Peer Review File

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Reviewer A

Introduction:

Comment 1: I would suggest updating the reference for the first paragraph. GLOBOCAN statistics were updated and data from 2022 already shows lung cancer as the most incident and deadliest. Also, the last sentence of this paragraph does not have a reference.

Reply 1: References have been updated for the 2022 version. The last sentence of this paragraph has been added as a reference.

Changes in the text: In line 95-97;In line 100.

Comment 2: Although the mentioned on the last paragraph that they the prognostic impact of Napsin A on this subset of patients, it was unclear the purpose of doing that. Is there something in current literature that correlates these two biomarkers or are they trying to find new correlations? A sentence or two to explain it would enhance the quality of the introduction section (the first time the hypothesis was mentioned was on line 224).

Reply 2: At present there is no conclusive evidence about the association between SMARCA4 and NapsinA. We combined the latest research reports and the content of this study to try to find new evidence of association between the two.

Changes in the text: In line 120-122.

Methods:

Comment 3: Line 103: PD is abbreviated, and the full form is not mentioned before. Review that.

Reply 3: Full name has been added.

Changes in the text: In line 151-152.

Discussion:

Comment 4: First paragraph could be more explanative. Are the data described/find the most common for SMARCA4 or there were any discrepancies between previous reports?

Reply 4: The first paragraph has been supplemented with more explanation.

Changes in the text: In line 240-245.

Comment 5: Also, it was surprising to see such few data on metastatic patients and see that most patients were early-staged disease on the TCGA cohort, while the table 2

describes a more common pattern for NSCLC cohorts. Do the authors have a comment on that?

Reply 5: There is not much explanation for the data on TCGA. We surmised that the enrolment population may have been case data from early screening and therefore most patients were early stage lung cancer patients.

Changes in the text: None.

Comment 6: Does the patients who were NapsinA+ and SMARCA4+ had other concurrent mutations such as TP53 or KEAP1, which naturally are also bad responders to systemic treatments? A comment for patients' concurrent mutations in this specific subset would enlighten the discussion.

Reply 6: Mutation data for TP53 and KEAP1 in SMARCA4 are supplemented in Appendix Table 1. For TP53 survival data, we performed K-M survival analysis of OS for both SMARCA4 mutant-NapsinA (+) and NapsinA (-) groups, which resulted in a statistically non-significant result of P=0.128.

Changes in the text: Annex Table 1

Annex Table 1

	TP53	KEAP
SMARCA4-Mut（n=20)	12（60%）	1（5%）
SMARCA4-Wt（n=40)	23（57.5%）	3（7.5%）
SMARCA4-Mut-NapsinA （+） (n=8)	6（75%）	1（12.5%）
SMARCA4-Mut-NapsinA （-） (n=12)	6（50%）	0（0）

Comment 7: The last paragraph mentioned potential pitfalls for the study. Do the authors believe that this sample size has enough power to describe such correlation between these two mutations among subjects, in fact yielding different prognosis? Do the authors believe that this correlation might be considered on novel RCT subgroup analysis?

Reply 7: SMARCA mutations are clinically rare mutations, and the data collected in our clinical centre consisted of 26 cases, of which 17 were available for survival analysis. Due to the small sample size, in order to ensure the accuracy of the results, we used propensity matching to select the negative cohort according to a ratio of 1:2 to avoid errors caused by different baseline information in the two groups. In addition, we have fully considered the small sample size when choosing statistical methods to ensure correct analyses at every step. We believe that this correlation can be

considered in new RCT subgroup analyses for more in-depth analyses and studies.
Changes in the text: None

Tables:
Comment 8: I would suggest that continuous variables such as age would be treated as mean and standard deviation. The subgroup is too small for comparisons.
Reply 8: Already add the average age.
Changes in the text: In Table 2

Additional comment:
Comment 9: I could not find the expression rate for KRAS mutations as well as STK11 mutations among subjects. Was no identification of those mutations?
Reply 9: KRAS mutations as well as STK11 mutations were present, but only the top 20 mutated genes in each of the positive and negative groups are shown in the text due to the large number of mutated genes. We have added the expression of KRAS and STK11 genes in Appendix Table 2.
Changes in the text: Appendix Table 2
Annex Table 2

	SMARCA4-Mut group (N=20), n (%)	*SMARCA4*-WT group (N=40), n (%)
KRAS	2(10%)	2(5%)
STK11	0(0%)	2(5%)

Reviewer B
Comment 1: Thank you for submitting your exciting work. The 5th edition of the WHO Classification of Thoracic Tumors introduces a new entity called "Thoracic SMARCA4-deficient undifferentiated tumor". I suggest including more details about this entity in your paper. It has a poorer outcome than SMARCA4-deficient conventional NSCLCs.
Reply 1: Already added.
Changes in the text: In line 111-113.

Reviewer C
Comment 1: Although SMARCA4 mutation is handled as the single type, there must be difference among type of mutation, i.e., SNV, deletion, etc. It would be better to clarify the type of mutations.
Reply 1: NonSynonymous_Substitution 7 case, Synonymous_Substitution 5 case, Intronic 4 case, Nonsense_Mutation 3 case, Splicing 1 case.

Changes in the text: In line 200-202.

Comment 2: They excluded three patients from the cohort after PSM. Considering the small number of patients, this may lead to imbalance. It would be better to exclude these patients before PSM.

Reply 2: Due to the rarity of SMARAC4 gene mutations in clinical practice and the small amount of data in this sample, we decided to retain the original enrolment population after comprehensive consideration. However, in order to avoid differences caused by the exclusion of three people at a later stage, we analysed the baseline data again for the excluded data to ensure the consistency of the two groups.

Changes in the text: Annex Table 3

Annex Table 3 Patient characteristics (retrospective cohort)

	SMARCA4-Mut group (N=17), n (%)	*SMARCA4*-WT group (N=40), n (%)	P value
Age (years)			0.583
＜65	9（53.0%）	18 (45.0%)	
≥65	8（47.0%）	22 (55.0%)	
Gender			0.392
Male	9	26 (65.0%)	
Female	8	14 (35.0%)	
Smoking status			0.754
Smoker	4（23.5%）	11 (22.5%)	
Never	13（76.5%）	29(77.5%)	
Lymph node metastasis			0.767
Yes	13（76.5%）	32 (80.0%)	
No	4 （23.5%）	8 (20.0%)	
Histology			0.140
Adenocarcinoma	11（64.7%）	32 (80.0%)	
Squamous cell carcinoma	2 （11.8%）	6 (15.0%)	
Other [a]	4 （23.5）	2 (5.0%)	
Stage			0.320

I-III	3 （17.6%）	12 (30.0%)	
IV	14（82.4%）	28 (70.0%)	
Pleural effusion			0.754
Yes	4（23.5%）	11 (27.5%)	
No	13（76.5%）	29 (72.5%)	
EGFR			0.612
Nonmutated	6（35.3%）	17 (42.5%)	
Mutated	11（64.7%）	23 (57.5%)	

[a]Large cell lung carcinoma with neuroendocrine features, *SMARCA4* undifferentiated lung cancer, undifferentiated lung cancer, sarcomatoid lung carcinoma (one case each) ;

Comment 3: More than half of patients received targeted therapy, which is not usually recommended for SMARCA4-mutated NSCLC. Please describe the detail.
Reply 3: The population in this study, not only had mutations in the SMARCA4 gene, but also co-mutations in several genes, such as epidermal growth factor receptor (EGFR) and TP53. Patients with mutations in the EGRF gene are usually prioritised for targeted therapy.
Changes in the text: None

Comment 4: The paragraphs from line 213 and line 228 are almost same.
Reply 4: Delete the original line 228
Changes in the text: None

Comment 5: In lines 204 and 206, SETBP1 and SETDB1 are referred. Which is correct?
Reply 5: SETBP1 is correct and has been modified.
Changes in the text: In line 262-268