Peer Review File

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Reviewer A

Unlike previous data, this paper showed the efficacy of PD1/PD-L1 inhibitors in some gene-rearrangement positive NSCLC.
I think it is worth the acceptance.

Response: Thank you.

Reviewer B

Immunotherapy is currently the standard of care for patients diagnosed with advanced non-small cell lung cancer - both in the first and second line of treatment. The evaluation of the value of this method in patients with molecular abnormalities, especially those with low incidence, is still an important issue. I therefore congratulate the authors on taking up the topic and updating their analysis of the previously published IMMUNOTARGET report. A case report of five patients with gene abnormailities in the RET, ALK and ROS1 genes is presented. The results presented are interesting and can have an impact on clinical practice, but I have a few comments.

1. Cases of reported objective responses or of PFS > 6 months with immune monotherapy among NSCLC patients harboring an ALK, NTRK, RET or ROS1 rearrangement were extracted- one of the presented patients had stable disease (it is not objective response, according the RECIST 1.1). Could the authors consider taking into account also patients with stabilised disease?

Response: Thank you for this comment. One of the major goals of this project was to see if any of the gene-rearranged cases with seeming 'benefit' from immunotherapy had good evidence to support the description of 'benefit.' As such to include shorter durations of stable disease would run the risk of inflating benefit. We have added wording to the discussion to clarify this.

2. Only patients whose clinical benefit persisted for > 6 months were included. Was a cut-off point of 3 months considered? This could increase the sample size and provide additional insights.

Response: Thank you. Please see the response above.

3. It would be valuable to consider additional clinical parameters that may influence the efficacy of immunotherapy - for example, the diameter of measurable lesions. Information on the safety of immunotherapy could also be included in the table.

Response: Thank you. Responses were determined by the research team at each contributing site to the IMMUNOTARGET registry as per RECIST 1.1 criteria. However, lesion size in the broader immunotherapy field has not specifically been associated with response to therapy. Safety data were not collected but as the host, not the tumor would determine this, it is unlikely this would be influenced by driver oncogene. We have added wording to the Methods section to clarify this.

4. Has immunotherapy been used in the described cases as a second-line treatment after failure of targeted drugs?

Response: Thank you. As per Table 1, column N this is already detailed. In one case of ROS1 rearrangement immunotherapy was used after failure of TKI, but in ALK rearrangement immunotherapy was used prior to TKI exposure.

5. What optimal treatment sequence do the authors currently recommend for patients with low incidence molecular abnormalities? Is there still a place for immunotherapy in monotherapy?

Response: Thank you. This is an important question. We have expanded in the discussion on this. Considering the very small sample size further exploration is needed to assess the features associated with underlying immune responsiveness in gene rearranged NSCLC. The data suggest responses can occur but are very rare. As per available data the general role of immune monotherapy is very limited in gene rearranged NSCLC.

Reviewer C

This is an interesting and important investigation, presented clearly and in a short and informative review. It is known that immune checkpoint inhibitors can benefit some gene-rearranged patients, and this manuscript provides further evidence of this by effectively summarizing the findings of the initial IMMUNOTARGET cohort, added 3 new cases to this cohort of gene-rearranged immune-responders and attempted to validate their gene-rearranged status. However, this manuscript has two weaknesses:
1) Methodology requires much more detail (see comments below)
2) While the study aims were good, the actual number of cases identified as immune-responding (n=5) is small and there is, unfortunately, a lack of demographic/clinical details which could impact patient response to ICI.

Major comments:
1) No clear methodology on how response and PFS were assessed, making this very subject to high variability/bias and could also be impacted by individual patient follow-up schedule. Since patient selection for this study was based on PFS > 6 months it is important to understand how this was determined and allow comparison to other studies.

a. Indicated in the Discussion (line 170) is that response was recorded as 'PFS rather than RECIST-based response criteria'. This is confusing; was progression not based on RECIST criteria as in the original IMMUNOTARGET analysis? If not, then what was the criteria for PFS?

Response: Thank you. We meant only that the investigators quantified benefit from the TKIs by PFS not response rate, but have deleted this line to avoid confusion.

b. Was best response based on RECIST criteria?

Response: Thank you. Yes, as per updated Methods section, this was based on RECIST.

c. Who determined response and progression (physician, reporting radiologist, other), or were there any supporting documentation to corroborate the response?

Response: Thank you. Data were reported and documented by physician at each site contributing to the IMMUNOTARGET registry and communicated to this study team via emails. We have clarified this in the Methods.

2) The authors have indicated they did not include the denominator (those treated with ICI without benefit). Although this is acknowledged in the paper, this makes it very difficult to understand how frequently a beneficial response to ICI might occur in gene-rearranged NSCLC or how responders and non-responders are similar or different. More clarity on why this was omitted would be useful.

Response: Thank you. We agree. This is one of the major limitations of this study as the data in the registry was from multiple sites and data for this study based on inclusion criteria was retrieved by individually emailing those sites, and it was very hard to determine exact value of denominator.

3) Lack of patient characteristics. Although again acknowledged by the authors, this is a large limitation of this study. Age, performance status, disease stage, and type/extent of metastatic disease, rate of CNS involvement, etc. would be useful to know. Additionally, other management methods such as radiation therapy (particularly to control thoracic or CNS disease) would be important to understand in the context of ICI therapy and the potential combined impact on systemic treatment response and PFS.

Response: Thank you. The primary goal was to see if ANY evidence of IO benefit in gene rearranged NSCLC (appropriately identified as such) existed. We agree that, as mentioned in the limitation of this study, we do not all that information and there could be certain confounding factors in these patients and have expanded on this in the discussion section.

Minor comments:

1) RET-rearranged patients: did these patients have prior TKI treatment? It is not clear from Table 1 whether this information is not available, or not applicable. If these patients were not previously treated with a targeted agent, do you have any information on why these patients were treated with ICI in the first-line setting? And with multiple TKI available for ALK and to a lesser extent ROS1, do you have information on why ICI was opted for in the 2L setting instead of another targeted TKI? Is this an accessibility/funding barrier in the treatment centres of this study?

Response: Thank you. The RET rearranged patients were not treated with a RET-specific TKI and one of the possible explanations could be lack of availability of RET TKI at the institution at the time. We mention this in the discussion now.

2) Since the majority of this study cohort was comprised of patients not in the original IMMUNOTARGET dataset, were selection criteria for these patients the same as those within the IMMUNOTARGET dataset?

Response: Thank you. Yes, the Selection criteria were the same as the initial IMMUNOTARGET data, but focusing to include patients with gene rearrangement NSCLC who had responses or PFS >6 months to immune monotherapy.

Reviewer D

The authors presented five cases of advanced non-small cell lung cancer with gene arrangement who achieved durable response to immune checkpoint inhibitor monotherapy. As a key message, the authors provided insights that some patients with driver oncogene can benefit from immunotherapy, although preceding studies have shown the inferior efficacy for such population. Despite of small number of cases, the data itself can have certain implications to develop treatment strategies for this population integrating immunotherapy in their clinical courses. However, in my opinion, several revisions are warranted before considering this manuscript for publication. Please see my comments below.

Major comments:

1. The authors provided data for only five cases who achieved durable response to immunotherapy, not in comparison with majority who did not show response. I think lack of data (e.g., total number of gene rearrangement cases, clinical background, etc.) on “non-responders” in their cohort impaired the comprehensibility of the literature. They did not find any clinical characteristic to differentiate responders. I recommend the authors to provide data both responder and non-responder. If not possible, please carefully provide the explanations on the inability to access to such data as a major limitation of this study.

Response: Thank you. As noted above, we agree this is one of the limitations of this study. As the data in the registry was from multiple sites and data for this study based on

inclusion criteria was retrieved by individually emailing those sites, and it was very hard to determine exact value of denominator.

2. Table 1: The authors should provide more detailed data on parameters (e.g., ECOG-PS, age, stage, number of organs involved, line of treatment etc.) which are important to predict prognosis on immunotherapy.

Response: Thank you. Unfortunately, as we expand on in the discussion lack of these parameters are one of the limitations of this study.

3. Table1, case with unspecified RET fusion: Please provide the reasons (e.g., irAE?) why duration of immunotherapy was largely shorter than PFS.

Response: Thank you. Unfortunately, safety was not captured and we don't have further information about the reason why immunotherapy was discontinued. As per the information we received patient continued response despite of immunotherapy discontinuation at 11.63 months.

Minor comments:

1. It is not clear whether no NTRK case achieved response to immunotherapy.

Response: Thank you. We could not find an NTRK case who responded or had PFS >6 months to immune monotherapy. We have clarified this in the Results section.