Peer Review File
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Reviewer A

The manuscript presents a unique case of an 8-year-old male patient diagnosed with transcription factor E (TFE) translocation renal cell carcinoma (tRCC). It describes the use of highly personalized treatment approaches, encompassing surgery, chemotherapy, targeted therapy, and immunotherapy. The manuscript is well-structured and the information is clearly organized. Nonetheless, there are some areas that require attention.

Major points- the answer

1. *To make the discussion more engaging, it would be helpful to include a de-identified summary of the test results for the 831 tumor-related genes. It's difficult to access driver mutations without detailed information. Regarding the PALB2 mutation, please specify the variant fraction and loss of heterozygosity (LOH) status. Additionally, are there any additional mutations in key cancer genes as identified by COSMIC?*

Reply: Thank you for your question. We have provided additional information in the fourth paragraph of the "Case presentation", which is highlighted in red. The results of testing for tumor-related genes, except as mentioned in the text, showed that the patient also had an amplification of *ASCL2*. This study did not search the COSMIC database for comparisons, thank you for your suggestions, we will follow up with an in-depth analysis.

2. *As the author mentioned, this tRCC contain a considerable density of tumor-infiltrating CD8+ T cells. However, this finding raises concerns about the tumor fraction of this sample, as the rate of mutation discovery is confounded by tumor fraction, potentially leading to an underestimation of the tumor mutational burden (TMB). In addition, where is the evidence of infiltration of lymphocytes in the tumor?*

Reply: Thank you for your question. Indeed, with respect to tumor-infiltrating CD8+ T cells, we are basing this on the references, infiltration of lymphocytes in the tumor ditto as well.

3. *TFE3 fusions typically occur in-frame with a partner gene that may be encoded on either chrX or on an autosome, suggesting such important fusions are highly like to be functional [1]. As only one chrX homolog is available for rearrangement in males, the TFE3 fusion may occur on the only copy of TFE3, potentially leading to its activation through this fusion. Given the importance of this fusion in tRCC, I would have liked to investigate biological functions and genomic features of the fusion partner - ideally by target sequencing.*

Reply: Thank you for your advice. Combined multi-omics research has been very fruitful in the field of oncology, including target sequencing as you mentioned, so more in-depth research is also urgent for the advanced tumors described in this paper.

4. *Regarding therapeutic approaches, Expert 3 has already provided a comprehensive summary. As there is insufficient evidence to strongly advocate for immunotherapy, prioritizing therapies targeting the TFE3-related pathway, such as PIK3CA/AKT/mTOR pathway, could be a promising treatment strategy.*

Reply: Thank you for your advice. Indeed, we have a long way to go by being reviewed by the present case study that combination therapy targeting the mTOR pathway may be effective, but it also needs to be confirmed by more clinical data.

Minor points:

1. *In the line 88, the authors mention that " Fluorescence in situ hybridization (FISH) testing for TFE3 on the tumor sample revealed a breakpoint frequency of 44%, surpassing the threshold of 20%.". It would be beneficial to provide a concise and detailed methodology of the FISH. This should elucidate how breakpoint frequency is determined and how the threshold is defined.*

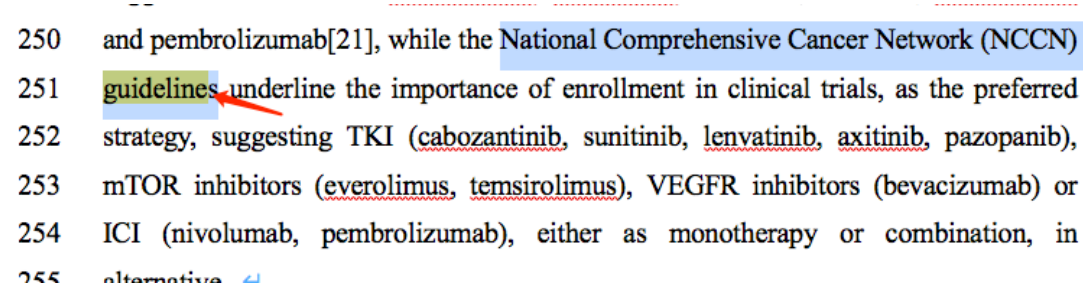
Reply: This part of the results was tested by the Molecular Testing Center of XXX Medical University, and we added a brief description "(44/100,randomly counting 100 tumor cells)" and labeled with red font.

[1] https://www.biorxiv.org/content/10.1101/2023.08.04.552029v1

Reviewer B

1. Reference

It seems that reference for this guideline is missing. Please provide. References should be cited consecutively and consistently according to the order in which they first appear in the text.


250 and pembrolizumab[21], while the National Comprehensive Cancer Network (NCCN)
251 guidelines underline the importance of enrollment in clinical trials, as the preferred
252 strategy, suggesting TKI (cabozantinib, sunitinib, lenvatinib, axitinib, pazopanib),
253 mTOR inhibitors (everolimus, temsirolimus), VEGFR inhibitors (bevacizumab) or
254 ICI (nivolumab, pembrolizumab), either as monotherapy or combination, in

Answer: Done.

2. The references in the text are out of order. The references should be cited in order of their appearance in the text. Ref. 14 should be cited between Ref. 13 and Ref. 15. Please revise.

Answer: Modified

3. The information of Ref. 18 in the main text differed from the information in the reference list. Please revise.

Answer: The original narrative was ambiguous and has now been revised.

Change "the group of Thouvenin and by Martinez Chanzà et al." to "Hirsch et al".

Answer: Modified

Otherwise, please indicate the citations of "Thouvenin et al." study and "Martinez Chanzà et al." study in this sentence. Change "the group of Thouvenin and by Martinez Chanzà et al." to "Thouvenin et al. (Ref. X) and by Martinez Chanzà et al. (Ref. X)".

Regarding more specifically MiT-RCC, evidence is scarce. According to retrospective analysis by the group of Thouvenin and by Martinez Chanzà et al., on 52 and 17 patients with metastatic MiT-RCC[9], cabozantinib seemed to provide benefit, either in first- or later-lines, with an objective response rate (ORR) of 17.3% and 29%, respectively.

482 [9] → HIRSCH L, MARTINEZ C N, FARAH S, et al. Clinical Activity and Safety of Cabozantinib
483 for Brain Metastases in Patients With Renal Cell Carcinoma. JAMA Oncol, 2021, 7(12):
484 1815-1823.

4. The authors mentioned "studies...", while only one reference was cited. Change "Studies" to "A study" or add more citations. Please revise. Please number references consecutively in the order in which they are first mentioned in the text.

Particularly, in retrospective studies, cabozantinib seemed to show better benefit when administered in first-line than in later-lines (mPFS of 6.8 months, 11.7 months for first-line, 6.5 months in later-lines)[23].

Answer: Modified