Peer Review File

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Reviewer A

Comment 1 : Line 76: Why did not use ECOG PS. Generally, ECOG PS was used in study about NSCLC. However, ECOG PS was used in the result paragraph.

Reply 1: We gratefully appreciated your comment. We have modified our text and Fig1 as advised. Thanks again for your valuable comment.

Changes in the text :

"Enrollment criteria in this study were as follows: (i) patients with histologically or cytologically confirmed NSCLC; (ii) Eastern Cooperative Oncology Group performance status (ECOG PS) scores 0-2; (iii) Following first-line chemotherapy, the patient exhibited recurrent tumor growth and demonstrated resistance to the first-line therapeutic approach; (iv) Patients with unresectable stage IIIB/IV NSCLC; (v) Patients not harboring epidermal growth factor receptors (EGFR) mutation or anaplastic lymphoma kinases (ALK) rearranged." (Line 94-100).

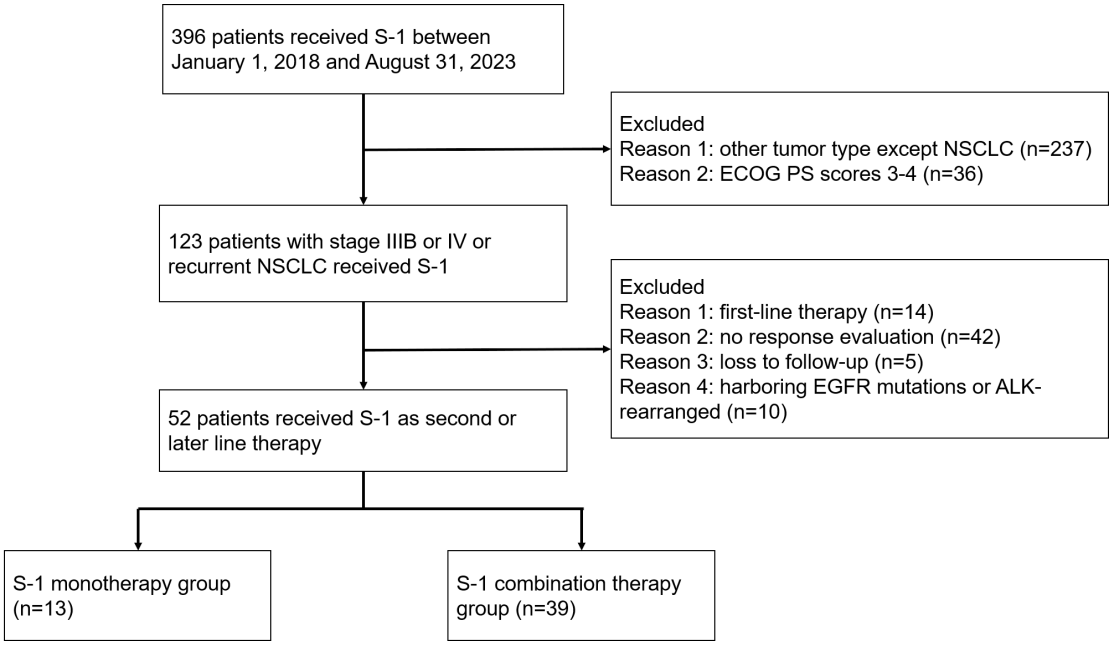

Fig1

Comment 2 : Line 77: Please clarify the patients who suffered from failure first-line chemotherapy. Toxicities or resistance?

Reply 2: We gratefully appreciated your comment. We have modified our text as advised. Thanks again for your valuable comment.

Changes in the text：

"Enrollment criteria in this study were as follows: (i) patients with histologically or cytologically confirmed NSCLC; (ii) Eastern Cooperative Oncology Group performance status (ECOG PS) scores 0-2; (iii) Following first-line chemotherapy, the patient exhibited recurrent tumor growth and demonstrated resistance to the first-line therapeutic approach; (iv) Patients with unresectable stage IIIB/IV NSCLC; (v) Patients not harboring epidermal growth factor receptors (EGFR) mutation or anaplastic lymphoma kinases (ALK) rearranged." (Line 94-100).

Comment 3： Line 78: Authors should suggest c-stage in patient characteristics.

Reply 3: We gratefully appreciated your comment. We have added c-stage in patient characteristics (Table 1) as advised. Thanks again for your valuable comment.

Changes in the text:

Table 1 Baseline patient characteristics at the time of S-1 initiation (n=52)

	Total (n=52)	S-1 monotherapy (n=13)	S-1 combination therapy (n=39)	*P* value
TNM Stage, n (%)				
IIIB	9(17.3)	3(5.8)	6(11.5)	
IV	43(82.7)	10(19.2)	33(63.5)	0.832

Comment 4： Line 81: Patients not harboring EGFR mutation or ALK rearranged was excluded in this study. I recommend to add the sentence into title. "Patients not harboring EGFR mutation or ALK rearranged"

Reply 4: We gratefully appreciated your comment. We have modified our text and Fige 1 as advised. Thanks again for your valuable comment.

Changes in the text：

"Enrollment criteria in this study were as follows: (i) patients with histologically or cytologically confirmed NSCLC; (ii) Eastern Cooperative Oncology Group performance status (ECOG PS) scores 0-2; (iii) Following first-line chemotherapy, the patient exhibited recurrent tumor growth and demonstrated resistance to the first-line therapeutic approach; (iv) Patients with unresectable stage IIIB/IV NSCLC; (v) Patients not harboring epidermal growth factor receptors (EGFR) mutation or anaplastic lymphoma kinases (ALK) rearranged." (Line 94-100).

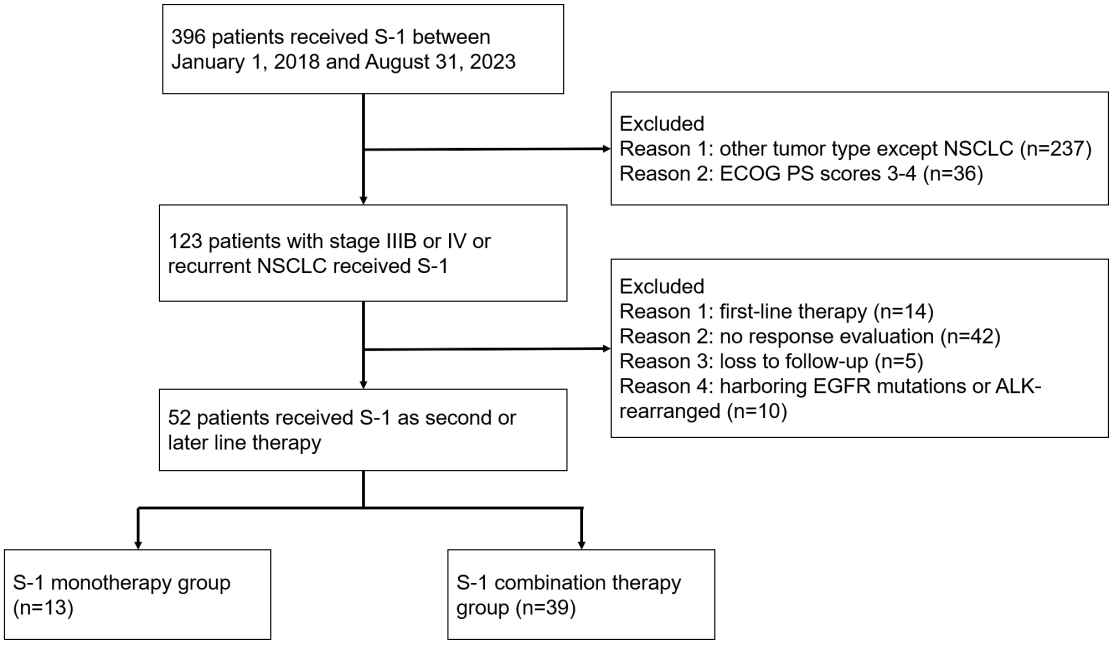

Fig1

Comment 5 : Line 91: Standard treatment method of S-1 is usually four-week administration and two week withdrawal.

Reply 5: We gratefully appreciated your comment. Thank you so much for your careful check, we feel sorry for our carelessness. Thanks again for your valuable comment.

Changes in the text :

"S-1 was administered orally at a daily dose in two divided doses after a meal for a duration of 4 weeks, followed by a drug-free interval of 2 week (one cycle)."(line 112-113).

Comment 6 : Table 1: There is no data about prior treatment.

Reply 6: We gratefully appreciated your comment. We have added previous first-line chemoimmunotherapy regimen in patient characteristics (Table 1) as advised. Thanks again for your valuable comment. Thanks again for your valuable comment.

Changes in the table :

Table 1 Baseline patient characteristics at the time of S-1 initiation (n=52)

		Total (n=52)	S-1 monotherapy (n=13)	S-1 combination therapy (n=39)	*P* value
Previous	**first-line**				

chemoimmunotherapy regimen				
Albumin paclitaxel + carboplatin/ cisplatin/ nedaplatin ±immunotherapy	22(42.3)	-	-	-
Pemetrexed + carboplatin/ cisplatin/ nedaplatin ±immunotherapy/ bevacizumab	20(38.5)	-	-	-
Gemcitabine + carboplatin/ cisplatin/ nedaplatin ±immunotherapy	8(15.4)	-	-	-
Immunotherapy monotherapy	2(3.8)	-	-	-

Reviewer B

Authors mentioned that the content of this paper is to investigate the efficacy and safety of S-1 combination therapy in advanced NSCLC patients as a second-line or later treatment option, as well as to compare its effectiveness with S-1.

They also mentioned that in conclusion, S-1 demonstrated efficacy and tolerability as a second-line or subsequent treatment for advanced NSCLC, whether administered as monotherapy or in combination. Moreover, combined therapy with S-1 and treatment line emerged as two significant independent predictors of OS.

Comment 1： In the conclusion, it should be clearly noted what the effectiveness of S-1 is compared to.

Reply 1: We gratefully appreciated your comment. We have modified our text as advised. Thanks again for your valuable comment.

Changes in the table：

"In conclusion, the study findings suggest that S-1 exhibits potential efficacy and tolerability with minimal toxicity as a second-line or subsequent treatment for advanced NSCLC, in comparison to standard treatment options such as docetaxel monotherapy or docetaxel plus ramucirumab, regardless of whether it is administered as monotherapy or in combination, whether administered as monotherapy or in combination."(line 270-274).

Comment 2 : They should also mention in comparison of Doce. plus, Ram. which was usual used for over 2nd line treatment of driver mutation negative NSCLC

Reply : We gratefully appreciated your comment. We have enriched Doce. plus, Ram in the introduction part and added *incidence of grade ≥3 pneumonitis* in table 4 as advised. Thanks again for your valuable comment.

Changes in the table :

"*For individuals with NSCLC lacking oncogenic driver mutations who have experienced progression after initial therapy, the standard treatment options include immune checkpoint inhibitor (ICI) or gemcitabine and docetaxel monotherapy or docetaxel plus ramucirumab(1), with a median progression-free survival (mPFS) of only 3 months (2-4). However, not all patients can tolerate subsequent chemotherapy regimens, such as patients with a performance status (PS) ≥ 2. Moreover, significant adverse effects such as bone marrow suppression and fatigue are observed in patients treated with gemcitabine or docetaxel. Additionally, the incidence of grade ≥3 pneumonitis is found to be elevated in relation to the combined treatment of docetaxel and ramucirumab.*"*(line 57-65).*

Table 4 Incidence of adverse events (AEs)

Treatment-related AEs, n (%)	Any Grade n (%)	Grade ≥ 3
Pneumonitis	5(9.6)	0(0.0)

Comment 3 : There is a bias of the number of cases treated radiotherapy and ICI as 1st line treatment in S-1 combination therapy compared to S-1 monotherapy, therefore they should mention in detail the interpretation of the treatment outcomes.

What they mentioned about S-1 being an independent predictor of OS is under the restricted situation that a limited number of patients, biased 1st line treatment (RT + ICI and consequent S-1 combination therapy etc.). Therefore, it is difficult to accept their bold conclusions as they stand based on the current situation.

Reply : We sincerely appreciate the valuable comments. A baseline assessment was conducted before performing a logistic regression analysis. The presence of unbalanced grouping was evaluated using a difference comparison method, with a P-value greater than 0.05 indicating comparability between groups. Then univariate logistic regression analysis was utilized to identify potential risk factors (age, sex, smoking status, ECOG PS scores, histologic features, liver metastases, brain metastases, liver metastases, pleural effusion, PD-L1 expression, previous surgical resection, previous radiotherapy, treatment regimens, line of therapy). Due to the limited sample size of this experiment,

we propose adopting an inclusion criterion of $p<0.2$, as recommended in a study published in JACC Cardiovascular Imaging (Impact Factor = 19.9)(5). Consequently, variables with a p-value less than 0.2 were included as covariates in the subsequent multivariate regression analysis (ECOG PS scores, brain metastasis, pleural effusion, treatment regimen, number of lines). As suggested by the reviewer, we also added more references to support this idea. The results obtained were consistent with the findings of the clinical trial(6-8), which demonstrated that combination therapy with S-1 significantly enhanced antitumor efficacy. Thanks again for your valuable comment.

Changes in the table：

"Additionally, results from multivariate logistic regression analysis indicated that the use of combination therapy involving S-1 independently predicted overall survival. This discovery aligned with the findings of the clinical trial(6-8), which demonstrated that combination therapy with S-1 significantly enhanced antitumor efficacy. However, the small sample size may limit the accuracy of the conclusions. A large multicenter sample are needed in future studies due to the possibility of bias in small sample sizes." *(Line 246-251).*