Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-2025-1518

Reviewer A

The authors examined the treatment completion rate of a combination of cisplatin and TS-1 as adjuvant treatment for completely resected early-stage NSCLC in an open-label phase II trial. They reported a treatment completion rate of 57.6%, with fewer treatment-related toxicities compared to historical controls. They also documented a 3-year RFS rate of 62.5% and a 3-year overall survival rate of 82.9%.

The study is formally negative, based on the statistical assumptions made by the authors. Additionally, the current results are difficult to interpret within the existing evidence and practice in this context.

(General Reply to Reviewer A)

We sincerely appreciate the reviewer's thorough and constructive comments. These suggestions have greatly improved the clarity, rigor, and contextualization of our manuscript. We believe the revisions in response to your comments have substantially strengthened the presentation of our study.

Major Comments

- The completion rate is a very unorthodox endpoint with little clinical relevance. It would be more appropriate to examine the rate of grade 3 and 4 toxicity, the rate of treatment discontinuation due to toxicity, or relapse-free survival (the best endpoint) from a practical perspective.

Reply 1:

We sincerely thank the reviewer for this important comment. We fully agree that RFS, OS, and adverse events are clinically the most relevant endpoints, and in fact, these were evaluated as secondary endpoints in our trial.

However, when this study was designed, the completion rate of adjuvant CDDP-based regimens such as CDDP+VNR was only around 50% in Japan, mainly due to toxicities. Therefore, our central hypothesis was that incorporating TS-1—an agent already widely used in advanced NSCLC—could allow reduction of both the cisplatin dose and the number of cycles, thereby decreasing toxicities while improving the overall treatment completion. For this reason, the completion rate of the entire protocol (CDDP+TS-1 followed by TS-1 maintenance) was deliberately set as the primary endpoint, while RFS, OS, and adverse events were evaluated as secondary endpoints.

Changes in the text:

We have revised the Introduction to explicitly clarify this rationale (Page 5, lines 79–90):

“To further improve tolerability, we designed a regimen in which the cisplatin dose and number of cycles were reduced, followed by alternate-day TS-1 maintenance to maximize treatment continuity. This strategy was expected to enhance the overall completion of adjuvant therapy and ultimately improve survival outcomes in patients with resected NSCLC.

- The description of the statistical analysis is inadequate. The authors did not clarify how they calculated the RFS and OS, nor did they specify the confidence intervals for the treatment completion rates.

Reply 2:

Thank you very much for this important comment. As advised, we clarified the definitions of OS and RFS in the Methods section (Page 7, line 129) and specified that 95% confidence intervals (CIs) were calculated. We also added the 95% CIs for the treatment completion rates in the Results section. In addition, 95% CIs for OS and RFS were incorporated into Figure 3, which was divided into Figure 3A (OS) and Figure 3B (RFS) to enhance readability.

Changes in the text:

Methods: Page 7, line 129 (definition of OS/RFS, description of 95% CI).

Results: Page 11, lines 195, 198–199 (95% CI for completion rates).

Figures: Figure 3 revised into 3A (OS) and 3B (RFS), with 95% CIs added.

- Why did the authors use cisplatin at 60mg/m2? This is not the most common dose in most adjuvant studies. Additionally, after three cycles, the total dose would be less than 210mg/m2, which has been shown to be the minimal accumulated cisplatin dose linked to improved DFS.

Reply 3:

We appreciate the reviewer’s insightful comment. We intentionally used cisplatin at a dose of 60 mg/m² for three cycles because the primary aim of this study was to improve treatment feasibility and tolerability. Previous reports have shown that the completion rate of conventional CDDP-based adjuvant chemotherapy (e.g., CDDP+VNR) was approximately 50% due to toxicities. By reducing the total cisplatin dose and number of cycles, and combining it with TS-1 maintenance therapy, we designed this protocol to minimize toxicity while maintaining feasibility. This rationale has been clarified in the Introduction.

Changes in the text:

Introduction: Page 5, lines 79–83

- It is challenging to position the findings of this study within the current treatment landscape, where cisplatin is being increasingly replaced by carboplatin, and pemetrexed is now the preferred drug in combination with cisplatin, rather than vinorelbine, for non-squamous NSCLC. Furthermore, as the authors correctly note, the use of adjuvant targeted therapy for EGFR-mutated and ALK-rearranged NSCLC and immunotherapy for other NSCLCs has significantly affected RFS and OS. This is particularly relevant here since 25% of patients had tumors with EGFR mutations. Overall, the results have primarily historical significance.

Reply 4:

We appreciate this thoughtful and important comment. We agree that the adjuvant treatment landscape has expanded substantially, including broader use of cisplatin–pemetrexed, increased reliance on carboplatin in selected situations, and the establishment of targeted therapies (e.g., for EGFR/ALK) and ICIs as standards of care. We have revised the Discussion to situate our findings within this contemporary context.

At the same time, in clinical practice there remain patients who are ineligible for, intolerant of, or unable to access targeted agents or ICIs because of performance status, comorbidities, contraindications, or socioeconomic/coverage constraints. For such patients, evidence on feasible, lower-toxicity platinum-based adjuvant approaches remains clinically relevant. Our single-arm feasibility study—designed and conducted in 2013–2018—specifically addressed tolerability and treatment continuity by reducing cisplatin dose/number of cycles and incorporating alternate-day TS-1 maintenance. We therefore position our results as complementary, offering an option that may be practical when standard adjuvant options cannot be delivered or completed.

Because the reviewer raised the potential impact of tumor genomics, we performed an exploratory subgroup analysis by EGFR mutation status (tested in 50 patients; 15 EGFR-mutant). We did not observe statistically significant differences in OS or RFS by EGFR status; however, we acknowledge the limited power due to small numbers. We have added these results with appropriate caution and provided the corresponding supplemental figure. Finally, we note in the Discussion that the results of the ongoing phase 3 Japanese study comparing CDDP+VNR with TS-1 monotherapy in the adjuvant setting will be important to interpret alongside our findings going forward.

Changes in the text:

Added exploratory EGFR subgroup analysis results to the Discussion and placed the corresponding Kaplan–Meier curves in Supplementary Figure 1 (see Discussion, Page 15, lines 290–296; Supplementary Figure 1).

- The study took place from 2013 to 2018, with patients followed until 2021. Why was the recruitment time so lengthy? Numerous technical and supportive enhancements occurred during that period, which could have affected the outcomes. Also, why did it take four years for the authors to publish their results?

Reply 5:

We acknowledge the lengthy recruitment and publication timelines. Enrollment was slower than expected because this trial overlapped with a period when many adjuvant clinical trials were simultaneously conducted in Japan, limiting eligible patient accrual. In addition, the follow-up period was extended due to fewer-than-expected events. Furthermore, the COVID-19 pandemic disrupted routine clinical follow-up and delayed data collection and analysis. We have added these explanations in the Limitations section.

Changes in the text:

Added explanation of extended accrual and delayed publication in Limitations (see Page 15-16, lines 297–312).

- The authors claim that their proposed treatment is less toxic, but it takes three times longer. Therefore, unless the regimen results in better outcomes—which does not seem to be the case—it is hard to argue that it has any advantage over cisplatin and vinorelbine, especially when compared to newer, less toxic regimens like carboplatin and pemetrexed.

Reply 6:

We appreciate this perspective. The rationale for our protocol was not to shorten treatment duration but to reduce toxicity while maintaining treatment adherence, as completion rates for CDDP+VNR are often limited by hematologic toxicities. In our study, we demonstrated a relatively high completion rate of TS-1 maintenance therapy and a low incidence of severe toxicities, suggesting potential utility for patients who may not tolerate other regimens, such as elderly patients or those with comorbidities. Importantly, despite the feasibility focus of our trial, the observed survival outcomes were also favorable, with 3-year OS of 82.9% and 3-year RFS of 62.5%. These results indicate that the regimen may maintain efficacy while improving tolerability. We have clarified this point in the Discussion (see Page 15, lines 278–289).

Minor Comments

- Some sentences from the Methods section, such as "A total 82 of 59 patients from eight institutions were enrolled from August 1, 2013, to October 31, 2018, 83 with an observation period extending through October 31, 2021," should be moved to the Results section.

Reply 7:

We agree with the reviewer's suggestion. To improve the clarity and consistency of the manuscript, we carefully revised the structure of the text so that descriptive information about patient enrollment and follow-up, which was previously in the Methods section, has now been moved to the Results section (see Page 9, lines 168–169). We also reviewed the manuscript in its entirety to ensure that methodological details and results are clearly separated.

Changes in the text:
Revised the Methods section to remove descriptive results, and added the enrollment details to the beginning of the Results section (Page 9, lines 168–169).

- The table of baseline characteristics should contain the R0 resection rates and the T and N distributions.

Reply 8:

Thank you for the suggestion. We have revised Table 1 to include R0 resection rates as well as the T and N classifications.

Changes in the text: Updated Table 1 with R0 status and T/N distributions (see Table 1)

- What was the median follow-up time?

Reply 9:

We thank the reviewer for this important point. The median follow-up time was 58.0 months (95% CI: 52.4–63.6), with a data cut-off of October 31, 2021. This has now been added to the Results section and the figure legends.

Changes in the text: Added median follow-up information in Results and Figure 3 legend (see Page 9, lines 168-169, Page 20 line 390).

Reviewer B

Thank you for submitting this manuscript on Phase 2 Feasibility Study of Adjuvant Chemotherapy with Cisplatin 1 (CDDP) and TS-1 Followed by Alternate-Day TS-1 Maintenance Ther apy, in Patients with Completely Resected Pathological Stage II-IIIA Non-Small Cell Lung Cancer

It is very much appreciated the effort and clarity with which the study was presented, particularly its focus on a novel maintenance therapy approach in this patient population. The methodology and rationale are well-articulated, and the results contribute meaningfully to the ongoing discussion regarding adjuvant treatment strategies for non-small cell lung cancer.

I have only a few minor comments.

(General Reply to Reviewer B)

We sincerely appreciate the reviewer's positive assessment of our manuscript and the valuable suggestions provided. We have carefully addressed each of the comments point by point as detailed below.

- Are there any correlations between relapse free survival and EGFR status or gender?

Reply 10:

Thank you for this important question. We conducted exploratory subgroup analyses. Among the 50 patients who underwent EGFR testing, no statistically significant differences in OS or RFS were observed between EGFR-mutated (n=15) and EGFR wild-type (n=35) patients (Supplemental Figure 1). This result has been incorporated into the Discussion (p.15, lines 290–296). Regarding gender, no statistically significant correlation with RFS or OS was found. However, given the limited sample size, these analyses should be interpreted with caution.

Changes in the text:

We added EGFR subgroup analysis results to the Discussion (p.15, lines 290–296) and included Supplemental Figure 1. Gender analysis was not added to the manuscript but addressed here in the response.

- For figure 3, I would suggest putting numbers at risk.

Reply 11:

We appreciate this suggestion. We have revised Figure 3 to include numbers at risk below the Kaplan–Meier curves for both OS and RFS to provide greater clarity regarding patient follow-up.

Changes in the text:

Revised Figure 3 (now divided into Figure 3A: OS and Figure 3B: RFS) with numbers at risk shown beneath each curve.

- TS-1 is, as you described in your manuscript, widely used in other carcinomas such as stomach cancer. Do you have any comments on histological types and relapse free survivals?

Reply 12:

Thank you for this insightful comment. In our study, adenocarcinoma was the predominant histological subtype (78%), followed by squamous cell carcinoma (17%) and others (5%). Due to the limited number of patients in the non-adenocarcinoma groups, we did not perform a formal subgroup analysis of relapse-free survival according to histological type, as the statistical power would be insufficient. Nevertheless, no clear differences in relapse patterns were observed across histological subtypes. We have clarified this point in the Discussion.

Changes in the text:

Discussion, p.15, lines 295–300: added a statement that no obvious differences in relapse-free survival were noted between adenocarcinoma and other histological subtypes, though the sample size was limited.

Reviewer C

I would suggest an extensive revision with a more clear introduction, more details on eligibility and a critical discussion. The manuscript should be clearly divided into introduction, materials and methods, results and discussion. At this moment results are provided in methods and discussion and the current discussion is flawed.

(General reply to Reviewer C)

We sincerely appreciate your thorough and constructive review of our manuscript. Your comments were very helpful in improving the clarity, accuracy, and structure of our study. In response, we have substantially revised the manuscript, including a clearer Introduction, a more detailed description of eligibility criteria, and a more structured division into Introduction, Methods, Results, and Discussion. We also revised the Discussion to avoid repetition of results and to provide more critical comparisons with standard regimens and recent clinical trials (e.g., ADAURA, IMpower010, JIPANG).

We carefully addressed each of your specific comments point by point. As advised, we clarified the rationale for the cisplatin dose, revised definitions of endpoints, added details regarding T and N status in Table 1, provided an exploratory subgroup analysis according to EGFR mutation status (Supplementary Figure 1), and corrected terminology in adverse event tables. We also restructured sections where sentences from Methods and Results had been mixed, ensuring the manuscript now strictly follows the IMRAD format.

Overall, these revisions have improved the manuscript significantly, and we are grateful for your insightful feedback.

My comments:

- R7: Cisplatin plus vinorelbine (CDDP+VNR) is the standard adjuvant chemotherapy for completely resected stage II/III non-small cell lung cancer.

> This is only one of the recommended options. Please modify.

Reply13:

We appreciate the reviewer's valuable suggestion. We agree that CDDP+VNR is not the sole standard regimen but rather one of several recommended platinum doublet options. We have revised the statement in the abstract and Introduction to clarify that platinum-based doublet chemotherapy is the standard adjuvant treatment, with CDDP+VNR being the most widely used regimen.

Changes in the text:
Page 4, line 50-54

- R15: This open-label, phase 2, multicenter, prospective study

> There is only one study arm, so this is not open-label. Modify to single-arm, phase 2.

Reply14:

We thank the reviewer for this clarification. As suggested, we have revised the description of our study design to "single-arm, phase 2, multicenter, prospective study," which more accurately reflects the study design.

Changes in the text:
Abstract: Page 1, line 13

Discussion: Page12 Line 227

- R45: with the most frequently used regimen being four courses of cisplatin plus vinorelbine.

> This is not supported by the references. In addition, referring to guidelines is required.

Reply 15:

Thank you for the suggestion. We have revised the statement to clarify that cisplatin plus vinorelbine (CDDP+VNR) has been one of the most frequently used regimens for adjuvant chemotherapy especially in Japan, and we have added appropriate references to international guidelines.

- R47: subsequent molecular-targeted agents and immune checkpoint inhibitors have become covered by insurance

> They are more than just insurance covered drugs. They are the standard of care. For this manuscript to be relevant, the current treatment standards should be reported.

Reply16:

Thank you for pointing this out. We agree that describing these therapies merely as “insurance covered” was misleading. We have revised the text to state that targeted therapies and immune checkpoint inhibitors have become the current standard of care in adjuvant settings for appropriately selected patients. We also added context to clarify the relevance of our study in this evolving treatment landscape.

Changes in the text:

Introduction Page 4 Lines 59-64

- R49: the most standard adjuvant chemotherapy

> This might be the case in Japan, but not everywhere around the world. Guidelines do not support this regimen as first choice.

Reply 17:

We appreciate the reviewer’s comment. We agree that cisplatin plus vinorelbine (CDDP+VNR) is not considered the universal standard worldwide. We have revised the text to state that platinum-based doublet chemotherapy is recommended as the standard, and that CDDP+VNR has been one of the most widely used regimens, especially in Japan.

Changes in the text:

Page 4 Lines 49-58

- R50: has been proven to add 5-15% to the 5-year survival rate

> This 15% has only been reported in one trial (Butts et al.); 5% is generally reported as the survival benefit.

Reply 18:

Thank you for this important correction. We agree that the survival benefit is generally reported to be approximately 5%, and the 15% figure was exceptional and not representative. We have modified the text accordingly.

Changes in the text:

Revised to: *"Adjuvant chemotherapy improves 5-year survival by approximately 5% compared with surgery alone."*

Page 4 Lines 49-58

- R52: need to develop an effective and sustainable postoperative adjuvant chemotherapy regimen

> Less toxic options, such as pemetrexed in non-squamous histology and perhaps gemcitabine in squamous histology (with less neutropenia) are available.

Reply 19:

We appreciate this important comment. We fully agree that less toxic regimens such as pemetrexed for non-squamous histology and gemcitabine for squamous histology are increasingly recognized as valuable options. The purpose of our study was to investigate whether the combination of cisplatin with TS-1, followed by alternate-day TS-1 maintenance, could represent another effective regimen with reduced toxicity and improved feasibility. In this sense, our trial was designed to demonstrate that CDDP + TS-1 may provide a comparable efficacy profile while minimizing treatment-related toxicities, thereby contributing to the development of sustainable adjuvant chemotherapy options.

- R59: adopted as a standard postoperative adjuvant therapy for gastric, breast, and pancreatic cancer

> Could you refer to a guideline here?

Reply20：

Thank you for the suggestion. We have revised the description to clarify that TS-1 is mainly used as a standard adjuvant therapy in Japan for gastric, pancreatic, and breast cancers, and we added appropriate references to the relevant Japanese guidelines and pivotal clinical trials.

Changes in the text:

Revised the sentence (Page 5, Line 69-73)

- R60: its efficacy has been confirmed in the treatment of advanced lung cancer

> Reference [13] is about gastric cancer. Please add a reference to lung cancer.

Reply21:

Thank you for pointing this out. We have corrected the reference and added appropriate citations demonstrating the efficacy of TS-1 in advanced non-small cell lung cancer.

- R61: several reports have demonstrated the use of TS-1 in combination with platinum 62 agents as a postoperative adjuvant chemotherapy

> All references are from Japan. Is this drug available outside of Japan? If no, please report this. If yes, please refer to relevant literature.

Reply 22:

Thank you for this important comment. TS-1 is approved and widely used not only in Japan but also in several other Asian countries, including China and South Korea. However, to our knowledge, its use as postoperative adjuvant chemotherapy for NSCLC has been investigated only in Japan. We have clarified this point in the text.

Changes in the text:
We added a clarification in the Introduction noting that although TS-1 is available in other Asian countries, postoperative adjuvant chemotherapy studies have been conducted exclusively in Japan (Page 5, line 73).

- R62: Ongoing phase II trials

> Please refer to all trials. Or modify to 'an ongoing phase I trial'.

Reply 23:

Thank you for your suggestion. We deleted and modified introduction.

Page4 Line 51

- R70: Based on these considerations, this study designed a regimen…

> This should not be part of the introduction. Move this to the methods.

Reply 24:

We appreciate this comment. We have revised the Introduction to include only the study purpose in summary form, while the details of the treatment regimen, schedule, and endpoint definitions have been moved to the Methods section.

Changes in the text: Introduction: now ends with "Based on these considerations, we conducted a phase II feasibility study of CDDP+TS-1 followed by alternate-day TS-1 maintenance as adjuvant chemotherapy in patients with completely resected pathological stage II–IIIA NSCLC." (Page 5, line 85) Methods: detailed regimen schedule, dosing, and endpoint definitions are provided.

- R80: Patients eligible for inclusion in the study met the inclusion and exclusion criteria.

> This is redundant. Please leave it out. Inclusion and exclusion criteria are not reported, apart from tumour stage. Please provide more details.

Reply25:

Thank you for the suggestion. We have modified the sentence to Patients were enrolled according to the inclusion and exclusion criteria (Supplemental Table 1). Specifically, we now indicate that detailed inclusion and exclusion criteria are provided in Supplemental Table 1.

Changes in the text:

Page 6 Line 94

- R82: A total 82 of 59 patients from eight institutions were enrolled from August 1, 2013, to October 31, 2021

> This should not be part of the methods, it belongs in the results section.

Reply 26:

We have moved and edited "methods" and "results" part to understand clearer.

Page 9 Lines 166-187

- R82: eight institutions.

> Please provide names.

Reply 27:

Thank you for the suggestion. We have added all institutions in the methods paragraph.

Page 6 Line 98

- R92: Cisplatin was administered at a dose of 60 mg/m²

> This is a rather low dose. I would expect 75-100 mg/m². This this the local practice in Japan?

Reply 28:

Thank you for pointing this out. Cisplatin at 60 mg/m² was intentionally selected in this study because the protocol aimed to reduce both the dose and number of cisplatin cycles by combining it with TS-1, thereby minimizing toxicity and improving the overall treatment completion rate. This rationale has been added to the Introduction, and it is consistent with the purpose of our trial design.

Changes in the text:

We clarified this rationale in the Introduction (Page 5, line 80) and maintained consistency in the Methods section.

- R96: TS-1 was administered orally twice daily for 14 consecutive days

> Why did you not administrate TS-1 on alternate days during chemotherapy, as this is claimed to reduce toxicity?

Reply 29: We appreciate the reviewer's question. While alternate-day administration of TS-1 has been explored mainly in the context of long-term maintenance therapy to reduce toxicity, the standard regimen at the time of our study design for combination chemotherapy with cisplatin was 14 consecutive days of TS-1 administration. Therefore, we adopted this schedule during the induction phase. In contrast, for the maintenance phase, we employed alternate-day TS-1 administration specifically to improve the one-year treatment completion rate, which was the primary endpoint of this study.

- R100: The primary endpoint of the study was the completion rate of the treatment protocol, defined as the completion of TS-1 monotherapy administered every other day.

> The primary endpoint should have been the completion of chemo + TS-1, followed by TS-1, because this is what you would like to compare to classical adjuvant chemotherapy.

Reply 30:

We thank the reviewer for this very important comment. We have revised the expression to make the definition of the primary endpoint clearer.

Page5 Line88-Page 6 Line91:

Revised as follows.

The primary endpoint was the completion rate of the entire protocol, while secondary endpoints included 3-year relapse-free survival (RFS), 3-year overall survival (OS), completion rates of each treatment component, and adverse events.

- R141: Indicating 142 that 54 out of 59 patients had lymph node metastatis.

> This cannot be reported solely based on TNM stage, only based on N descriptor.

Reply 31:

Thank you for your feedback.

As requested, I have added details regarding the T factor and N factor to Table 1.

Changes in the text:

Added T and N distribution data to Table 1.

- R147: 15 patients (25.4%) had EGFR mutation.

> Although adjuvant chemotherapy is still in the guidelines for EGFR mutatated tumours, we are aware that chemotherapy is less efficient compared to non-AGA NSCLC. Could the inclusion of AGA could have biased the findings? Is there any evidence for TS-1 in EGFR mutated NSCLC?

Reply32

Thank you for your feedback. EGFR mutation testing was performed in 50 cases, of which 15 were mutation-positive. As an exploratory subgroup analysis, we evaluated OS and RFS according to EGFR mutation status (Supplementary Figure 1). Although the number of cases was limited, no significant differences in OS or RFS were observed between mutation-positive and mutation-negative patients. We have added these results to the Discussion (Page 15, lines 290-300).

Changes in the text:

Added exploratory analysis results for EGFR mutation status to the Discussion.

Included Supplementary Figure 1 showing OS and RFS by EGFR mutation status.

R154: The overall completion rate for the protocol treatment was 57.6%.

> The completion rate is 79.1%, namely the patients who started TS-1, as defined in your protocol. This section should be rewritten to define clearly the endpoints.

Reply 33

Thank you for this important comment. We agree that the original description was misleading. The primary endpoint of our study was indeed the completion rate of the entire treatment protocol, defined as the completion of three cycles of CDDP + TS-1 followed by one year of alternate-day TS-1 monotherapy. We have revised the wording in theresults section to clarify this point.

Page 10 Lines 191- (As follows)

The primary endpoint of this study was the completion rate of the entire treatment protocol, defined as the completion of three cycles of CDDP + TS-1 combination therapy followed by one year of alternate-day TS-1 monotherapy.

Page 5 Line88-91

- R158: protocol discontinuation

> Modify to treatment discontinuation

Reply 34

Thank you for the suggestion. We have modified "protocol discontinuation to treatment discontinuation)

Changes in the text:

Page 14 Line 274

- R188-191:

> This information has already been reported previously.

Reply 35

We have deleted the duplicate sentence.

Page8 Lines 135-136

- R193-195:

> Please provide more details on current standard of adjuvant treatments, either in the introduction or in the discussion.

Reply 36:

Thank you for this suggestion. We have expanded the Introduction and Discussion to provide a more comprehensive overview of the current standards of adjuvant therapy, including targeted therapies such as osimertinib for EGFR-mutated NSCLC and immune checkpoint inhibitors such as atezolizumab for PD-L1–positive NSCLC. These additions clarify the evolving landscape of adjuvant treatment and position our study in the proper clinical context.

Changes in the text:

Page 4 Lines 48-64

Page14 Line 277-288

- R202: superior to traditional platinum-based regimens

> Please provide references to trials applying non-vinorelbine regimens.

Reply 37:

We appreciate this comment. We have revised the statement and added appropriate references, including the JIPANG trial (CDDP+PEM vs. CDDP+VNR) and other studies, to better support this point.

Changes in the text:

Discussion, Page 12, Line 25: revised wording and added new references.

- R211-241:

> The discussion should not repeat your results without context. You should compare to outcomes with classical regimens.

Reply 38:

Thank you very much for your feedback.

We have also made revisions to the discussion section, comparing and analyzing the results with those from the ADAURA trial, the Impower 010 trial, and the JIPANG trial.

- TABLE 2A:

> Neutrophils, platelets, creatinine, ... are not adverse events. Neutropenia, thrombocytopenia and elevated creatinine, … are. Please modify.

> The protocol should be provided with the study, but not as supplementary tables, which are only to be used for patients characteristics and results.

Reply39:

Thank you for pointing this out. We have carefully revised Table 2A to ensure that only proper adverse event terms are used, such as *neutropenia, thrombocytopenia,* and *increased creatinine*, in accordance with CTCAE terminology. Regarding the supplementary tables, we have moved the treatment protocol (dose reduction/interruption criteria) from the supplementary material to an Appendix table, as suggested.

Changes in the text:

Table 2A revised to reflect adverse event terminology.

Supplemental Table 2 moved to Appendix Table, Page XX.

Reviewer D

The author is conducting a prospective clinical trial to evaluate the efficacy of adjuvant therapy with CDDP + TS-1 followed by maintenance therapy with TS-1 as adjuvant therapy after surgery for non-small cell lung cancer. While treatments using molecularly targeted drugs and ICIs are currently considered standard therapy based on the results of prospective trials, the platinum doublet regimen may warrant further consideration and could provide important insights. It may be necessary to consider prospective trials evaluating TS-1 maintenance therapy and ICI treatment as standard therapy in the future.

The paper is well-written, and there appear to be no major revisions required. Publication in this journal is recommended.

Reply 40

Thank you very much for taking the time to review my work despite your busy schedule. I truly appreciate it.