Peer Review File

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Reviewer A

Comment 1: No information on previous chemotherapy regimens is given for this study: I think it is relevant to know how patients were pretreated? Did all adenocarcinomas receive platinum/pemetrexed? Did squamous tumours receive platinum/gemcitabine in first line? What did patients receive in second line (if any): docetaxel?

Reply 1: We would like to thank the reviewer for the pertinent queries. As mentioned by the reviewer, the information regarding previous chemotherapy regimens would be informative for readers. We have included new tables summarizing the details of the regimens for first- and second-line treatments according to histological types (Table S1A, B). Additionally, we performed a subgroup analysis for the histology and prior therapy (Table S2). In patients with squamous histology and prior gemcitabine treatment, there were statistically significant differences in PFS ($p = 0.0346$) and ORR ($p = 0.0235$), respectively. Because this was a post-hoc analysis, we should consider the possibility of multiplicity. However, the effect of nab-paclitaxel tended to be higher in patients with squamous cell carcinoma in the phase III study (J-AXEL); this result is reproducible and may have clinical applicability.

Changes in text and supplemental data:

We have added the following sentence in the Results section (page 17, line 18):

The details of regimens for first- and second-line treatments are summarized according to histological types (*Table* S1, S2).

We have added the following sentences in the Results section (page 19, line 3):

"Subgroup analysis was performed regarding ORR and PFS in patients with or without squamous histology, prior docetaxel (DTX) treatment, prior pemetrexed (PEM) treatment, prior gemcitabine treatment, and driver mutations (*Table* S2). In patients with squamous histology and prior gemcitabine treatment, there were statistically significant differences in PFS ($p = 0.0346$) and ORR ($p = 0.0235$), respectively. There was no statistical difference in the therapeutic effect with other covariant factors (*Table* S2). Multiplicity must be considered while interpreting this result. However, the effect of nab-paclitaxel tended to be higher in patients with squamous cell carcinoma in the phase III study.[12] Differences in the effects of nab-paclitaxel depending on histology have been shown in multiple studies and may be applicable to clinical practice."

The results have been added in additional supplemental tables (*Tables* S1 and S2).

Comment 2: At least 10 patients had an oncogenic driver. Nothing is reported on their previous treatment. Did you do a sub-analysis for driver and non-driver patients? Patients

with EGFR mutations are generally less responsive to chemotherapy. Could this explain the lower response rate?

Reply 2: We would like to thank the reviewer for the insightful comments. We performed a subgroup analysis regarding the driver mutation status (Table S2). There was no statistical difference in the therapeutic effect with the driver mutation status. We believe that the driver mutation status did not affect the response rate and PFS. A similar subgroup analysis was performed in the phase III study (J-AXEL). As mentioned by the reviewer, the therapeutic effect of nab-paclitaxel tended was favorable in the *EGFR* mutation negative/unknown group. An appropriate cytotoxic chemotherapy regimen for driver mutation-positive patients remains an unanswered clinical question.

Changes in supplemental data: We have added additional a supplemental table (Table S2).

Comment 3:

What does 'postoperative' mean in the patient characteristics table? Are these patients who relapsed after surgery and adjuvant chemotherapy?

Reply 3: We would like to thank the reviewer for this query. The word "postoperative" was used to refer to patients with post-operative recurrence. We have replaced "postoperative" with a more appropriate term "post-operative recurrence" in Table 1. We have also categorized the relapsed cases after chemoradiation therapy separately and have revised the figures.

Changes in table: Modified and corrected the "clinical stage" column in Table 1.

Comment 4: Most patients (94.3%) had an acceptable ECOG PS score of 0–1. If PS 2 is not acceptable, why then allow these patients in your study? Also, it is AN acceptable ECOG…

Reply 4: We would like to thank the reviewer for this comment. Only two (5.7%) patients with PS 2 were included in this study. As described in Table 4, in most of the similar prospective studies, the PS 2 patients were included. However, the proportion of this population was relatively lower; for example, 2.4% in Sakata's study (ref. 7) and 7.3% in Harada's study (ref. 11). In the pivotal phase III study (J-AXEL), this population was not included. Thus, the efficacy and safety of nab-paclitaxel for PS 2 patients remains an unanswered clinical question in our practice. Considering the safety profiles of nab-paclitaxel, this agent may be acceptable for this population; however, the prospective data are not enough. Further investigations will be needed for this population.

Comment 5: In this setting, docetaxel (DTX), pemetrexed (PEM), and S-1 have been established as having clinical benefits for recurrent NSCLC. Please explain S-1 for the interest of the readers, as it seems uncommonly used for NSCLC outside of Asia.

Reply 5: We would like to thank the reviewer for this suggestion. As you mentioned, S-1 is a local drug in Asian countries. We have added brief information about S-1 in the Discussion

section. This agent has been used in second- or third-line setting because of the feasibility and safety profiles, such as low frequency of alopecia and neurotoxicity. However, the response rate was relatively lower in the pivotal phase III study. Thus, we believe that nab-paclitaxel is a new therapeutic option, with a high response rate and safety, for use in clinical practice.
Changes in text: We have added the following sentences in the Discussion section (page 22, line 7):
"S-1 is an oral cytotoxic drug that comprises tegafur, gimeracil, and oteracil potassium. S-1 demonstrated non-inferiority in OS to DTX as second- or third-line therapy for patients with advanced NSCLC in a randomized, phase 3 study.[24]"

Comment 6: What is the added value of this study if there are at least 6 single-arm studies already available?
Reply 6: We thank the reviewer for raising an important issue. In this study, we performed the PRO evaluation using the PNQ score to evaluate the effects of nab-paclitaxel on QOL. There has been no single-arm trial including the QOL analysis using the PNQ score system. Additionally, we assessed the concordance between the patient-based PNQ scores and physician-based CTCAE using the weighted kappa coefficient. This analysis revealed an obvious gap between objective evaluation by patients and subjective evaluation by investigators, especially motor peripheral neuropathy. We want to promote careful assessment of AE using PRO tools when using taxane-based regimens. For these reasons, we believe that the results of our study will be informative for physicians.

Comment 7: Could you compare results and toxicity also to classical (i.e. not nab) paclitaxel monotherapy?
Reply 7: We thank the reviewer for this comment. We usually use the solvent-based paclitaxel with bolus administration. It is often used with CBDCA in the initial treatment. A direct comparison was performed in combination with CBDCA in the first-line setting (CA031 trial, ref. 3). The frequency of sensory neuropathy was significantly higher in the solvent-based paclitaxel arm ($p<0.001$). The weekly solvent-based paclitaxel therapy was evaluated in two phase II trials (Juan et al. JJCO, 2002; Ceresoli et al. Lung Cancer, 2004). The response rate was 35% and 15%, respectively. But the assessment tool in these studies was the WHO response criteria, which is different from our study and from other studies using nab-paclitaxel. Thus, it is difficult to compare the efficacy results of weekly solvent-based paclitaxel therapy with those obtained in our study.

Comment 8: ORR for this study seems lower than in most other studies, although similar PFS is reached. Could the authors further speculate on why this is the case?

Reply 7: We have presented a summary of prospective trials using nab-paclitaxel in Table 4. Based on these results, there is no obvious correlation between high response and longer PFS. The results of this study, ORR 18.5% (95% CI, 10.9–29.6) and median PFS 3.4 months (95% CI, 2.5–4.3), are reproducible compared with other studies.
Furthermore, the feasibility to maintain dose intensity for a long period of time is also an important factor for longer PFS. We carefully set the rescheduling method for dose adjustment (Figure S1). As a result, the dose reduction rate was 15.3% and the schedule modification was 29.2% (p16, line 263) in our study. In the phase III study, the dose reduction rate was 27.3%. We believe that maintaining an appropriate dose and schedule for a long period of time is one of the reasons why PFS was relatively better in this study.

Comment 9: All studies seem to have been conducted in Japan/Asia. Could these findings be generalized to non-Asian patients?

Reply 9: The reviewer has raised an important issue whether or not the chemotherapeutic agents being studied mainly in the Asian/Japanese population show the same efficacy in non-Asians. Results for the Japanese subgroup have been shown in a global phase III study evaluating the efficacy of a combination of carboplatin and nab-paclitaxel (ref. 3, 14). The overall results and the results for the Japanese subgroup were similar. Although in this trial nab-paclitaxel was used in combination with carboplatin, this result might be applicable to nab-paclitaxel monotherapy.
Changes in text:
We have changed the following sentence in the Discussion section (page 24, line 13):
"The present study has several limitations. First,"
We have changed the following word in the Discussion section (page 25, line 1):
"Another" to "Second, a"
We have added the following sentences in the Discussion section (page 25, line 8):
"Third, because this study and other studies using nab-paclitaxel were mainly performed on Asian patients, these findings might not be directly generalizable to non-Asian patients. With regard to the effect of nab-paclitaxel in combination with carboplatin, it has been shown that the overall results were similar to those obtained for the Japanese subgroup in a global phase III study.[3,14] This indicates that the results of nab-paclitaxel trials conducted on Asian subjects might be applicable to non-Asian populations."

Comment 10: The language of this study is generally good, with some small errors.
Reply 10: We apologize for the small errors. We have got the manuscript reviewed and re-edited by "Editage" (www.editage.com).

Reviewer B

The manuscript of Shoji et al entitled "Phase II study of nanoparticle albumin-bound paclitaxel monotherapy for relapsed non-small cell lung cancer with patient-reported outcomes 3 (NLCTG1302)" reports on a reasonably large phase 2 experience with nab-paclitaxel in the second line setting in patients with advanced NSCLC. While the study certainly appears to be a significant experience and highlights reasonable activity and tolerance for this regimen, there are a number of concerns that limit enthusiasm overall listed below.

Comment 1: The study completed accrual in 2016, therefore it is quite old data and very specifically was conducted in the pre-IO era. Therefore, the most relevant current questions-activity following prior IO cannot be assessed.

Reply 1: We agree with the reviewer's comment. We have mentioned this important point in the "Limitations" section (see Page 24, line 13). The subgroup analysis in Phase III trials showed a tendency for better efficacy in the ICI-pretreated group (J-AXEL). Thus, we expect the therapy reported in this study would be as effective or better not only in patients who have not been treated with ICI but also in those who have been treated. However, little is known about nab-paclitaxel monotherapy after immunotherapy and further studies are needed

Comment 2: Also, it was conducted in a mixed patient population of squamous/non-SQ patients. As a result of KN407, standard of care does include a taxane for squamous patients front-line- unclear what activity of nab-paclitaxel would be following a front-line regimen including a taxane- commonly nab-paclitaxel

Reply 2: We agree with the reviewer's comment. KN407 regimen has been the standard therapy for advanced Sq-NSCLC in clinical practice. Thus, we believe that the results of this study can be utilized mainly after the second-line treatment in the case of Non-Sq NSCLC treated with chemo/IO in the first-line setting. However, we often experienced the long-term response cases treated with chemo/IO combination. In such cases, nab-paclitaxel monotherapy may be a treatment option regardless of the histology.

Comment 3 Not clear if radiological assessment was confirmed by independent review or not. This is important for a study where primary endpoint is response rate (and this primary endpoint was surpassed by a mere 1%) as investigator assessments of course tend to be somewhat more optimistic

Reply 2: We acknowledge the reviewer's concern. The response rate was assessed by investigator assessment in this study. The lack of an independent central review is considered an important limitation in this study, and we have described this limitation in the manuscript

(see page 15, line 10; page 22, line 16). We have presented a summary of prospective trials using nab-paclitaxel in Table 4. Based on these results, it has been shown to be as effective as other prospective trials. We also performed the PRO analysis to evaluate the QOL regarding neuropathy due to nab-paclitaxel. In most other trials, the PRO analysis was not performed. Thus, we believe that the reliability and priority of our results for the nab-paclitaxel monotherapy will be maintained.

Changes in text: We have added the following sentences in the Methods section (page 15, line 10):

The primary endpoint was ORR, assessed by investigator's review.

We have also added and modified the following sentences in the Discussion section (page 22, line 16).

"The primary endpoint of this study was the ORR, assessed by the investigators. The lack of an independent central review is an important limitation in this study. However, we observed therapeutic effects similar to those reported previously for nab-paclitaxel monotherapy. The median PFS time was slightly shorter than that reported in previous clinical trials. This may be due to 36.9% of the enrolled patients being on the third-line chemotherapy."

Comment 4: The study also fails to consider docetaxel-ramucirumab as an alternate in the Discussion section.

Reply 2: We would like to thank the reviewer for the valuable comment. We have described the consideration regarding the docetaxel-ramucirumab therapy.

Changes in text: We have added following sentences in the Discussion section (page 23, line 7):

"In our clinical practice, a combination of DTX and ramucirumab has been the standard therapy with high response rate, longer PFS, and OS compared with the DTX monotherapy. However, there are some cases where it is difficult to use ramucirumab due to the risk of bleeding or problematic comorbidities. In such cases, nab-paclitaxel may be a useful option as an alternate regimen with a high-response rate and tolerability."