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Peer Review File

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Reviewer A

This paper reports the use of CDDP + PEM as adjuvant therapy in resectable cases, with good results suggesting the potential of CDDP + PEM as an adjuvant therapy.

The number of cases is small and the level of evidence is low.
This is a trial to select candidates for a phase III study. The authors make no mention of what kind of Phase III trial they would consider based on these results. They should mention about phase III trial.

Reply: Thank you for pointing out this. When we planned this trial, adjuvant Pemetrexed plus Cisplatin was not reimbursed in South Korea. Thus, the purpose of this trial was to support the adjuvant Pem-Cis regimen as one of the adjuvant chemotherapy regimen, and we had no plan to proceed to a phase III trial. We added this comment to the discussion section as one of limitations

Changes in the text: Discussion section (Page 15, line 5-7)
- Lastly, we had no plan to proceed to a phase III trial. When we planned this trial, Adjuvant Pem-Cis was not reimbursed by national health insurance in South Korea. Thus, the purpose of this trial was to support Pem-Cis as one of the adjuvant chemotherapy regimen.

It is known that immunohistochemistry for TTF-1 in tissues can predict the effect of pemetrexed. Was TTF-1 immunostaining performed in this study? We would like to have that information, even if just partially.

Reply: In several previous studies, TTF-1 immunohistochemistry (IHC) positivity was associated with better clinical outcomes in non-squamous NSCLC patients who were treated with pemetrexed-based chemotherapy, but the majority of studies were investigated in advanced or metastatic NSCLC. Although we did not investigate TTF-1 IHC prospectively, TTF-1 IHC was performed in 73 patients (69.5%), and a majority of patients showed positivity (n=65, 89.0%). There was no significant difference in disease-free survival between TTF-1 IHC positive and negative patients (p=0.386). We added this sentence to the result section and Table 1.

Changes in the text: Result section Survival outcome (Page 9, line 13-16)
- Although we did not investigate TTF-1 IHC prospectively, TTF-1 IHC was performed in 73 patients (69.5%), and a majority of patients showed positivity (n=65,

89.0%). There was no significant difference in disease-free survival between TTF-1 IHC positive and negative patients (p=0.386).

As the authors discuss, there are several reports of short DFS in cases with driver gene mutations. In such cases, we would like to know the site of recurrence. There is no information on the site of recurrence in the entire study. It is important to know whether the recurrence is distant metastasis or local recurrence.

Reply: Thank you for your valuable comments. The characteristics of relapsed patients, site of recurrence and their subsequent treatment in the overall and EGFR mutation-tested population were described in Table 2 and Results (Page 9, line 1-9) and Discussion (Page 13, line 18-20) section. Patients with EGFR mutation were more likely to be relapsed, but there was no difference in relapse pattern (local vs distant metastasis).

Reviewer B

This is a phase II prospective study of adjuvant chemotherapy of pemetrexed plus cisplatin in patients with stage IB-IIIA curative resected NSCLC. The author found that adjuvant pem-cis improved 2 yr disease free survival compared to historical control. The study was well conducted, however, several issues should be concerned.
The major concern of this study was the primary endpoint of 2 yr DFS compared to historical control without adjuvant chemotherapy. In general, for patients with stage IB-IIIA resected patients, adjuvant chemotherapy is considered standard of care because adjuvant chemotherapy improved overall survival. Therefore, the hypothesis of this study did not have any rationale to compare pem-cis with no adjuvant chemotherapy. It would have more rationale if this regimen is compared with previous chemotherapy as historical control in terms of side effects or DFS. Altogether, the primary end point should be changed.

Reply: Thank you for pointing out this. We agree with the reviewer's concern. Although we cannot compare DFS directly with prior trials, DFS (78.1%, 95% confidence interval: 70.6~86.4%) was numerically longer than that of chemotherapy group (63.2%) in ANITA trial. We added a sentence in the discussion section about this point.

Changes in the text: The following sentence was added as the 3rd sentence in Discussion section (Page 10, line 16-18)
- Although we cannot compare DFS directly with prior trials, the 2-year DFSR was numerically longer than historical control (50%) and chemotherapy group of ANITA trial (63.2%).

Reviewer C

The authors conducted a phase II study of adjuvant pemetrexed plus cisplatin in

patients with completely resected stage IB to IIIA adenocarcinoma of the lung. They found that the 2-year disease-free survival rate was 78.1%, and the primary endpoint was met.
There are several comments, as below.

1. Cisplatin-based adjuvant chemotherapy is well-known to prolong disease-free and overall survival in patients with completely resected non-small cell lung cancer of pathological stage IB to IIIA. Therefore, the authors should refer to the intervention group (chemotherapy) in the ANITA trial when they decided the threshold, not the control group (observation).

Reply: Thank you for pointing out this. We agree with the reviewer's concern. Although we cannot compare DFS directly with prior trials, DFS (78.1%, 95% confidence interval: 70.6~86.4%) was numerically longer than that of chemotherapy group (63.2%) in ANITA trial. We added a sentence in the discussion section about this point.

Changes in the text: The following sentence was added as the 3rd sentence in Discussion section (Page 10, line 16-18)
- Although we cannot compare DFS directly with prior trials, the 2-year DFSR was numerically longer than historical control (50%) and chemotherapy group of ANITA trial (63.2%).

2. Relatively low frequency of p-stage IIIA patients seemed to contribute longer disease-free survival in this study than that in historical control.

Reply: Thank you for pointing out this, and we agree with reviewer's comment.
The proportion of pathologic stage IIIA patients (24.8%) in the present trial was numerically lower compared with that in the control arm of ANITA trial (36.7%). However, these two studies applied different editions of TNM classification: the 1986 version in the ANITA trial and the 7th edition in the present trial. The T descriptors have changed with version updates, while the N descriptors have remained consistent. The proportions of pathologic N stage (N0, N1, N2) between the two trials were similar: 46.7%, 30.5%, 22.6% in the present trial, and 43.4%, 31.4%, 24.5% in the control arm of ANITA trial.
We added this paragraph to the Discussion section.

Changes in the text: Discussion section (Page 10, line 23 – Page 11, line 7)
- The relatively low percentage of stage IIIA patients in this trial might have contributed to a longer DFS compared with the control arm of ANITA trial. The proportion of pathologic stage IIIA patients (24.8%) in the present trial was numerically lower compared with that in the control arm of ANITA trial (36.7%).

However, these two studies applied different editions of TNM classification: the 7th edition in the present trial and the 1986 version in the ANITA trial. The T descriptors have changed with version updates, while the N descriptors have remained consistent. The proportions of pathologic N stage (N0, N1, N2) between the two trials were similar: 46.7%, 30.5%, 22.6% in the present trial, and 43.4%, 31.4%, 24.5% in the control arm of ANITA trial.

Reviewer D

Although not unique, this is a well designed study. Pemetrexed and cisplatin combination is already being used in patients with NSCLC in adjuvant settings and as authors pointed out there are several trials confirming this. However i can see the utility of this trial in Korean population in the real world. Therefore this evidence is important in population specific settings. I do have couple of minor suggestions for the manuscript before formally accepting this for publication:

- Please give more detail about the historical control and survival numbers in historical control. Since this is an open label trial without any control, readers should not have to wait until the discussion to know about the historical control, authors are comparing their results with? I would suggest to clarify this in the introduction/ background section.

Reply: Thank you for pointing out this. We added comments about DFS of control and chemotherapy group as historical control in the introduction section.

Changes in the text: The last paragraph of Introduction (Page 5, line 5-8)
- To confirm the efficacy of Pem-Cis, a single-arm Pem-Cis adjuvant chemotherapy trial was conducted in patients with completely resected lung adenocarcinoma (LUAD). The primary endpoint was to confirm the superiority of a 2-year disease-free survival rate (DFSR) compared to historical control without adjuvant treatment (50%).

-Page 3, line 3, please proved the reference for the percentage of the patients experiencing relapse after 5 years.

Reply: Thank you for pointing out this. We added a sentence for the percentage of relapse as 5-year postoperative survival rates with a corresponding reference in the Introduction (Okami J et al., J Thorac Oncol 2019;14(2):212-222).

Changes in the text: The second paragraph of Introduction (Page 4, line 11-13)
- In a study of Japanese registry, the 5-year postoperative survival rates were reported

to be 64.1% for stage IIA, 56.1% for stage IIB, and 47.9% for stage IIIA.

-Also please provide the exact sample size calculation number. Although had provided the method to calculate the sample size but have not provided the exact number calculated based on that method.

Reply and Changes in the text: Thank you for pointing out this. As calculated by the statistical method described in the manuscript, the required number of patients for enrollment was 105. We added the exact number in the Method section (Page 6, line 24), and the exact number of ITT population (n=105) was described in figure 1.