Peer Review File

Article information: https://dx.doi.org/10.21037/atm-21-1492

Reviewer A

Although the authors present a retrospectively analyzed and relatively small patient cohort, the importance of the topic and the well presented findings and dicussion let me tend to accept the manuscript for publication.

I would however recommend, that the mauscript, especially the abstract, the introduction and methods sections are revised by an english native speaker for clear and concise language.

I would like to thank the reviewer. I am grateful for your very thankful comment. We are sure of improving our manuscript with the additional information using the comments received from several reviewers.

Please note that English proofreading was finished by editage proofreading service.


editage

Editing Certificate

MANUSCRIPT TITLE

Survival benefit of immune checkpoint inhibitor monotherapy in patients with non-small cell lung cancer recurrence after complete pulmonary resection

AUTHORS

Firstname Lastname, Firstname Lastname and Firstname Lastname

ISSUED ON

June 01, 2021

JOB CODE

OAURO_11

Vikas Narang

Chief Operating Officer - Editage

Question to the authors:

Are there any patients that have received radiotherapy - especially sabr for metastasis after resection, but prior to CPI? It is known, that sabr to a lesion can increase respone of CPI in the whole body.

Thank you for your indication.

We prepared supplemental 2B and inserted the following sentences in results;

Eight patients (8/35, 22.9%) received local radiotherapy before ICI. There were no significant difference in the therapeutic outcomes after recurrence with or without radiotherapy (40.0% vs 48.2%, p = 0.98) (Supplemental Figure 2B).

Reviewer B

Manuscript is well written and provides additional information on immunotherapy treatment.

The biggest limitation is the small number of patients.

I would like to thank the reviewer. I am grateful for your very thankful comment. We are sure of improving our manuscript with the additional information using the comments received from several reviewers.

I would suggest some design improvements:

1) Evaluate the effect of ICI in different PD-L1 groups (also analyse those who did not undergo PD-L1 testing so far (n = 7))

Thank you for your indication.
We prepared the supplemental figure 1 and inserted the following sentences in Results;
The proportion of response for ICI was increased according to the TPS score (p < 0.01) (Supplemental Figure 1).

2) Assess the effect of ICI in groups with known gene changes vs not mutated. It is known from the past that no effect has been found in these in controlled studies, so their study can provide important information even when ICI is given in later than 2nd line treatment.

Thank you for your suggestion. We simply introduced the efficacies in Table 2.
Therefore, we inserted these following sentences in Results;

In addition, the 5-year therapeutic outcome from recurrence was equivalent between 1st and 2nd lines and more than 2nd line (46.6% (n =19) vs 49.2% (N = 16); (p = 0.08)).

While there is no significant difference in 5-year therapeutic outcomes from recurrence with or without ALK or EGFR {75.0% (n = 8) vs 37.1% (N = 27); (p = 0.08)}.

3) Why were so many different ICIs chosen? As I understand, it is a single institution study? Important to get information in the article about clinicians' considerations and experiences in the choice of drug.

Thank you for your indication.
We inserted these sentences in Materials and Methods:
The context of ICIs including the registration of clinical trials at the initial administration after the diagnosis of recurrence is decided by our institutional cancer board comprising thoracic surgeons, oncologists, and radiologists.

4) You mention the recurrence site published in other studies. Important information about this in your study is missing.

Thank you for your indication. We added these sentences in Results;
The median time from surgery to recurrence was 15.0 months (interquartile range; 8.9 to 21.9). The recurrence sites were locoregional in 19 (54.3%) and distant in 16 (45.7%).

Abstract:
Missing aim in Introduction.

Thank you for you advise. Reviewer D is a similar indication, too.

Selected patients in non-small cell lung cancer (NSCLC) responded to the treatment of immune checkpoint inhibitors (ICIs) have the survival benefit for advanced stages or metastatic status.

Introduction:
Missing references in several places in the first section

We added the references.

Materials and Methods

Missing information on there is single institution study?

Thank you for your suggestion. However, we stated that 'We retrospectively analyzed the clinical data of 51 patients diagnosed with recurrence after complete pulmonary resection for NSCLC who received ICI monotherapy since January 2016 during the therapeutic course, including nivolumab, pembrolizumab, atezolizumab, and ipilimumab, at Aichi Cancer Center Hospital.'

When did recurrence occur?

Where did the recurrence occur? Recurrence site?

Thank you for your indication. We added the following information into Results;
The median time from surgery to recurrence was 15.0 months (interquartile range; 8.9 to 21.9). The recurrence sites were locoregional in 19 (54.3%) and distant in 16 (45.7%).

What was the postoperative control routines?

Thank you for your advice.
We inserted the following sentences into Materials and Methods;
In the follow-up duration, chest to upper abdominal Computed Tomography was routinely performed on a semi-annual basis. Brain Magnetic Resonance Imaging and Positron Emission Tomography were added 1, 2 and 5 years after surgery.

«51 patients diagnosed with recurrence after complete pulmonary resection for NSCLC between December 2009 and October 2017». How many all patients were operated during this period? What was the incidence rate of recurrence?

Thank you for your indication. I am sorry for my vague expression.
We retrospectively analyzed the clinical data of 51 patients diagnosed with recurrence after complete pulmonary resection for NSCLC who received ICI monotherapy since January 2016 during the therapeutic course, including nivolumab, pembrolizumab, atezolizumab, and ipilimumab, at Aichi Cancer Center Hospital. One hundred eight hundred twenty-five patients underwent pulmonary complete resection between December 2009 and October 2017, and 381 patients (20.9%) were diagnosed as recurrence.

"51 patients diagnosed with recurrence after complete pulmonary resection …» Should be moved to Results.

Thank you for your advice.
Fifty-One patients diagnosed with recurrence after complete pulmonary resection for NSCLC who received ICI monotherapy during the therapeutic course. The CONSORT flowchart for patient selection and inclusion is shown in Figure 1. Thirty-five patients (68.6%) were candidates in this retrospective and single-institutional study.

Not stated abbreviation and minimum information for TPS

Thank you for your invitation.
We inserted.

Results
A lot of information is already in Table 1, so the first chapter in Results can be shortened.

Thank you for your suggestion. We added.

ECOG information can also be moved to Table 1.

Thank you for your suggestion. We moved it to Table 1.

Has the stated ECOG been assessed before starting with ICI or preoperatively?

We inserted before starting with ICIs into Materials and Methods.

Why has Nivolumab been chosen the most times? Interesting to read about their experiences

Thank you for your suggestion. Pembrolizumab was approved by FDA at the same time as the first line. In addition, this cohort include the checkmate trials for recurrent NSCLC at those time.

Discussion
In Abstract it is stated that «The 5-year overall survival (OS) rate from recurrence was 47.5%».
What survival was there before ICI treatment was introduced?

Thank you for your indication. We changed 'therapeutic outcome'.

«In this study, the presence of EGFR mutation or ALK rearrangement did not significantly influence the survival of patients with recurrence after complete pulmonary resection compared with ICI monotherapy". Information about this is not presented in Results.

Thank you for your suggestion. We provided and inserted into Results;

While there is no significant difference in 5-year therapeutic outcomes from recurrence with or without ALK or EGFR {75.0% (n = 8) vs 37.1% (N = 27); (p = 0.08)}.

«NCCN guideline» Missing reference and abbreviation.

Thank you for your discovery of the hypos. I inserted.

Reviewer C

In this work, Kuroda et al, reports on the impact of the response to ICI Monotherapy (defined as DCR (PR+CR+SD)) on the survival (PFS to be more accurate) of NSCLC patients with recurrence after complete pulmonary resection and the relationship between DCR to CRP, PNI, PET parameters pre resection, pre starting ICI, and delta change. They showed an association between DCR to ICI and PFS. As well as association between CRP/PNI and DCR.

The authors appropriately identify the limitations of this 35 patients retrospective study including the PDL1 missing data, EGFR/ALK incident in East Asia and impact of TKI on prognosis.

I would like to thank the reviewer. I am grateful for your very thankful comment. We are sure of improving our manuscript with the additional information using the comments received from several reviewers.

I have only minor suggestions for improved clarity, can the authors show the effect of DCR on OS. Also, the authors are using the term "survival" when describing PFS. The term "survival" usually is referred to OS, knowing the OS and PFS are not the same.

Thank you for your advice. We use 'OS', but I think that the usage of this word is confused. Therefore, we changed 'OS' in 'the therapeutic outcome after recurrence' in all text.

There was no significant difference in the therapeutic outcomes after recurrence with or without radiotherapy (40.0% vs 48.2%, $p = 0.98$) (Supplemental Figure 2B).

Reviewer D

This is a small retrospective analysis trying to determine the role of ICIs response influenced the surivival of NSCLC patients with recurrence. The study encompassed a long time period (when ICIs were not yet approved for this diagnosis!?). Nowhere in the article is it stated how patients in 2009 were able to receive ICIs for NSCLC. Nowhere in the article is it stated why patients with EGFR mutation or ALK rearrangement would

be candidates for ICIs (when it is clear that they do not respond to ICIs). This thing needs to be addressed prior to being able to evaluate the specifics of the work.

I would like to thank the reviewers. We are sure of improving our manuscript with the additional information using the comments received from several reviewers.

Minor revisions:
Abstract: Change the introduction line, it is irrelevant.

Thank you for this indication. We investigated the role of ICI responder in clinical course after recurrence. Therefore, we changed them in these following sentences; Reviewer B is a similar indication, too.
Selected patients in non-small cell lung cancer (NSCLC) responded to the treatment of immune checkpoint inhibitors (ICIs) have the survival benefit for advanced stages or metastatic status.

Introduction
"As a radiological biomarker, 18 21 F-flurodeoxyglucose positron emission tomography/computed tomography (18 22 F-FDG PET/CT) reflects the interaction between 23 the metabolic tumor burden and immune pathways"
Comment: I strongly disagree with this statement, to date, there is no radiological modality or tracer being widley used in the clinic that can determine the immune tumor microenviorment. As a matter of fact, the usage of 18 F-FDG PET/CT has many limitations when it comes to distinguishing true progression from inflammatory responses in patients with NSCLC and SCLC.

Thank you for your suggestion. We used your provided sentences and inserted these following sentences in Discussion:
In addition, there is no radiological modality or tracer being widely used in the clinical practice that can determine the immune tumor microenvironment. In other words, the use of ^{18}F-FDG PET/CT for effect measurement is still controversial.

Methods:

I am unsure how the cut-offs for the lab values were chosen, it seems to me that a cut-off for CRP is very arbitrary and not useful, other publications have chosen a cutoff of 10 in order to really establish an ongoing inflammatory process. I also cannot accept that the only reasoning for the blood work comes from referring to an older publication made by the authors. This needs to be elaborated further in this paper.

Thank you for your indication. Only 1 patient (2.8%) had the value of CRP > 10 in this cohort. Our previous report revealed that Clinical parameters, such as PS, CRP levels (≥ 1 mg/dl), serum LDH, and smoking status, were significantly associated with the response duration and survival in patients treated with nivolumab. This reported is cited by 32 articles. In addition, the mean and median CRP were 1.37 and 0.67 at 1 month after operation and 1.71 and 0.49 before ICI. We inserted the 3 classifications (CRP: only increase, +1.0 mg/dl, and + 2.0 mg/dl) in Table 3.

Also, were all the blood work pre- and post-surgery done at the same time? Meaning, just before the patients were operated? How was 1 month after surgery chosen as a cut-off? Seems to me like a very narrow scope in order to delineate changes in the patients.

Thank you for your indication. In our institution, all patients suffer the blood work two days before operation, 1 month and 3 months after surgery. We inserted the following sentences in Materials and Methods; Perioperatively, the blood works were performed two days before surgery, and 1 month after surgery.

In addition, Shinohara et al. reported the increase of CRP6w may serve as a prognostic biomarker in patients with resected NSCLC (Shinohara et al. Anticancer Res. 2019 39(4)2193-98). We want to investigate whether postoperative chronic inflammation affect the clinical course in this cohort.

Results:

Please be advised of my major revision comments. It is incomprehensible to me how

patients with EGFR and ALK can be candidates for ICIS. And the same goes for patients diagnosed in 2009 with this diagnosis. The authors need to address these concerns prior to further

We are sorry for this mistake.
Surgery since 2009, and ICI since 2016.
We changed in Materials and Methods as followings;
We retrospectively analyzed the clinical data of 51 patients diagnosed with recurrence after complete pulmonary resection for NSCLC who received ICI monotherapy since January 2016 during the therapeutic course, including nivolumab, pembrolizumab, atezolizumab, and ipilimumab, at Aichi Cancer Center Hospital. One hundred eight hundred twenty-five patients underwent pulmonary complete resection between December 2009 and October 2017, and 381 patients (20.9%) were diagnosed as recurrence.

We published in 2020 that ICI treatment was significantly less efficacious in patients with ALK rearrangement than in patients with EGFR mutations. It was true that we used the ICI in the patients with TKI failure as late-line at those days.