Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-22-957

Reviewer A

Comment 1: I would recommend the authors discuss Pless et al (SAKK 16/00) more in depth with regard to induction chemotherapy vs induction chemoRT.
Reply 1: Thank you for addressing an important point. We added the outcome and adverse event.
Changes in the text: We added "As the same result, Pless et al showed no survival difference between chemotherapy and chemoradiotherapy while the adverse events in chemotherapy were not increased in chemoradiotherapy".

Comment 2: In the U.S., most academic medical centers are no longer performing induction chemoRT, especially in light of CheckMate 816. I would recommend the authors discuss these nuances in further detail.
Reply 2: According to the comment, we lighted the ICI treatment advantage compared to the chemotherapy and chemoradiotherapy.
Changes in the text: We added "In future, ICIs may be a standard induction therapy instead of chemotherapy and chemoradiotherapy."

Reviewer B

Comment 1: Title: Consider revising to, "The beginning of a new era in induction treatment for operable".
Reply 1: Thank you for the revision of incorrect sentence. We changed the title as Reviewer B's comment.
Changes in the text: The beginning of a new era in induction treatment for operable non-small cell lung cancer: A narrative review.

Comment 2: Authors: Consider including a radiation oncologist in your team
Reply 2: Thank you for the sufficient proposal including a radiation oncologist in our team. We would recruit the radiation oncologist, although our team was consisted of surgeon, pathologist, and onco-immunological researcher. Dr. Kuroda is familiar with

radiation oncology and wrote some papers (Nakada T, Takahashi Y, Sakakura N, Iwata H, Ohtsuka T, Kuroda H. Prognostic Radiological Tools for Clinical Stage IA Pure Solid Lung Cancer. Curr Oncol. 2021). Unfortunately, we could not find the fellows who is radiation oncologist.

Abstruct

Comment 3:"chemotherapy" vs. "systemic therapy" as some would not lump TKI and IO as "chemo" per se

Reply 3: The reviewer B pointed out incorrect sentence in the abstract. The comment is essential. We changed “chemotherapy” to “systemic therapy” easy to follow.

Changes in the text: Recently, the outcomes of systemic therapy for NSCLC have dramatically changed (P3 L4)

Comment 4: Consider phrasing the results section in the present tense

Reply 4: We changed all sentence related with the misunderstanding of “chemotherapy”. We changed the sentence in the results.

Changes in the text: Results: We revised chemotherapy to systemic therapy including chemotherapy, TKI, and ICIs.

Comment 5: Consider consolidating the two sentences describing the safety and efficacy of CRT vs. Chemo

Reply 5: The description was very complicated and included duplication. So, we consolidated the two sentences (safety and survival outcome) as reviewer B suggested.

Changes in the text: The safety and survival outcome did not differ between the two arms. (P3 L14)

Comment 6: EGFR TKI obviously would only be indicated for the subset of patients who qualify, consider adding that caveat - and the importance of measuring EGFR mutation in the "induction" setting.

Reply 6: The comment is very important. We added the caveat that induction EGFR-TKI is effective to the subset of harboring EGFR mutation and emphasized the importance of measuring mutation in the induction setting.

Changes in the text: Epidermoid growth factor receptor (EGFR) tyrosine kinase inhibitors as induction therapy in the patients with proven EGFR mutaions may be a sufficient choice for the improvement of OS. (P3 L16)

Comment 7: Consider consolidating last three sentences regarding ICI -- these data are

very preliminary (I agree), and more work is needed to understand how downstaging with ICI will affect long-term outcomes.

Reply 7: Thank you for the comment. We consolidated the sentence as follows;

Changes in the text: In ongoing single arm clinical trials, the administration of ICIs as induction therapy was associated with a good pathological response and satisfactory safety, which will lead to the better survival outcome. (P4 L1)

Comment 8: General comment - you mention stage IIIA in conclusion - are you planning to only focus on this group?

Reply 8: We would like to focus on stage I-IIIA in the manuscript. We consider that induction systemic therapy is effective in stage IIIA rather than other stages (I and II). Therefore, we mention the stage IIIA in the abstract.

Changes in the text: None.

Introduction

Comment 9: Surgery being the only curative treatment is certainly dogma in some centers. I would argue that 'curative effects' are mostly driven by treating patients with Stage I disease, which is usually accomplished with surgery

Reply 9: I understand what reviewer B implies. The dogma is driven by treating patients who are operable and healthy to undergo surgery. So, I think “Surgery is the only curative procedure” is inaccurate sentence because radiotherapy is also the curative treatment strategy as the same as surgery. We changed it as bellows:

Changes in the text: Surgery is the one of the curative treatment choices (P5 L3)

Comment 10: -I think it would be better to explain how TKIs and ICIs have known utility in NSCLC (met or post-progression or adjuvant) vs. making claims about the utility before presenting evidence-can say that these are "exciting areas" to tee up the rest of the paper.

Reply 10: We are appreciated with the essential comment. We added the reason why TKIs and ICIs may be a better therapeutic strategy than chemotherapy. The main reason is EGFR-TKIs and ICIs have relevant effects on the EGFR mutation haboring NSCLC and NSCLC with highly PD-L1 expression. These population is greatly expected to N2 down staging and tumor shrinking, which leads to resect cancer completely and suppress circulating tumor cells.

Changes in the text:

- We believe the efficacy and tumor volume reduction is the most important to

accomplish completely resection for the choices of induction systemic therapy. (P5 L17-18)
- It is necessary to elucidate the possible application of EGFR-TKIs in induction therapy "because EGFR-TKIs have relevant effects on the EGFR mutation haboring NSCLC". (P6 L4-5)
- Patients with highly PD-L1 expression is greatly expected to N2 down staging and tumor shrinking, which leads to resect cancer completely. (P6 L9-11)
-We consider these new drugs may control long-term progression and restrain distant metastasis due to the cytotoxicity reaction for the circulating tumor cells and residual lymph node cancer cells. (P6 L14-16)

Comment 11: - Page 6 sentence 6 needs to be addressed, not clear.
Reply 11: We changed the "chemotherapy" to "systemic therapy". We think it makes sense clear.
Changes in the text: In this manuscript, we review the efficacy of induction "*systemic therapy*" for operable NSCLC referring RCTs and investigate the possible application of EGFR-TKI and ICI treatment in NSCLC induction therapy.(P6 L17)

Method
Comment 12: - Typos in Table 1, "is" vs. "are", "diplicated" vs. "duplicated"
Reply 12: Thank you for pointing out my grammatical errors. We revised as reviewer B illustrated.
Changes in the text: "Duplicated articles are" excluded by the review authors (Table 1).

Comment 13: - Consider PRISMA diagram
Reply 13: We added PRISMA diagram as Table S2.
Changes in the text: Please refer "Table S2".

Results
Comment 14:
- should include how many studies were screened
- how many were excluded
- reasons for exclusion (e.g. duplication)
Reply 14: We added PRISMA diagram as Table S2.
Changes in the text:

The included and excluded process is demonstrated in Table S2 with the regard of the narrative review of RCTs (P7 L11-12)

Comment 15: - did you investigate comparing induction regimens? not clear
Reply 15: In the review, the induction regimens of chemo and chemoradiotherapy are not investigated. We think the mention to the chemotherapy regimen confuse readers and we delete the sentence concerning chemotherapy regiment as follows; "Although these chemotherapeutic regimens were quite different from recent regimens, the two RCTs were conducted among patients with stage IIIA disease.".
Changes in the text: We deleted the sentence above mentioned.

Comment 16:
- you focus on sometimes stage IIIA and sometimes on stage I-IIIA. It's challenging to make broad conclusions
- Would it be more useful to focus on advanced NSCLC?
Reply 16: We consider the intent of reviewer B's comment. It is very clear to focus on advanced NSCLC, although many studies included stage I-IIIA patients. So, we reviewed the impact of induction systemic therapy with a total of I-IIIA NSCLC. We think it is difficult to focus on only current stage IIIA(UICC ver.8) because previous study had done with the previous UICC staging.
Changes in the text: None.

Comment 17:
- The conclusions that were drawn from section 1 in results were very interesting, but the overall narrative was hard to follow
Reply 17: Thank you for the favor comment. To make overall narrative better to be understood, we clarified that the effect of chemotherapy on stage I to IIB disease is controversial.
Changes in the text: Induction chemotherapy and EGFR-TKIs for stage IIIA NSCLC may contribute to the improvement of survival outcome although the effect of systemic therapy on stage I-II reminds controversial.(P4 L4-6)

Comment 18:
- The conclusion drawn about the complete resection rate being equal was also interesting... thanks for bringing attention to this. Describing circulating tumor cells vs. micrometastatic disease is stylistic

Reply 18: Thank you for the attractive comment. The research concerning ctDNA(https://www.science.org/doi/10.1126/sciadv.abi8618?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed) is very interesting. The amount of ctDNA may be a better biomarker for the prediction of distant metastasis and selection of induction therapy.
Changes in the text: None.

part 2
Comment 19: - INT0139 tested CRT, not chemo (line 5, page 11)
Reply 19: Thank you for the comment. The study is CRT vs CRT followed by surgery. This is the reference to illustrate the severity of pneumonectomy after CRT, not to illustrate the prognosis of chemoradiotherapy vs. chemotherapy.
Changes in the text: None.

Comment 20: - https://pubmed.ncbi.nlm.nih.gov/29338734/ consider citing for the fact that CRT has some benefits in terms of R0 resection, but potentially no impact on survival
Reply 20: Thank you for the comment. We added the sentence and the reference reviewer B demonstrated.
Changes in the text: Interestingly, chemoradiotherapy has benefit in terms of R0 resection, although there is no survival contribution by a meta-analysis Chen et al. reported [36]. The curative resection and pathological response may be surrogate marker, but special attention is needed to consider the results of clinical trials with advance NSCLC. (P12 L11-15)

Comment 21: - I think there is more to discuss in the landscape of EGFR TKI - consider mentioning the ongoing trials including those with Osimertinib
Reply 21: Thank you for the comment. We tried to search ongoing study using clinical trial gov(https://clinicaltrials.gov/), but there is no clinical trial concerning induction Osimertinib.
Changes in the text: None.

Comment 22: - might be helpful to discuss how "saving" TKI for adjuvant or for relapse might be better than isolating TKI resistant clones
Reply 22: The comment is very impressive and important for the use of TKI as induction therapy. Early use of TKI makes TKI resistant clones as the reviewer B pointed out. We added the discussion.

Changes in the text: In addition, the timing to use EGFR-TKIs is a crucial matter because early administration of EGFR-TKIs may lead drug resistant clones. We should investigate optimal timing to use EGFR-TKIs, whether adjuvant, induction or recurrence is best for NSCLC treatment. (P14 L10-13)

Comment 23:

- the final section could use some restructuring, rewording - the tables are quite good
- also should be mentioned that ICI induction may allow for downstaging of previously unresectable tumors (IIIB)

Reply 23: Thank you for the favorable comment. We added the sentence of downstaging of ICIs.

Changes in the text: Thus, ICIs addressed the great effect of cancer cell elimination in several clinical trials, we expect the downstaging of previously unresectable NSCLS and the control of lymph node metastasis when we use ICIs as induction setting.(P17 L6-9)

General Comments;

Comment 24: the scope of this study is challenging - I would consider focusing on II-III vs. including stage I trials as well.

Reply 24: Thank you for the Reviewer B's comment. Please refer reply17.

Changes in the text: None.

Comment 25: there are some sections eg. EGFR that are missing important data that helps give context

Reply 25: We added the important data to validate the impact of EGFR-TKIs.

Changes in the text:

-Recently, two RCTs showed that EGFR-TKI induction therapy "for patient with adenocarcinoma haboring EGFR mutations" tended to improv OS and PFS in comparison to platinum-based regimens [37,38] (Table 4). (P13 L9)

- although OS was not different between the two arms (45.8 months vs. 39.2 months; HR, 0.77; 95% CI, 0.41 – 1.45; P = 0.417).(P13 L16-17)

Reviewer C

Comment 1:
- regarding the search results, it is not clearly mentioned how many papers were retrieved and how many were excluded in the different categories, for which reason?
Reply 1: Thank you for focusing on the important point. We added the PRISMA diagram to clarify the papers search, the number of them and exclusion reason.
Changes in the text: The included and excluded process is demonstrated in Table S2 with the regard of the narrative review of RCTs (P7 L11-12).

Comment 2:
- the two last parts of this manuscript discussing the role of TKIs and ICIs are well described and updated; the first part on induction chemotherapy is quite confusing and the clinical implications are less clear. The authors should make a clear distinction between the different stages and their subdivisions of the 8th TNM classification, and provide some guidelines for clinical use which is the purpose of a literature review (differentiate between stages IA-IB-IIA-IIB-IIIA)
Reply 2: Thank you for pointing out an important issue on our manuscript. Certainly, the subgroup analysis in each stage is essential; however, it is very difficult to clarify it by a narrative review. The systematic review and meta-analysis can show the survival outcome in each stage. But, it includes hard matter to intergrade the different staging criteria.
So, we added the caution and limitations in the review due to the different staging criteria and mediastinal lymph node staging.
Changes in the text:
However, these results should be interpreted carefully because the clinical trials were performed more than 10 years ago. The TNM classification and mediastinal lymph node staging are different in each era. (P10 L16-18)

Comment 3:
- in the conclusions they only refer to stage IIIA although in the manuscript stages I to IIIA are mentioned.
Reply 3: I'm sorry to confuse the Reviewer C because the conclusion is unclear. We added the results of stage I-II disease having induction chemo- and chemoradiotherapy.
Changes in the text:
Abstract: "although the effect of systemic therapy on stage I-II reminds controversial." (P4 L4-6)

Conclusion: However, current evidence does not support the application of induction therapy in the treatment of early-stage NSCLC “(stage I and II)”. (P17 L13)

Comment 4:

-in table 2 only induction therapy versus no induction therapy is included and these are older studies (the most recent one is from 2013!) dealing with previous TNM classifications in an era where mediastinal staging was mostly done without PET scan and EBUS, EUS. More than 10 years ago combined modality therapy was already indicated for proven stage IIIA NSCLC including surgery, chemotherapy and radiotherapy for this specific stage. Large trials were performed to define better the role of surgery after induction therapy. I propose that the authors include a table with RCT evaluating multimodality therapy for stage IIIA (INT 0139 is mentioned but only for its high mortality; EORTC 08941 [Van Meerbeeck J.] and ESPATUE trial [Eberhardt W] are the most important ones with clinical relevance).

Reply 4: Thank you for pointing out very important limitations of the manuscript part1 and 2. We consider that different TNM classification in each era and different mediastinal staging due to the lack of PET-CT scan and EBUS may lead to wrong conclusion. We added the limitation in the text.

Second, we think evaluating multimodality therapy for stage IIIA (eg. INT0139, EORTC08941 and ESPATUE trial) is valuable. These trials are well designed and the consideration of multimodality therapy is important; however, the manuscript is aimed to demonstrate the impact of surgery with induction systemic therapy in advanced NSCLCs. So, we would like to focus on the trials designed to perform surgical resections (the control arm is chemoradiotherapy in these three trials).

Changes in the text: However, these results should be interpreted carefully because the clinical trials were performed more than 10 years ago. The TNM classification and mediastinal lymph node staging are different in each era.(P10 L16-18)

Comment 5:

- the English language and structure need to be thoroughly revised. Some phrases are difficult to understand as page 4 lines 4-5 and page 6 lines 6-8. There are quite a lot of typing errors as e.g. page 5 line 16 remains (instead of reminds) and tables 2-4 treatment modality (instead of mordality) and treatment regimen (instead of resimen)

Reply 5: Thank you for correcting our grammatical errors. We changed the incorrect and unclear sentence to be clearly understood.

Changes in the text:

-previously page4 lines 4-5: Induction chemotherapy and EGFR-TKIs for stage IIIA NSCLC may contribute to the improvement of survival outcome although the effect of systemic therapy on stage I-II remainds controversial. (P4 L4-6)
- previously page 6 lines 6-8: We would like to elucidate whether ICI therapy for operable NSCLC as induction therapy improves the poor OS. (P6 L11-12)
- previously page 5 line 16: removed the sentence.
- tables 2-4: We modified it.

Comment 6: - page 3 abstract line 15: please add "in patients with proven EGFR mutations"
Reply 6: Thank you for the proposal. We added the sentence in abstract.
Changes in the text: Epidermoid growth factor receptor (EGFR) tyrosine kinase inhibitors as induction therapy “in patients with proven EGFR mutations” may be a sufficient choice for the improvement of OS.(P3 L16)

Comment 7: - page 5 introduction line 4: please add "with the exception of stage I disease" as this stage has a good overall survival
Reply 7: We added the sentence as you suggested.
Changes in the text: although NSCLC remains associated with poor overall survival (OS) “with the exception of stage I disease”.(P5 L5)

Comment 8: - page 6 line 6: please add "for operable stage IIIA NSCLC"
Reply 8: In the review, we would like to elucidate the possibility of induction therapy among patients with operable NSCLC not IIIA disease.

Comment 9: - page 12 line 13: in the EMERGING-CTONG 1103 trial there was no difference in overall survival between both arms, this should be mentioned
Reply 9: We added the OS in the EMERGING-CTONG 1103.
Changes in the text: although OS was not different between the two arms (45.8 months vs. 39.2 months; HR, 0.77; 95% CI, 0.41 – 1.45; P = 0.417) (P13 L16-17)

Comment 10: -page 14: in the Checkmate 816 trial event-free survival was also significantly better in the treatment arm with ICI.
Reply 10: Thank you for the important comment. We added the EFS in the Checkmate 816.
Change in the text: The median EFS was longer in the nivolumab plus platinum doublet

arm than chemotherapy alone (30.2 vs. 20.8 months; HR 0.63: 97.38%CI 0.43-0.91; P = 0.005) (P15 L15-17)

Comment 11: - induction therapy with ICI may give rise to an inflammatory response making dissection of the pulmonary artery branches quite difficult; this should be mentioned

Reply 11: Thank you for the favorable comment. We added the difficulty of dissection of pulmonary artery.

Change in the text: Of note, inflammatory response following ICI therapy greatly influenced on the surgical procedure. It makes dissection of the pulmonary artery branches difficult. The influence of ICI on surgical procedure should be taken carefully. (P16 L11-13)

Comment 12: -in the discussion part the authors should also address the controversial topic of induction versus adjuvant therapy as they partially did on page 8 lines 15-16 (superiority of adjuvant chemotherapy)

Reply 12: Thank you for the sufficient comment. We added the benefit of adjuvant chemotherapy in ICI.

Change in the text: Certainly, the benefit of adjuvant ICI therapy has been proven in Impower010 [39]; however, it is unclear that ICI induction therapy can contribute to the prognosis of NSCLC. (P15 L17-P15L1)

Reviewer D

Comment 1: the cut-off studies review date of January 1, 2022, has greatly limited the discussion of the new era of neoadjuvant ICI-based therapies. In May 2022 CheckMate-816 was published (Forde e al NEJM May 26, 2022) with EFS and OS outcomes and subset and the NADIM trial published (Provencio et al JCO online May 16, 2022) with predictive baseline and post-neoadjuvant chemoIO ctDNA clearance OS outcomes. Given the title of the review an updated manuscript including a discussion of these results (and remarkable 75% Kaplan-Meier 4-year OS) are vital to the completeness of the narrative.

Reply 1: We are sorry to demonstrated the old data. We added and updated the data according the reviewer D's comment.

Change in the text:

Checkmate -816

The median EFS was longer in the nivolumab plus platinum doublet arm than chemotherapy alone (30.2 vs. 20.8 months; HR 0.63: 97.38%CI 0.43-0.91; P = 0.005) (P15L15-17).

NADIM

NADIM is a single-arm phase II trial among patients with stage IIIA NSCLC who were administrated with neoadjuvant nivolumab plus paclitaxel and carboplatin [51]. The 3-year OS reached 81.9% (95% CI, 66.8-90.6) and showed the possibility of ctDNA clearance as the favorable predictive biomarker for OS in induction ICI therapy. (P16 L16-P17 L1)

Comment 2: A deeper discussion of what outcomes are known, such as in NEOSTAR nivo-ipi higher MPR/PCR than nivo alone, but equal OS, and a discussion of ICI alone versus chemo-ICI. Without this, the narrative is outdated.

Reply 2: Thank you for the important implication. NADIM suggested that ctDNA is a better predictive biomarker for OS than pCR. We added the importance of ctDNA clearance and the elucidation of predictive biomarker in discussion of ICI induction therapy.

Change in the text:

Interestingly, the OS predictivity of pCR was inferior to ctDNA clearance (C-index for OS: 0.72 vs 0.82). The result implies that ctDNA may be a better predictive biomarker for the response of ICI treatment. Thereby, it is essential to elucidate the most favorable biomarker for the prediction of benefit of induction ICI therapy. (P17 L2-5)

Comment 3: Further phrasing and spelling checks are needed. Such as: p6 line 14, 15, and 16, article and study should be articles and studies; p10 line 11, remind should be remains; p14 line18, no chemotherapy-related deaths were observed (the not after the first no is not needed); chemoradiotherapy followed by a pneumectomy carries carries the very high mortality, not chemotherapy; among some others.

Reply 3: Thank you for pointing out the phrasing and spelling errors.
Change in the text:
article to "**articles**" (P7 L3)
study to "**studies**"(P4 L4, 5, P8 L7)
remind to "**remain**" (P11 L3)
no chemotherapy-related deaths to "**Chemotherapy-related deaths**"(P16 L6)