Original Article

PD-1/PD-L1 inhibitor activity in patients with gene-rearrangement positive non-small cell lung cancer—an IMMUNOTARGET case series

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Background: Prior IMMUNOTARGET registry data had suggested that responses to immune [anti PD(L)1] monotherapy in gene-arranged non-small cell lung cancer (NSCLC) were rare or absent, depending on the specific oncogene.

Methods: IMMUNOTARGET sites reporting prior registry data or new individual cases of gene rearranged NSCLC seeming to benefit from immune monotherapy were explored in detail looking to both validate their diagnosis of a functional gene rearrangement and to look for features potentially differentiating them from other such cases associated with low response rates.

Results: Five cases of NSCLC with a gene rearrangement with reported responses or prolonged stabilization from immune monotherapy were identified in total. All had little or no prior smoking history and had programmed death-ligand 1 (PD-L1) values ranging from zero to 100%. A confirmed rearrangement partner was reported in only 2 of the cases (CD74-ROS1 and KIF5B-RET), however in one of the other three cases [analplastic lymophoma kinase (ALK)], significant benefit from a relevant prior targeted therapy was noted, also consistent with the rearrangement status being correctly assigned.

Conclusions: Not all driver oncogene subtypes of NSCLC are equally responsive to immune monotherapy, however even among patients with well-validated gene rearranged NSCLC which has traditionally been considered immune hyporesponsive, objective responses can occur. Additional explorations of the features associated with and underlying the immune hypo-responsiveness of most, but not all, cases of gene-rearranged NSCLC are required.

Keywords: Anaplastic lymphoma kinase (ALK); Ros proto-oncogene-1 (ROS1); rearranged during transfection (RET); programmed cell death 1 (PD-1); programmed death-ligand 1 (PD-L1); case series

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Introduction

IMMUNOTARGET represents an international collaborative effort to document the benefit of anti-programmed cell death 1 (anti-PD-1) or anti-programmed death-ligand 1 (anti-PD-L1) immune monotherapy among patients with advanced non-small cell lung cancer (NSCLC) harboring at least one identified oncogenic driver (1). Within the initial publication of the group 551 patients were analyzed, treated within 24 centers from 10 countries. Objective response rates (ORR) and progression free survival (PFS) did appear to vary by driver with, notably, anaplastic lymphoma kinase (ALK)-rearranged NSCLC (n=23) appearing to derive no discernible benefit from the immunotherapy (0% ORR and a median PFS 2.5 months). This is consistent with an overall perception that ALK and potentially other gene-rearranged subtypes of NSCLC may be particularly PD-1/PD-L1 inhibitor refractory (2). There are now four different gene-rearranged subtypes of NSCLC with approved targeted therapies [ALK, neurotrophic tyrosine receptor kinase (NTRK), rearranged during transfection (RET) and Ros proto-oncogene-1 (ROS1)]. The initial IMMUNOTARGET dataset did not include any NTRK-rearranged cases. RET-rearranged NSCLC (n=16) was similarly reported in the initial dataset to be hypo-responsive [6% ORR (1/16), 2.1 months median PFS], however ROS1-rearranged NSCLC (n=7) was associated with a 17% ORR (without data on duration of benefit available), although this also represented only a single responding case (1/6). However, whether any of these 'benefitting' cases represented either valid gene rearrangement cases, or valid PD-1/PD-L1 inhibitor benefit has to questioned.

In order to test the hypothesis of whether there was complete PD-1/PD-L1 inhibitor refractoriness in gene-rearranged NSCLC we sought additional details from the IMMUNOTARGET sites submitting these and any additional cases of gene-rearranged NSCLC reported to be responding or otherwise deriving benefit with immune monotherapy. In particular, we sought to question whether any apparent examples of benefit were occurring in unequivocally diagnosed gene-rearranged cases. As false positive diagnoses of driver oncogenes can occur, we explored the potential validity of these data by annotating, among other datapoints, the diagnostic methods used, the smoking history and PD-L1 status of the cases and whether they had had documented prior benefit from a relevant targeted therapy. We present the following article in accordance with the AME Case Series reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-329/rc).

Methods

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 from both the existing IMMUNOTARGET registry and, during 2019 and 2020, participating IMMUNOTARGET sites were also directly queried via email for any additional cases to submit. Responses were determined by the research team at each contributing site to the IMMUNOTARGET registry as per RECIST 1.1 criteria. Individual investigators with potential cases were then contacted and asked to complete additional details in relation to the following: reported gene rearrangement present, immunotherapy used, best response on immunotherapy, PFS on immunotherapy, duration of response on immunotherapy, duration of immunotherapy, pack years of smoking, histology of NSCLC, PD-L1 tumor proportion score (local assays), tumor mutation burden (local assay) oncogene diagnostic used, initial targeted therapy for driver oncogene, response/benefit from initial targeted therapy, whether the immunotherapy was given before or after the targeted therapy and any additional comments on the features of the case. Participating centers were responsible for patients' consent and institutional approval. All contributors were trained in Good Clinical Practice. The study was a purely academic collaboration granted by both Toulouse and Lucerne Hospitals and was not funded by industry. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data were abstracted retrospectively in accordance with local institutional permissions. Prospective informed consent of the patients was not a part of the study.

Results

Significant case details were available on 5 cases of gene-rearranged NSCLC reported to have either objectively responded or achieved stable disease >6 month on immune monotherapy (ALK = 2 cases, RET = 2 cases, ROS1 = 1 case). No NTRK immune 'benefiting' cases were identified. The details of each case are contained in *Table 1* and the images showing a complete response on nivolumab from the first ALK$^+$ case were previously published (3).

Table 1 Details of immune-benefitting gene rearranged NSCLC cases

Reported gene rearrangement present	Oncogene diagnostic used	Immune monotherapy utilized	Best immunotherapy response	Immunotherapy PFS (months)	Immunotherapy duration of response (months)	Duration of immunotherapy (months)	Smoking pack years	NSCLC histology	PD-L1 (tumor proportion score)	Initial TKI	Response/ benefit from TKI	Immunotherapy given before or after initial TKI
ALK	IHC, FISH	Nivolumab	CR	21	16	21	0	Adeno	100%	Ceritinib	PFS 4.96 months	Before
ALK	IHC, FISH	Nivolumab	SD	6.28	NA	6.31	0	Adeno	0%	Crizotinib	PFS 30 months	After
RET (KIF5B-RET)	Nanostring	Atezolizumab	PR	8	3	8	3	Adeno	>1%	No TKI used	NA	NA
RET (mutation or translocation not specified)	Not reported	Pembrolizumab	PR	23.69	Not reported	11.63	0	Unknown	Not reported	No TKI used	NA	NA
ROS1 (CD74-ROS1)	FISH, NGS	Nivolumab	PR	36	36	36	0	Adeno	100%	Crizotinib	PFS 12.02 months	After

NSCLC, non-small cell lung cancer; PFS, progression free survival; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; RET, rearranged during transfection; ROS1, Ros proto-oncogene-1; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NGS, next generation sequencing; CR, complete response; SD, stable disease; PR, partial response; NA, not applicable.

No cases had information on tumor mutation burden and so these data are not included in the table.

Of the five immune-benefiting cases, all had little or no prior smoking history, and had PD-L1 values ranging from zero to 100%. With regard to the potential for false positive gene rearrangement diagnoses, beyond the appropriate association with low/no smoking history, a confirmed rearrangement partner was reported in only 2 of the cases (CD74-ROS1 and KIF5B-RET), however in one of the other three cases (ALK), significant benefit from a relevant prior targeted therapy was noted, also consistent with the rearrangement status being correctly assigned. In one ALK case only modest tyrosine kinase inhibitor (TKI) benefit (PFS 4.96 months) was noted. In only one case (described as 'RET positive' without additional data, potentially not even differentiating between a rearrangement or mutation) was their no relevant partner reported by next generation sequencing (NGS) or equivalent, and no prior exposure to a RET inhibitor to independently assess RET dependency. In one of the cases immunotherapy was given before the TKI but no excessive toxicity was reported when the TKI was started per the treating physicians.

Discussion

Although not all gene-rearranged subtypes of NSCLC have been studied with the same level of detail, certain key features traditionally associated with these oncogene-driven forms of lung cancer suggest that they are less likely to be responsive to PD-1/PD-L1 inhibitors than other forms of NSCLC. Specifically, they tend to occur in never or light smokers and in younger patients, all of which may lead to a lower tumor mutation burden (2). Although the creation of a gene fusion and subsequent fusion protein will inevitably create a potential neoepitope at the fusion point not found in non-malignant cells, the products of driver oncogenes are rarely immunogenic themselves (2). Although gene-rearranged tumors may have elevated PD-L1 levels, when studied in ALK rearranged lung cancer these levels are not associated with $CD8^+$ tumor infiltrating lymphocytes (4). Consequently, PD-L1 levels may not have the same predictive potential for immunotherapeutic benefit as they are being increased directly in relation to the oncogene's signaling cascade rather than induced to mediate immune evasion from an initiated T-cell mediated attack.

While the prior IMMUNOTARGET registry presentation only included 2 cases of apparent immune-responding gene-rearranged NSCLC (1 × RET and

1 × ROS1), we have been able to study these two cases and three others, identifying 5 apparent benefiting cases (2 × ALK, 2 × RET and 1 × ROS1) to explore in further detail (*Table 1*). We have not re-evaluated the denominator to include those treated who did not benefit in addition to these 'benefitting' cases. Instead, we have proposed optimal methodology for validating them as potentially true gene-rearranged cases to permit their representativeness of immune-responding gene rearranged NSCLC to be assessed. Four of these cases were associated with prolonged objective responses to immunotherapy (range, 3–36 months) and one with stable disease of 6.28 months. PFS durations ranged from 6–36 months. No cases were reported with non-adenocarcinoma histology and all cases had little or no smoking history, consistent with true gene-rearranged disease. Two of the four cases with reported PD-L1 scores had scores of 100%. One of the immune benefiters had levels only described as >1% without a specific level being described, however the other immune benefiter had a PD-L1 score of zero. Only one of the four benefiting cases with details on the diagnostic assay utilized NGS (CD74-ROS1). One utilized nanostring technology (KIF5B-RET) and two were diagnosed by only immunohistochemistry or fluorescence in situ hybridization (FISH) (both ALK). While immunohistochemistry and FISH have both been associated with false positive results, one of the ALK cases in this series appeared to derive prolonged benefit from initial crizotinib consistent with a true ALK rearrangement being present, although crizotinib does have activity against other molecular targets including ROS1 and MET (5-7). This case was previously written up as one of the first ever cases of an ALK positive tumor responding to immunotherapy (3). In this publication, a second ALK responding case is now also described. In the other ALK case in the series there was evidence of more abbreviated treatment benefit (duration <5 months) with ceritinib as their initial TKI.

Our data are limited in number and multiple potentially relevant additional details were absent. Immune monotherapy 'benefit' was defined as more than 6 months of stable disease or an objective response. Shorter durations of stable disease could have been explored but the concern was that as true immune benefit tends to be prolonged including shorter durations would inappropriately over-inflate the benefit seen. While several geographically separated pleural nodules were shown to be responding in the previously published case, being able to review all of the scans of those who 'responded' to either the immunotherapy or the targeted therapy, or of knowing if additional local therapies such as radiation could have confounded the apparent benefit seen would be desirable (3). Details on the patients performance status, number of organs involved, size of deposits, etc. are lacking. Details on potentially relevant co-mutations such as TP53 or immunohistochemical evidence of the presence or absence of infiltrating T lymphocytes in the presence of high or low PD-L1 scores were not available (4). In addition, accurate denominators of comparably profiled cases to truly quote an expected benefit rate from immunotherapy in well or poorly characterized potential gene-rearranged NSCLC cases are missing. Nevertheless, the concept of immune benefit in some true cases of gene rearranged NSCLC appears valid albeit with the continued impression that these cases represent exceptions compared to other subtypes of NSCLC. In a recent small series in RET-rearranged cases, 3 of 9 RET-rearranged cases were reported to manifest an objective response to immune monotherapy (8). However, it should be noted that all of these RET cases were diagnosed by FISH and no data on prior response to RET targeted therapy was provided, possibly due to limited access to specific RET TKIs at the time. As immune monotherapy has rapidly moved out of standard practice, beyond first line use among those with high PD-L1 levels in those without a known driver oncogene, and chemo-immunotherapy is now much more commonly employed, parsing out benefit from immunotherapy in driver oncogene subtypes treated with chemoimmunotherapy in the future will likely be impossible (9). Not least because a significant proportion of gene rearranged NSCLC can be hyper-responsive to the pemetrexed contained in many chemoimmunotherapy regimens (10). Of note, the pemetrexed-free IMpower 150 regimen of carboplatin, paclitaxel, bevacizumab and atezolizumab did appear to show a non-significant trend to PFS benefit in a retrospective analysis of 34 ALK^+ NSCLC cases included in the trial compared to the same regimen without the atezolizumab (11). However, we do not know that these cases were balanced in terms of other risk factors between the arms, nor have we seen a large randomized data set with this or any other chemoimmunotherapy regimen in ALK-rearranged NSCLC or other gene-rearranged NSCLC to see if the data hold up under more scrutiny.

These new data from IMMUNOTARGET continue to suggest that not all driver oncogene subtypes of NSCLC are equally responsive to immune monotherapy, however even among patients with ALK rearranged NSCLC responses, in which no prior unequivocal benefit had been reported, objective responses can occur. Nevertheless, as these cases

appear to be exceptional in nature, the role of PD-1/PD-L1 directed immunotherapy in gene-rearranged NSCLC has to be considered very unlikely to add benefit and, arguably, should be deprioritized in any treatment decision-making. Additional explorations of the features associated with and underlying the immune hypo-responsiveness of most, but not all, cases of gene-rearranged NSCLC are required. Comparable explorations in other driver oncogene-addicted subtypes should be considered.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-329/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-329/prf

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Participating centers were responsible for patients' consent and institutional approval. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data were abstracted retrospectively in accordance with local institutional permissions. Prospective informed consent of the patients was not a part of the study.

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