Peer Review File

Article Information: https://dx.doi.org/10.21037/tau-23-588

Reviewer A

The editorial comment succinctly describes the key findings of the keynote 426 study with 43 months follow-up, including the limitations of the treatment protocol perceptible at a longer follow up.
Reply: Thank you.

Reviewer B

The authors provide a great comment in a neutral position against the article described about extended follow-up of KEYNOTE-426 trial. The readers may be able to easily and fully understand about advantage and disadvantage of the combination therapy consisted of pembrolizumab and axitinib. I think this editorial comment is worthwhile for publication.
Reply: Thank you.

Reviewer C

I have some concern with statements in this editorial commentary:

1) IO combinations have demonstrated long term durable response compared to TKI therapy alone. This is also the fact for the final result of the Pem/Axi combination. I am not sure why the authors challenge this fact? There is clear superiority of combination therapy.

Reply: This is very important point. Although Pem/Axi showed superiority over sunitinib, looking at the survival curve, the Kaplan-Meier curve made a downward slope to the right. So, we described "it has not been demonstrated that the responses are durable". We think this point needs to add.
Changes in the text: P2, Line 47
→looking at the survival curve, the Kaplan-Meier curve made a downward slope to the right. So,

2) The authors summarize, "that this final report showed that pembrolizumab plus axitinib is effective in the early stages of treatment, we recommend it when patients need an early response

to treatment". I do not entirely agree to this statement and feel it needs correction. There are other IO/TKI combinations that have much greater ORR and show improved early response. Therefore, this Axi/Pembro combo is good, but not superior to other combos. Thus, we cannot draw this conclusion from the final results.

Reply: I understood that other IO/TKI combinations, such as Nivolumab/Cabozantinib and Pembrolizumab/Lenvatinib, showed excellent efficacy. But, these IO/TKI regimens cannot be directly compared. Although I avoided including details about other IO/TKI regimens, we revised this conclusion.
Changes in the text: P3, Line 86
It → the ICI plus TKI therapy that include this

Reviewer D

This paper is the Editorial Comment for the 43 months follow-up analysis paper of KN426.
In favorable risk, both PFS and PFS2 were better in P+A than in su. However, the OS is almost the same. I predict that various factors are intricately related and lead to this result. The authors argue that the IMDC risk classification is based on TKI treatment, making interpretation of favorable risk difficult. As the author indicates, P+A is certainly effective in the early stages of treatment.
I don't think there are any major problems with this paper.

Minor
1. 3-year landmark OS remained superior at 63 months in the combination arm in line 35. The correct is 63%. You should also modify line 36 as well.

Reply: I apologize my mistake. I revised these points.
Changes in the text: P2, Line 35, 36
Months → %

Reviewer E

1. page 2 line 36. The authors should clarify this data that the HR here is regarding the median PFS. This is a change from the prior focus of the sentence of data regarding landmark analysis.

Reply: Thank you for your advice. These data were quoted from the original paper.
We added this point because the HR is regarding the median data.
Changes in the text: P2, Line 36

→, which was for the median OS,

2. page 2, line 39-21. Please include the range on not just report the HR.

Reply: Thank you for your advice. We added these data with the HR.
Changes in the text: P2, Line 41
→HR 0.68; 95% confidence interval, 0.58-0.80

3. page 2, lines 42-44. This argument might be strengthened further if you state the durability of responses for comparison in the sunitinib arm. Some readers might feel that 45% of patients not progressing at 3 years is a durable response for many patients (which it is).

Reply: This is very important point. Looking at the survival curve, the Kaplan-Meier curve made a downward slope to the right, unlike the durability of treatment efficacy seen with IOIO. We think this point needs to add.
Changes in the text: P2, Line 47
→looking at the survival curve, the Kaplan-Meier curve made a downward slope to the right. So,

Reviewer F

This article provided an overview of the results from the KEYNOTE 426 trial, including an extended follow-up. The detailed outcomes were presented in an easily understandable manner. The long-term observation revealing the continued superiority of Pembrolizumab plus axitinib for IMDC intermediate/poor-risk patients was intriguing. This is particularly noteworthy considering that Pembrolizumab was stopped at 35 cycles as per the protocol, and three-quarters of sunitinib recipients received ICI in the second-line therapy. The manageable nature of axitinib may be attributed, in part, to its short half-life.

Reply: I agree that the treatment duration of pembrolizumab and the half-life of axitinib are also important points.

Reviewer G

This commentary provides a thoughtful response to the 43-month follow-up data from the phase III keynote-426 trial, where the combination therapy of pembrolizumab and axitinib was compared to sunitinib alone as the primary drug therapy for metastatic/unresectable clear cell

renal carcinoma. The commentary effectively outlines key points that require attention.

The authors pointed out that the efficacy of pembrolizumab plus axitinib could not always be durable, as well as that there was no difference in OS compared to the sunitinib alone group in the IMDC favorable group. They also pointed out that the article was inadequate in that there was no sub-group analysis of the IMDC poor risk alone.

The commentary underscores the authors' perspective that the efficacy and adverse effects of IO plus TKI combinations are influenced by the characteristics of the TKIs employed. The authors also commend the manageable adverse effects of axitinib compared to cabozantinib and lenvatinib could contribute positively to the overall profile of pembrolizumab plus axitinib combination therapy.

For the reader's better understanding, two points that should be corrected are discussed below.
(1) In the opening paragraph, this commentary states that avelumab plus axitinib, along with nivolumab plus cabozantinib and pembrolizumab plus lenvatinib, suggest better outcomes than sunitinib alone. The characteristics of pembrolizumab and axitinib compared to avelumab plus axitinib should also be mentioned.

Reply: Thank you for your advice. The difference between pembrolizumab plus axitinib compared to avelumab plus axitinib is a difference in ICIs, but the difference has not been clearly established in clinical.
We added this point in the opening paragraph.
Changes in the text: P1, Line 27
→ In addition, the difference between the combination of avelumab plus axitinib and the combination of pembrolizumab plus axitinib was the type of ICI, but both showed similar efficacy.

(2) It should be noted that the keynote-426 study only included patients with clear cell renal carcinoma. This ensures that readers recognize the specific patient population under consideration.

Reply: Thank you for your advice. We revised this point.
Change in the text: P1Line 28
→as treatment of clear cell RCC

Changes in the text for abbreviation: P1, Line 26
→ (RCC)