Peer Review File
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Reviewer A

General considerations

I understand this is a small case series from a single centre which focuses on efficacy and safety of Osimertinib in relapsed resected EGFR ex19del/p. L858R NSCLC (I very much appreciate this is a rare clinical scenario and it probably took years to have enough patients on follow-up – well done).

Interestingly, I can't find previous studies focusing on this – therefore, there is an element of novelty.

Comment 1:

I don't really see anywhere an explanation of why this is a piece worth writing/publishing/reading -> something along the lines of 'ongoing debate as to whether adjuvant osi after resection vs. starting osi at recurrence is the best option', 'no other case series in this space' -> 'we curated a case series at our institution in which we documented patterns of recurrence and efficacy and safety of Osimertinib after recurrence'. Ultimately, you want to convey that recurrence may well lead to poor PS or brain mets, and those patients will do badly – much better to try adjuvant Osimertinib a go and delay those occurrences (and avoid them if possible).

This may well be obsolete in a week with OS data from ADAURA been presented at ASCO. Could you include considerations stemming from this into your revised version?

Reply 1:

We changed the introduction and discussion as well as abstract, in order to clarify the strength of this manuscript as indicated. We also added OS data from ADAURA and the reference.

Changes in the text:

In p3; lines 3-4, we changed the sentence from

"it remains controversial whether all eligible patients should receive osimertinib as adjuvant therapy following tumor resection."

to

"there is still some ongoing debate, as osimertinib has been approved based on disease-

free survival rather than overall survival. We curated a case series in which we documented patterns of recurrence and efficacy and safety of osimertinib after recurrence."

In p6; lines 8-9, we changed the sentence from
"However, because overall survival has not yet matured, there is a debate as to whether all eligible patients should be treated with osimertinib."
to
"Furthermore, the planned final analysis of overall survival (OS) showed a better survival in the osimertinib arm with a hazard ratio of 0.49, without reporting any new adverse events of special interest (2). Nevertheless, there is still an ongoing debate regarding whether adjuvant osimertinib after surgical resection or starting osimertinib at the time of disease recurrence is the best option."

In p7; lines 3-5, we changed the sentence from
"We retrospectively analyzed the clinical outcomes of patients who received osimertinib as first line treatment after surgery to examine why it is important to use osimertinib as adjuvant therapy."
to
"To answer this question, we curated a case series at our institution in which we documented patterns of recurrence and the efficacy and safety of osimertinib after disease recurrence."

In p15; lines 13-15, we changed sentences from
"Although the adverse events were more commonly observed than in the clinical trials, no treatment related mortality occurred. The use of osimertinib as adjuvant therapy is recommended unless contraindicated."
to
"While starting osimertinib at the time of recurrence effectively rescues most patients, recurrence with poor PS and brain metastasis is associated with abysmal outcomes; since the drug is well tolerated, starting treatment in the adjuvant setting is sensible."

In p18 line 4, we added reference 2. Tsuboi M, Herbst RS, John T, et al. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. N Engl J Med 2023. online ahead of print.

Detailed suggestions

Comment 2:
Lines 7-8: leptomeningeal metastasis is not the primary foci of this manuscript – please remove; how about you remove ‘adverse event’ and include ‘osimertinib’, ‘relapsed resected NSCLC’, ‘case series’

Reply 2:
We changed the keywords as indicated.

Changes in the text:
In p4; lines 8, we changed keywords from
“Adjuvant therapy, leptomeningeal metastasis, molecular targeting therapy, adverse event”
to
“Adjuvant therapy, osimertinib, molecular targeting therapy, relapsed resected NSCLC, case series”

Comment 3:
What is known and what is new paragraph
I wouldn’t use the word ‘controversial’ to describe adjuvant Osimertinib. It is widely used and recommended by guidelines. I would say that there is still some ongoing debate in the scientific community as Osimertinib has been approved based on DFS rather than OS.
‘Pts treated with osi after recurrence have high rate of adverse events’ -> this needs to be a separate bullet point

Implications
I’m not sure this study leads to the implications mentioned here…

Reply 3:
We changed what is known and what is new paragraph as indicated.

Changes in the text:

In p5; lines 6-10, we changed sentences from

- Osimertinib treatment is effective in advanced lung cancer, but adjuvant osimertinib treatment is still controversial.
- The treatment outcome is poor in patients with brain metastasis or with deteriorated PS, and patients treated with osimertinib after disease recurrence have a high

incidence of severe adverse events.

to

- There is still some ongoing debate in the scientific community as osimertinib has been approved based on DFS rather than OS.
- The treatment outcome is poor in patients with brain metastasis or with deteriorated PS.
- Patients treated with osimertinib after disease recurrence have a high incidence of severe adverse events.

Comment 4:

Page 6, Lines 3-5

Wordy. Cut down words by paraphrasing. Make sure 'phase III study comparing osi…' and 'ADAURA trial' are in the same sentence

Reply 4:

We cut down words by paraphrasing as indicated.

Changes in the text:

Page 7, lines 2-8, we changed sentences from

"Osimertinib has been approved as adjuvant therapy in various countries, following the positive result of a phase III study comparing osimertinib given daily for three years with placebo after complete resection of lung cancer with *EGFR* mutation. The study, as known as ADAURA study, demonstrated a superior disease-free survival in the osimertinib arm with a hazard ratio of 0.17 among patients with stage II to IIIA disease (a primary endpoint), which exceeded an expectation and the trial was unblinded in April 2020 (1)."

to

"Osimertinib has been approved as adjuvant therapy in various countries following a positive result of superior disease-free survival (DFS) in the osimertinib arm with a hazard ratio of 0.17 among patients with stage II to IIIA disease (a primary endpoint). This phase III study (ADAURA), which compared osimertinib given daily for three years to a placebo after complete resection of lung cancer with EGFR mutation, exceeded an expectation and the trial was unblinded in April 2020 (1)."

Comment 5:

'We retrospectively analyzed the clinical outcomes of patients who received

4 osimertinib as first line treatment after surgery to examine why it is important to use
5 osimertinib as adjuvant therapy.' -> can you please elaborate further on this and how it relates to the ongoing scientific debate

Reply 5:
We changed the sentence as indicated.

Changes in the text:
In p7 lines 3-5, we changed the sentence from
"We retrospectively analyzed the clinical outcomes of patients who received osimertinib as first line treatment after surgery to examine why it is important to use osimertinib as adjuvant therapy."
to
"To answer this question, we curated a case series at our institution in which we documented patterns of recurrence and efficacy and safety of osimertinib after disease recurrence."

Comment 6:
Page 9-10
There are two paragraphs detailing ethical considerations – is it a copy and paste which didn't work out as planned? Please edit

Reply 6:
We deleted duplicated paragraphs as indicated.

Changes in the text:
In p17, lines 7-11, we deleted sentences below
"Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the internal review board of Oita University Faculty of Medicine (IRB No. 698).
Consent to participate: Informed consent was obtained from all individual participants included in the study."

Comment 7:
Line 3-4. I'm not sure I understand. Can you explain what you mean? 'disease recurrence in most patients was revealed by follow-up CT or MRI, they

4 had no measurable disease'. You mean that most had no measurable disease and therefore you preferred time on treatment over ORR?

Reply 7:
Yes, we chose time on treatment over ORR, because the most patients had no measurable disease.

Changes in the text:
Not available

Comment 8:
Lines 6-9. We scan them more often – CTTA every 3 month, MRIH every 6. Appreciate there may not be a lot of evidence behind these practices – can you dig out any relevant guidelines to justify the practice in your institution?

Reply 8:
The follow-up schedule we describe here is for postoperative survey after curative resection, not for advanced setting. We also cited an NCCN guideline.

Changes in the text:
In p9; line 9, we added a citation (15),
and added a reference in p19; line 8,
15. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20:497-530.

Comment 9:
Page 11.
Lines 2-4. It is not very clear that we are looking at Osimertinib commenced after disease relapse, rather than adjuvant Osimertinib - ?am I right or am I getting it wrong? Could you make it more explicit please.

Reply 9:
We changed sentence the sentence as indicated.

Changes in the text:

In p11; lines 3-4, we changed the sentence from
"Twenty patients received osimertinib (male, n=6; median age, 86 years [range 55-85 years]) (Table 1)."
to
"During the period, twenty patients who received first-line osimertinib treatment after disease recurrence were identified (male, n=6; median age, 86 years [range 55-85 years]) (Table 1)."

Comment 10:
Line 6. Change to 'in all but two' -> too many numbers in one line, it's confusing
Line 13. 'Poorer outcomes', rather than poor survival – you are using DoT as an OS surrogate

Reply 10:
We corrected the words as indicated.

Changes in the text:
In p11; line 6, we changed the word "in all but 2" to "in all but two"
In p11; line 13, we changed the word "poorer survival" to "poorer outcomes"

Comment 11:
Line 14-16. You have extremely small numbers of patients with PS 1/PS 3, driving quite bizarre results (worse DoT for pts with PS 1 vs. PS3). Lump PS 0 and 1 together and compare with PS 3 or take out PS survival analysis all together because the numbers are really too small to generate useful conclusions

Reply 11:
We put PS1 and PS3 together and re-calculate the median DoT and logrank p value.

Changes in the text:
In p11; line 14-16, we changed the sentence from
"PS was also related to DoT, although the number of patients with poor PS was small (DoT not reached in PS0, 2.5 months in PS1, 6.4 months in PS3, p=0.002, Figure 1C)."
to
"PS was also related to DoT, although the number of patients with poor PS was small (DoT was not reached in PS0, 2.5 months in PS1-3, p=0.0005, Figure 1C)."

We also re-calculate and corrected the Figure 1C.

Comment 12:
Page 12, lines 12-13. PS deterioration seems to be a surrogate for clinical progression here – elaborate.
Line 14. Mechanism of resistance -> 'not certain', replace with 'unknown'.
Line 15. ;small cell, … and went on to receive carbo/etop/atezo'.
Line 17.Remains on maintenance atezolizumab

Reply 12:
We corrected these mistakes as indicated.

Changes in the text:
In p12; lines 13, we deleted "and/or PS deterioration"
In p12; line 14, we changed the words from "not certain" to "unknown"
In p12; line 15, we combined the sentences by changing ". The patient received" to "and went on to receive"
In p12; line 17, we changed the words from "is still on" to "remains on"

Comment 13:
Page 13. Lines 3-5. The fact that high specificity for activating EGFR mutations translates into a very favourable toxicity profile is implicit in this sentence – make it explicit

Reply 13:
We changed the sentence as indicated.

Changes in the text:
In p13; lines 3-5, we changed the sentences from
"Because osimertinib is highly selective for mutant EGFR (16), it can also be delivered to patients with a deteriorated PS, elderly patients, and patients with co-morbidities."
to
"Because osimertinib also demonstrates high specificity to activating EGFR mutations, it shows a very favorable toxicity profile (18). Therefore, it can also be delivered to patients with a deteriorated PS, elderly patients, and patients with comorbidities."

Comment 14:

Lines 5-7. I'm not entirely sure this point is relevant here? Either make the relevance clearer or remove

Line 9. 'either resectable or advanced' -> suggest removing

Reply 14:

We removed the sentence and words as indicated.

Changes in the text:

In p13; lines 5-7, we deleted the sentence below

"In the ADAURA study, a proportion of patients who were not treated with adjuvant platinum doublet in the osimertinib arm also showed superior DFS in comparison to the placebo arm (17)."

In p13; line 9, we deleted the words "either resectable or advanced"

Comment 15:

Lines 9-11. 'Patients should be carefully examined for CNS
10 metastasis, as it frequently leads to a decline in PS, analogous to the impact of bone
11 metastasis'. Please clarify by CNS examination – do you mean MRI head? By the time there are focal neurological abnoirnalities detectable on clinical examination, CNS metastases tend to be quite advanced…

Reply 15:

Yes, we mean MRI head for CNS examination.

Changes in the text:

In p13; line 10, we added "with brain MRI"

Comment 16:

Lines 11-12. 'Although osimertinib is effective not only for patients with CNS metastasis
12 but also for patients with a deteriorated PS' -> these two concepts are disjointed, rewrite so that they are in two different sentences

Line 13. New paragraph here is needed – don't continue within same paragraph with new concepts

Reply 16:

We rewrote the sentences as indicated.

Changes in the text:

In p13; lines 11-12,

“Although osimertinib is effective not only for patients with CNS metastasis but also for patients with a deteriorated PS, the PFS is shorter in patients with a poor PS (19-21).”

to

“Although osimertinib is effective for patients with CNS metastasis, the PFS is shorter in those patients (23).”

and we also added a new reference below (23) for this subject;

23. Xie L, Nagpal S, Wakelee HA, et al. Osimertinib for EGFR-Mutant Lung Cancer with Brain Metastases: Results from a Single-Center Retrospective Study. Oncologist 2019;24:836-43.

Then, we moved the latter part of this sentence to the previous paragraph by adding p13; line 7

“However, the PFS is shorter in patients with a poor PS when they are treated with osimertinib (19-21).”

Comment 17:

Page 14

Line 1. Do we have hard data on this (CNS penetration of osi) eg Kp u,u? If from preclinical studies that’s ok.

Reply 17:

We added the comparison of gefitinib, elrotinib and osimertinib CNS penetration data and reference as indicated.

Changes in the text:

In p13; line 20, we added the sentences below

“The difference between the drugs, especially in patients without CNS metastasis, is not clear. In patients with CNS metastasis, the CNF penetration rates were similar between drugs, with gefitinib being 1.13 to 1.30% (26,27) and osimertinib being 0.79 to 1.47% (28,29).”

and also added references 26-29 listed below.

26. Togashi Y, Masago K, Masuda S, et al. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. Cancer Chemother Pharmacol 2012;70:399-405.

27. Zhao J, Chen M, Zhong W, et al. Cerebrospinal fluid concentrations of gefitinib in patients with lung adenocarcinoma. Clin Lung Cancer 2013;14:188-93.
28. Jenkins S, Yang JC, Ramalingam SS, et al. Plasma ctDNA Analysis for Detection of the EGFR T790M Mutation in Patients with Advanced Non-Small Cell Lung Cancer. J Thorac Oncol 2017;12:1061-70.
29. Yamaguchi H, Wakuda K, Fukuda M, et al. A Phase II Study of Osimertinib for Radiotherapy-Naive Central Nervous System Metastasis From NSCLC: Results for the T790M Cohort of the OCEAN Study (LOGIK1603/WJOG9116L). J Thorac Oncol 2021;16:2121-32.

Comment 18:
Lines 2-4. Now you are referring safety data from FLAURA rather than ADAURA – make it clearer please (adequate comparison as this cohort is having 1st line tx of relapsed disease).

Reply 18:
We made it clearer by adding FLAURA to the text.

Changes in the text:
In p14; line 2-3, we changed the sentence from
"As for adverse events, the incidence of interstitial pneumonitis is the greatest concern in advanced lung cancer treated with osimertinib (all-grade, 3.9%; grade ≥3, 2.1%) (25)"
to
"As for adverse events, the incidence of interstitial pneumonitis is the greatest concern in advanced lung cancer treated with osimertinib (all-grade, 3.9%; grade ≥3, 2.1%, FLAURA trial) (31)"

Comment 19:
Line 13. I think there are more papers exploring this – safety of Osimertinib rechallenge +/- steroid cover after pneumonitis. Can you check and reference them if more case reports/case series are available?
Lines 17-18. The same group (TRACERx Lung consortium) have recently published another paper on the matter – 2023, Nature Medicine I think. Does ADAURA include MRD monitoring via ctDNA analysis?

Reply 19:

We added and updated references as indicated.

Changes in the text:
In p14; line 13, we added reference (37) below
37. Kodama H, Wakuda K, Yabe M, et al. Retrospective analysis of osimertinib re-challenge after osimertinib-induced interstitial lung disease in patients with EGFR-mutant non-small cell lung carcinoma. Invest New Drugs 2021;39:571-7.
In p14; lines 19, we updated the reference from (33)
33. Jamal-Hanjani M, Wilson GA, McGranahan N, et al. Tracking the Evolution of Non-Small-Cell Lung Cancer. N Engl J Med 2017;376:2109-21.
to (40)
40. Abbosh C, Frankell AM, Harrison T, et al. Tracking early lung cancer metastatic dissemination in TRACERx using ctDNA. Nature 2023;616:553-62.

Comment 20:
Page 15
Line 11-15. The conclusion is rather weak. I think the overall message here is that, while starting osimertiinib at recurrence effectively rescues most patients, recurrence with poor PS and brain mets is associated with abysmal outcomes; since the drug is well tolerated, starting treatment in the adjuvant setting is sensible.

Reply 20:
We changed the conclusion as indicated.

Changes in the text:
In p15; lines 13-15, we changed the sentences from
“Although the adverse events were more commonly observed than in the clinical trials, no treatment related mortality occurred. The use of osimertinib as adjuvant therapy is recommended unless contraindicated.”
to
“While starting osimertinib at recurrence effectively rescues most patients, recurrence with poor PS and brain metastasis is associated with abysmal outcomes; since the drug is well tolerated, starting treatment in the adjuvant setting is sensible.”

Comment 21:
References -no 13 – CTCAE – please add author/title and not just the website link

Reply 21:
We modified the reference 13 (now it is 14) as indicated (there were no author listed).
Changes in the text:
We modified reference from
13.https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed on March 12, 2023).
to
14. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. 2017.
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed on March 12, 2023).

Reviewer B

Comment 1: CNF/IALT should be defined upon first use in the Main Text.
Reply 1: We carefully followed your kind comments and revised as indicated.

Comment 2: Figure 1
The full term of DoT is “duration of osimertinib treatment”.
A space should be added between the words “DoTMonth”.
Reply 2: We carefully followed your kind comments and revised as indicated.

Comment 3: Table 1
Column headers are needed.
y.o. needs to be defined.
The median age reported in the table and the Main Text are different.
Reply 3: We carefully followed your kind comments and revised as indicated.

Comment 4: Please indicate the source of the data included in this study.
Reply 4: We carefully followed your kind comments and revised as indicated.