Peer Review File

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Reviewer A

Comment 1: How many cases have you started drug treatment for postoperative recurrence after ICI became an additional indication? Was there a difference in PRS before and after ICI became available?

Comment 2: What were the reasons why ICI could not be used patients from December 2015 onwards?

Reply 1 and 2: Thank you for your comments on this important perspective. We added the following data as advised (Comment 1 and 2), in Discussion part. (see Page 15, line 238-243)

Changes in the text: One hundred fourteen patients of those who underwent systemic therapy has started after ICIs became an additional indication, and there was no significant difference in PRS of the periods between before and after ICIs became available ($p = 0.296$; data not shown). Patients except for 79 patients who received ICIs in clinical course were unable to receive ICIs after ICIs approval, mainly due to interstitial pneumonia or decreased PS.

Comment 3: Details of the ICI regimen used should be summarized in a supplement mental table.

Reply 3: Thank you for your meaningful comment. We should summarize ICIs regimen for detailed information. We added the following sentence in Results part and a supplementary Table. (see Page 12, line 189-190 and Supplementary Appendix)

Changes in the text: Details of the ICI regimens are shown in Supplementary Table 1. (Page 12, line 189-190)

Supplementary Table 1: ICIs regimen of postoperative recurrent non-small cell lung cancer without EGFR mutations or ALK rearrangements.

	ICI use in clinical course (n = 79)	
	1st line (n = 54)	2nd line or later (n = 25)
	number of patients (%)	
Combination with cytotoxic chemotherapy		
yes	29 (54)	0
no	25 (46)	25 (100)
ICIs regimen		
pembrolizumab	45 (83)	7 (28)
atezolizumab	7 (13)	7 (28)
nivolumab	1 (2)	11 (44)
ipilimumab	1 (2)	0

ICI, immune checkpoint inhibitor

Comment 4: Were there any differences in RR and PRS rates in patients with high PD-L1 expression (> 50%) compared to patients with PD-L1 expression negative?

Reply 4: Thank you for your important comment. As you pointed out, not only comparison of patients with PD-L1 expression-positive or PD-L1 expression-negative, but also compared to patients with high PD-L1 expression is necessary. We classified patients by PD-L1 expression >50%, 1-49%, and <1%, and 1st line RR and PRS data were re-evaluated. We revised manuscript in Results part and Table 4. (see Page 13, line 206-210 and Table 4)

Changes in the text: Among the ICI group (n = 79) during the clinical course, the response rates during the first-line therapy among patients with PD-L1 expression ≥ 50%, 1-49% and <1% were 41.7%, 38.8% and 33.3%, respectively. The 3-year PRS rates for those with PD-L1 expression ≥ 50%, 1-49% and <1% were 48.7%, 47.9% and 42.1%, respectively (Table 4). There was no statistically significant difference in the response rates at first-line treatment and PRS between patients with any PD-L1 expressions. (Page 13, line 206-210)

Table 4. Comparison of response ratio and postoperative recurrence between patients examined PD-L1 expression in postoperative recurrent non-small cell lung cancer using ICIs.

	Use of ICIs in clinical course (n = 79)			
PD-L1	≥ 50 % (n = 26)	1-49 % (n = 26)	< 1% (n = 16)	p value
1st line RR	41.7 %	38.8 %	33.3 %	≥ 50 % vs < 1 %; 0.663 ≥ 50 % vs 1-49 %; 0.856 1-49 % vs < 1% ; 0.778
3-year PRS	48.7 %	47.9 %	42.1 %	≥ 50 % vs < 1 %; 0.885 ≥ 50 % vs 1-49 %; 0.834 1-49 % vs < 1% ; 0.971

ICI, immune checkpoint inhibitor; RR, response rate; PRS, post-recurrence survival

Reviewer B

Comment 1: The authors state in the method section that their study design was a case-control study. However, I do not find any control that was selected for comparison with the case (those with postoperative recurrence).

Reply 1: Thank you for your precise point. We mistook statement about our study design. We revised manuscript about our study design. (see Page 7, line 96)

Changes in the text: We used a retrospective cohort study design.

Comment 2: Analysis of ICI use at any treatment stage as a variable would not be appropriate because any patient that was alive in the study period may use ICIs in the future. Instead, they should analyze ICI use as first-line treatment as a variable.

Comment 3: The authors should exclude patients undergoing local treatment for postoperative recurrence.

Reply 2 and 3: Thank you very much for your important comment. As you advised, we re-analyzed univariable and multivariable including a factor of ICI use at first line instead of ICI use in clinical course, and We excluded patients undergoing local treatment at recurrence. We revised our manuscript in Material and Methods part, Results part, and Table 2. (see Page 10, line 159-160; Page 11, line 176-181, and Table 2)

Changes in the text: The study size except for 15 patients who underwent local treatment (n = 240) was… (Page 10, line 159-160)

Multivariable analysis revealed that squamous cell carcinoma (HR, 2.165; 95% CI, 1.494–3.138; p < 0.001), pathological stage III (HR, 1.697; 95% CI, 1.209–2.381; p = 0.002), and ECOG (Eastern Cooperative Oncology Group) performance status ≥ 2, (HR, 3.925; 95% CI, 2.523–6.107; p < 0.001) were significantly associated with worse PRS. Conversely, ICI use at first line (HR, 0.586; 95% CI, 0.371–0.924; p = 0.022) .... (Page 11, line 176-181)

Table 2. Univariable and multivariable analysis of post-recurrence survival for patients with non-small cell lung cancer without EGFR mutations or ALK rearrangements except for patients receiving local treatment (n = 240).

		Univariable			Multivariable		
Variable		Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value
Age at recurrence (years old)	≥ 75	1.583	1.110 − 2.258	0.011	1.317	0.908 − 1.911	0.147
Sex	male	1.185	0.798 − 1.760	0.400			
Smoking history	ever	1.551	0.922 − 2.610	0.098			
Neoadjuvant chemotherapy	yes	0.861	0.434 − 1.710	0.670			
Initial surgical procedure	Bi or pneumonectomy	1.195	0.584 − 2.447	0.625			
Adjuvant chemotherapy	yes	0.639	0.451 − 0.906	0.012	0.781	0.536 − 1.136	0.196
Histological type	Sq	2.092	1.460 − 2.997	< 0.001	2.165	1.494 − 3.138	< 0.001
Pathological stage at initial surgery	Stage IIII	1.660	1.201 − 2.295	0.002	1.697	1.209 − 2.381	0.002
Distant recurrence	yes	1.281	0.907 − 1.810	0.159			
ECOG performance status	≥ 2	5.216	3.444 − 7.900	< 0.001	3.925	2.523 − 6.107	< 0.001
ICI use at first line	yes	0.527	0.340 − 0.816	0.004	0.586	0.371 − 0.924	0.022

ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor

Comment 4: line 47-48: please cite appropriate references.

Reply 4: Thank you for your comment. We modified references in Introduction part. (see Page 6, line 72-74)

Changes in the text: Lung cancer is the leading cause of cancer-related mortality worldwide(1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers(1, 2).

Comment 5: Regarding ICI use for postoperative recurrence, please refer to the below paper as well.

Yuasa I, Hamaji M, Ozasa H, Sakamori Y, Yoshida H, Yutaka Y, Menju T, Hirai T, Date H. Outcomes of immune checkpoint inhibitors for postoperative recurrence of non-small cell lung cancer. Gen Thorac Cardiovasc Surg. 2023 Sep;71(9):534-541. doi: 10.1007/s11748-023-01920-z. Epub 2023 Feb 22. PMID: 36811789.

Reply 5: Thank you for your advice. We referred the paper and revised our manuscript as follows. (see Page 15, line 246-249)

Changes in the text: Yuasa et al. reported that the median OS of postoperative NSCLC patients receiving ICIs as first line treatment was 25.0 months, compared with 22.8 months in this study, and these results were similar(25).

Referred to Reviewer's comments, we revised abstract.

Changes in the text:

Conversely, ICI use at first line was associated with… (Page 3, line 39-40)

…nor in PRS among those with PD-L1 expression ≥ 50%, 1-49%, and <1% in surgically resected specimens. (Page 4, line 43-44)