Editorial

Immune checkpoint inhibitors for patients with gene-rearranged non-small cell lung cancer

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Introduction

Although first-line targeted therapies are the current standard-of-care treatment for non-small cell lung cancer (NSCLC) with driver alterations, therapeutic resistance is inevitable. Immune checkpoint inhibitor (ICI) regimens are one of the standard-of-care options after disease progression on targeted therapies. ICI improved the outcomes of metastatic NSCLC without driver alterations. Although the clinical benefit of ICI for patients with epidermal growth factor receptor *(EGFR)* alteration is limited, their efficacy in patients with other driver alterations is unknown because each driver alteration occurs in 1% to 5% of patients with NSCLC (1-3).

The IMMUNOTARGET registry was the first global multicenter registry to report the clinical outcomes of patients with NSCLC with *EGFR*, *KRAS*, *ALK*, *BRAF*, *ROS1*, *HER2*, *RET*, and *MET* alterations (2). The overall response rate in gene rearrangement was low in this registry [ALK, 0% (n=23); RET, 6% (n=16); ROS1, 17% (n=7)]. Similarly, prior studies have reported a limited response to ICI for gene-rearranged NSCLC regardless of programmed death-ligand 1 (PD-L1) status, but all of them have limitations due to small sample sizes and retrospective analyses (3-7). On the other hand, some patients with gene-rearranged NSCLC responded to ICI for a long time (8). Thus, in the case of gene-rearranged NSCLC, detailed information on who will benefit from ICI remains a major unmet need.

Mushtaq *et al.* (9) described the details of five cases with gene-rearranged NSCLC who had durable responses to ICI monotherapy in the IMMUNOTARGET registry (RET, n=1; ROS1, n=1) and an additional survey (ALK, n=2; RET, n=1; ROS1, n=1). Clinicopathologic features were used to determine whether these cases had true gene rearrangement. All cases had adenocarcinoma histology and no or little smoking history, which is consistent with true gene-rearranged NSCLC. Next-generation sequencing (NGS, CD74-ROS1) and nanostring technology (KIF5B-RET) were used to identify fusion partners in two cases. The ROS1 and RET cases received the robust clinical benefit of ICI and had immunotherapy PFS of 36 and 8 months, respectively. Only immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) was used to diagnose two ALK cases. In patients with ALK

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rearrangement, 0.2–21% had discordant IHC and FISH results, and a single assay could result in false positive cases (10). While one of the two ALK cases had long-term benefits from crizotinib, indicating a true ALK rearrangement, another case had only <5 months of PFS, suggesting a false positive. The former ALK case had a 6.3-month immunotherapy PFS after receiving the clinical benefit of ICI. One RET case was recently described as "RET positive" with no prior exposure to RET inhibitors, raising questions about the existence of true RET rearrangement. The authors not only show that ICI is ineffective in gene-rearranged NSCLC but also cast doubt on the registry study's diagnostic methods.

When we investigate cases of gene rearrangement that benefit from ICI, it is critical to validate whether they are true gene rearrangements, not least because the subset is small. The diagnostic methods used for molecular testing in previous studies varied (*Table 1*). Moreover, some studies have not reported details of molecular testing (11,12). As mentioned in ALK IHC, variations in diagnostic methods may result in the inclusion of false positive cases. For example, RET FISH had high sensitivity and low specificity, resulting in a high proportion of false positive results (18). Thus, the study using RET FISH may have included false positive cases, resulting in a higher ORR of 38% with ICI monotherapy, as opposed to the poor ORR of other studies (0–7.7%, *Table 1*) (6). Similarly, ROS1 FISH can result in a false positive, so confirmation by another method, such as NGS, is recommended (19). Multiplex DNR and/or RNA NGS techniques are recommended in the first-line setting due to their high sensitivity and specificity; however, they are not reimbursed in some countries or situations. In these cases, at the very least, confirmation is required, such as IHC screening followed by FISH confirmation (10).

A multicenter study is required to investigate the infrequent clinical outcomes of a small subset, such as gene-rearranged NSCLC that benefits from ICI. However, several important pieces of information were not reported in previous studies (*Table 1*). It is recommended to report diagnostic methods, fusion partners, and ICI-benefiting details for each case: sex, age, smoking, histology, and benefit from prior targeted therapy. Additionally, co-occurring genomic alterations would need to be documented because some co-alterations, such as *STK11/KEAP1* or *SMARCA4* alterations, can influence ICI efficacy (20,21). Although many items on case report forms influence the speed, with which data are collected for studies, the critical information associated with the validation of driver alterations should be collected. A global RET registry with a multicenter network is currently being established to collect clinical outcomes on ICI and their associations with clinicopathologic features (22). More registry work is needed in other cases of gene-rearranged NSCLC.

A post hoc analysis of prospective clinical trials may be able to address the issue of inconsistency in molecular testing caused by retrospective studies. ICI monotherapy has moved out of the standard of care in patients with driver alterations; it is difficult to use ICI monotherapy as a comparator arm. In a clinical trial of gene-rearranged NSCLC, ICI chemotherapy (ICI chemo) can be used as the comparator arm, allowing us to estimate ICI efficacy. Several phase III trials for first-line treatment of gene-rearranged NSCLC are currently underway to compare the efficacy of targeted therapy versus ICI chemo. LIBRETTO-431 (NCT04194944) is a randomized phase III trial comparing selpercatinib with carboplatin or cisplatin and pemetrexed chemotherapy with or without pembrolizumab in patients with metastatic RET-rearranged NSCLC who have not previously received treatment (23). Another phase III trial, AcceleRET Lung (NCT04222972), compares pralsetinib with chemotherapy with or without pembrolizumab as first-line treatment for metastatic RET-rearranged NSCLC (24). Further post hoc analysis of patients in the control arm who received ICI chemo is warranted to investigate, which clinicopathologic features affect the response to ICI, despite the fact that chemotherapy confounds their results. The Impower150 study [bevacizumab plus carboplatin plus paclitaxel (BCP) versus atezolizumab plus BCP] included 34 patients with ALK-rearranged NSCLC; however, no information on patients who responded to ABCP regimens was provided (25). On the other hand, similar phase III trials have not been conducted in patients with ROS1-rearranged NSCLC, and the clinical benefits of ICI regimens in patients with other driver alterations, such as *MET*, *BRAF*, *HER2*, *NTRK*, and *NRG1*, remain unknown. To understand the intertumor and intratumor heterogeneity of the immune response in these rare populations, international collaboration is required.

Table 1 Efficacy of ICIs and diagnostic methods in patients with ALK/RET/ROS1-rearranged positive NSCLC

Reference	Gene rearrangement	Treatment	ORR	Median PFS (months)	Diagnostic methods used for molecular testing	Details of ICI-benefiting cases
Multicenter analysis by Mazieres *et al.* (2)	ALK (n=23), RET (n=16), ROS1 (n=7)	ICI monotherapy	0% (ALK), 6% (RET), 17% (ROS1)	2.5 (ALK), 2.1 (RET), NA (ROS1)	Local testing on validated platforms	NA[a]
Multicenter analysis by Negrao *et al.* (4)	ALK (n=19), RET (n=14), ROS1 (n=3)	ICI monotherapy	NA	2.7 (overall)	CLIA certified laboratory assays (most of them were FoundationOne assays)	NA
Single-center analysis by Dudnik *et al.* (7)	RET (n=4), ROS1 (n=1)	ICI monotherapy	0% (RET), NA (ROS1)	3 (RET), 0.1 (ROS1)	FoundationOne assay	NA
Flatiron health electronic health record analysis by Jahanzeb *et al.* (11)	ALK (n=83)	ICI monotherapy (n=74) or ICI chemo (n=9)	NA	2.3	Not specified	NA
Flatiron health electronic health record analysis by Bodor *et al.* (12)	ALK (n=65)	ICI monotherapy (n=65)	NA	2.3	Not specified	NA
Single-center analysis by Oya *et al.* (13)	ALK (n=7)	ICI monotherapy	NA	1.8	RT-PCR, IHC, or FISH	NA
Single-center analysis by Gainor *et al.* (14)	ALK (n=6)	ICI monotherapy	0%	NA	FISH	Not applicable
Multicenter analysis by Guisier *et al.* (6)	RET (n=9)	ICI monotherapy	38%	7.6	FISH	NA
Single-center analysis by Offin *et al.* (15)	RET (n=16)	ICI monotherapy (n=15), dual ICIs (n=1)	0%	3.4	MSK-IMPACT, FoundationOne, multiplex PCR, FISH, or RT-PCR	NA
Single-center analysis by Lee *et al.* (16)	RET (n=13)	ICI monotherapy (n=12), dual ICIs (n=1)	7.7%	2.1	FISH or NGS	Available
Single-center analysis by Uehara *et al.* (5)	RET (n=2)	ICI chemo (n=2)	50%	NA	NGS (Oncomine Dx Target Test)	NA
Multicenter analysis by Choudhury *et al.* (17)	ROS1 (n=39)	ICI monotherapy (n=28), ICI chemo (n=11)	13% (ICI monotherapy), 83% (ICI chemo)	2.1 (ICI monotherapy), 10 (ICI chemo)	FISH or NGS. The details of NGS panels were described in the paper	Available

[a], it is available in the article that accompanies this editorial (9). ICI, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; NA, not available; CLIA, clinical laboratory improvement amendment; chemo, chemotherapy; RT-PCR, reverse transcription polymerase chain reaction; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing.

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Footnote

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