncology in recent years. Lately, Harel et al. proposed a predictive signature of ICI response of NSCLC based on plasma proteomic profiling, including CXCL8 and CXCL10 proteins (3).

4) There are a lot of similar bioinformatics work. I would recommend the authors discuss their method advantages over the other bioinformatics work (e.g. PMID: 34956864) that also uses survival analysis to help reveal potential biomarkers.
Reply: Thank you very much for your valuable comments. We have revised accordingly.
Changes in the main text: Page 32, line 683~686: "However, we could not further determine the cellular sources of expression of these genes and their correlations with other known druggable targets like by single-cell RNA sequencing (4) and multiplex immunofluorescence (5)."
Page 33, line 694~695: "Additionally, we also parsed the different tumor microenvironment landscapes concerning different genomic alteration patterns, benefiting from a multi-omics setting."

Reviewer B
This is a very interesting, complete and strong study to understand the hallmarks of lung cancer in a very specific population (early stage, NSCLC, Chinese population) and maybe we can improve clinicals benefits knowing better biologically the disease. With now the strategy of neo adjuvant (except for EGFR and ALK patients), it would be very interesting to do the same study and compare results to see in which way it differs.
Reply: Thank you very much for your valuable comments. In the present study, we found that higher tumor mutational burden level, higher tumor neoantigen burden level, wild-type EGFR status, and early tumor stage correlated with higher CD8+ T lymphocyte infiltration in the tumor microenvironment. Accordingly, our concurrent study also observed that higher pretreatment lymphocyte count levels correlated with superior response of non-small cell lung cancer patients receiving neoadjuvant immunochemotherapy (6). Additionally, we attempt to undertake a prospective cohort study to investigate the prognostic and predictive effects of these genomic, transcriptomic, and TCR repertoire-associated markers on (neo-adjuvant) immunotherapy efficiency and have obtained phased achievements (7, 8).
Changes in the main text: None.

References
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