Review of: "Advancements in the Detection and Treatment of Rare ALK Fusion Mutations in Hepatocellular Carcinoma: A Case Report and Literature Review"

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Potential competing interests: No potential competing interests to declare.

The authors Qiu Yan et al highlight the significant clinical benefit with the use of ALK inhibitors for the rare ALK fusion mutation in HCC and advocate for the integration of NGS into standard clinical practice in this subset of patients.

To enhance the good proposal of the review, it could be interesting to discuss some issues that might offer crucial insight:

- About the cost impact of using NGS in clinical practice. NGS would be the gold standard to detect ALK rearrangement, but probably, we are far from using NGS in every HCC patient, as there are no other significant known oncodrivers (with implications for the decision of therapy) in this disease, and it is an expensive technology. It should also be discussed whether to widely use IHC as a first instance, as it is a costless and fastless technology, for other future clinical studies.
- In the article, the authors did not promote the use of DNA NGS for detecting ALK cng+ or mutations. There is some data about the implication of ALK copy number gain+ as a possible prognostic factor of outcome in advanced stages. Could this information increase the appeal for using NGS?
- Is there a correlation between ALK cng+ and rearranged ALK?
- It could be interesting to underscore some data about the correlation of ALK mutated/rearranged patients with a poor prognosis. The review provides data only about the COX7A2L-ALK fusion and its more aggressive profile.
- It could be interesting to know the percentage of ALK rearranged-positive tumors on the total of HCC cases diagnosed.
- Could the mutation of ALK, found after treatment with ALK inhibitors of first or second generations, be covered by the spectrum of activity of an inhibitor of third-generation ALK TKI?
- From our knowledge in NSCLC, it could be interesting to underscore if there are or not some prevalent characteristics in these patients, such as patient age, gender, ethnic group, radiological and histopathological characteristics, if mentioned, in order to use NGS maybe in a specific subgroup of patients.
- It could be interesting to know, if there are available data, something about the tolerance of the therapies with ALK inhibitors in this subset of patients revised, because it is known that they can worsen liver function.

In the final part of the discussion section, it is mentioned the ASCEND-8 clinical study. The study evaluated the doses of 450 mg or 600 mg of ceritinib taken with a low-fat meal versus 750 mg in a fasted state in patients. So maybe it could be revised the dose of ceritinib.

Last observation: it would be more appropriate to take into account the use of the term “mutations”, in favor of using “rearrangement mutations” or “fusion mutations” in order not to create misunderstanding. (as in the statement in the abstract “both DNA- based and RNA-based, in detecting these mutations legging to targeted treatment approaches with alk inhibitors” and in the discussion section “NGS approaches offer a more inclusive detection of actionable mutations, thereby facilitating tailored therapeutic strategies”

To the editor: This paper has relevance to the field, it deals with unmet needs, and could also provide the foundation for a future systematic review. I think to reconsider it after improving these minor revisions.