Editorial Commentary

Immune checkpoint inhibitors and driver oncogenes in non-small cell lung cancer

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Lung cancer is the leading cause of cancer-related death throughout the world. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and lung adenocarcinoma (LUAD) is the major subtype of NSCLC. The majority of NSCLC patients are diagnosed at advanced stages, but chemotherapy has only limited efficacy. Molecular targeted therapies against driver oncogenes such as *EGFR* mutations and *ALK* fusions have prolonged the survival of patients with advanced NSCLC (1), but most patients ultimately acquire resistance to the targeted therapies by multiple mechanisms, making such patients difficult to 'cure'. Recently, immune checkpoint inhibitors (ICIs), including antibodies to programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1), have been introduced as a cancer treatment with a durable response, raising an expectation for a 'cure'. The PD-L1 tumor proportion score (TPS) has been routinely used as a predictive biomarker for ICIs in a clinical setting. In addition, tumor mutational burden (TMB) and $CD8^+$ tumor-infiltrating lymphocytes (TILs) are thought to be potential predictive biomarkers for ICI therapy. However, there has been no perfect biomarker for predicting ICI efficacy, and nearly half of patients develop early disease deterioration. In particular, the therapeutic roles of ICIs for oncogene-driven NSCLC remain suspicious (2).

Mazières *et al*. recently reported the results from the IMMUNOTARGET registry regarding the efficacy of ICI monotherapies for NSCLC with several driver oncogenes (3). They retrospectively evaluated the clinical efficacy of ICI monotherapy in 551 NSCLC patients with genetic alterations in *KRAS*, *EGFR*, *BRAF*, *MET*, *HER2*, *ALK*, *RET* and *ROS1*. This study is clinically meaningful because the effectiveness of ICIs was analyzed not only for patients with mutations in *KRAS* and *EGFR* but also for those with rare driver oncogenes whose clinical data of ICI therapies are limited. Overall, the objective response rate (ORR), progression disease (PD) rate, median progression-free survival (PFS) and median overall survival (OS) from the initiation of ICI treatments were 19.4%, 56.7%, 2.8 and 13.3 months, respectively. Of note, this cohort included 271 (49.2%) patients with *KRAS* mutations who exhibited a high ORR (26%), a low PD rate (50.8%), and long PFS (median PFS: 3.2 months) compared to those with other driver oncogenes. Their findings seem equivalent to the clinical outcomes in pivotal phase III trials and a meta-analysis of ICI monotherapies (4), indicating that NSCLC patients with *KRAS* mutations likely respond to ICIs.

The *KRAS* proto-oncogene is commonly mutated in NSCLC, as found in 25% to 30% of patients with LUADs. Considering that effective therapeutic strategies targeting KRAS have not yet been established, it is worth assessing the therapeutic roles of ICIs in patients with NSCLC carrying *KRAS* mutations. Several lines of evidence have shown that ICIs are effective in *KRAS*-mutated NSCLC. Previous phase III trials and a meta-analysis showed prolonged OS by ICI monotherapies compared with docetaxel in NSCLC patients with *KRAS* mutations (4). Consistent with these findings, a recent whole-genome

sequencing analysis of tumors from patients receiving ICIs demonstrated that a *KRAS* mutation was significantly associated with the response to ICIs, even after correcting for TMB (5). In *KRAS*-mutated NSCLC patients in the IMMUNOTARGET registry, PD-L1-positive expression was significantly correlated with longer PFS (median PFS: 7.2 *vs.* 3.9 months), but PFS did not correlate with smoking history or *KRAS* mutation subtypes (3). Another recent study comparing ICI efficacy with or without *KRAS* mutations showed a trend toward a better ORR and prolonged PFS in *KRAS*-mutated NSCLC, with increased benefits for a high rate of PD-L1-positive tumor cells (6). It has been indicated that oncogenic *KRAS* induces PD-L1 overexpression through activation of its downstream pathways in NSCLC, whereas PD-L1 expression levels vary greatly among *KRAS*-mutated NSCLC tumors, implying that other unknown mechanisms could determine the PD-L1 expression status (2,7). These observations suggest that the PD-L1 expression status is essential for predicting the efficacy of ICIs in *KRAS* mutation-positive NSCLC. On the other hand, a recent study demonstrated that a *STK11/LKB1* mutation, which commonly harbors a concomitant *KRAS* mutation, was the most prevalent genomic driver of primary resistance to ICIs in *KRAS*-mutated LUADs (8). This may be explained by the fact that tumors carrying both *KRAS* and *STK11/LKB1* mutations exhibit an 'immune-inert' phenotype with low levels of immune markers, including PD-L1 (9). *STK11/LKB1* mutations also cooccur in 16% of LUADs accompanied with *EGFR* mutations (10), possibly affecting the unfavorable clinical outcomes of *EGFR*-mutated NSCLC patients receiving ICI therapies. Thus, it should be noted that concomitant molecular abnormalities may influence the effect of ICIs in NSCLC carrying such driver oncogenes.

In contrast to *KRAS* mutations, ICI monotherapies have been consistently shown to be ineffective in phase III trials and a meta-analysis in NSCLC patients with *EGFR* mutations (4). Accumulating evidence suggests that immunological environments characteristic of *EGFR*-mutant tumors are implicated in poor responsiveness to ICIs. NSCLC tumors carrying *EGFR* mutations lack $CD8^+$ TILs, which are indispensable to the antitumor immunologic effect (11). The oncogenic activation of EGFR signaling contributes to promoting tumor-mediated immune suppression and tolerance mediated by regulatory T cells (Tregs), tolerogenic dendritic cells (DCs) and myeloid-derived suppressor cells (MDSCs) (12). Intriguingly, a recent study showed that $PD\text{-}1^+$ Tregs amplified by PD-1 blockage induce rapid cancer progression, so-called hyperprogressive disease (13), which may confer a high PD rate (67%) of ICI therapy in *EGFR*-mutated NSCLC patients in the IMMUNOTARGET study (3). In this cohort, PFS was significantly different across *EGFR* mutation subtypes; the PFS times of patients with T790M mutations and exon 19 deletions were shorter than those with L858R mutations and other mutations. Recently, Hastings *et al.* reported that clinical outcomes with PD-1 or PD-L1 blockade were worse in patients with *EGFR* exon 19 deletions but similar to those with *EGFR* L858R mutations compared to those with wild-type *EGFR* (14). While further studies are needed to elucidate appropriate therapeutic strategies for *EGFR*-mutated NSCLC, the therapeutic roles of ICIs may differ according to the *EGFR* mutation subtypes of NSCLC.

In the IMMUNOTARGET study, none of 23 patients with *ALK* fusions responded to ICI monotherapies with a high PD rate (68%) (3). Previous studies have indicated that ICI monotherapies are less beneficial for patients with *ALK* fusions as well as for patients with *EGFR* mutations (15). While a positive relationship between *ALK* fusions and PD-L1 upregulation has been indicated, elevated PD-L1 expression appears unreliable for predicting favorable clinical outcomes (2). Thus, it seems that *ALK* tumor-specific microenvironments such as insufficient $CD8^+$ TILs are relevant to ICI resistance (11). Similarly, the IMMUNOTARGET results showed poor responses to ICI monotherapies for the oncogenic fusions of *ROS1* (ORR: 16.7%; PD rate: 83.3%) and *RET* (ORR: 6.3%; PD rate: 75%; median PFS: 2.1 months) (3). Offin *et al.* retrospectively investigated the efficacy of ICIs in 74 NSCLC patients with *RET* fusions (16) (*Table 1*). The majority of *RET*-positive tumors lacked PD-L1 expression (58%) and significantly lower TMB compared to the patients without *RET* fusions. Of 13 patients whose responses were assessable, none responded to ICIs, but 62% showed PD irrespective of PD-L1 expression and the TMB status. Together with these findings, it is unlikely that ICIs are beneficial to NSCLC with fusion oncogenes of *ALK*, *ROS1* and *RET*. Nevertheless, previous case reports have shown that some NSCLC patients with *ALK* or *ROS1* fusions markedly respond to ICIs (20,21), suggesting that there would be determinants of the response to ICIs in NSCLC patients harboring such fusion oncogenes.

BRAF mutations are found in approximately 3% of NSCLCs, and approximately half of *BRAF* mutants are V600E mutations. In agreement with the

Table 1 Summary of the efficacy of ICI in NSCLC with rare oncogenic drivers in previous studies

Oncogene	Mutation subtype	ORR, %	PD rate, %	Median PFS, months	Median OS, months	Reference
RET	–	6.3	75	2.1	21.3	IMMUNOTARGET (3)
	–	0	62	3.4	NA	Offin *et al*. (16)
BRAF	V600E	24.3[1]	45.9[2]	1.8	8.2	IMMUNOTARGET (3)
	Non-V600E			4.1	17.2	
	V600E	25	58	3.7	NR	Dudnik *et al*. (17)
	Non-V600E	33	44	4.1	NR	
MET	Amplification	15.6[3]	50[4]	1.3	8	IMMUNOTARGET (3)
	Exon 14 mut			4.7	25	
	Exon 14 mut	16.7	54.2	1.9	18.2	Sabari *et al*. (18)
HER2	–	7.4	66.7	2.5	20.3	IMMUNOTARGET (3)
	–	6	81	1.8	17.1	Negrao *et al*. (19)

[1], ORR for patients with all BRAF mutations; [2], PD rate for patients with all BRAF mutations; [3], ORR for patients with all MET alterations; [4], PD rate for patients with all MET alterations. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progression disease; PFS, progression-free survival; OS, overall survival; NA, not applicable; NR, not reached.

IMMUNOTARGET results, a retrospective study demonstrated favorable clinical outcomes in *BRAF*-mutated NSCLC patients receiving ICIs (17) (*Table 1*). Additionally, these results showed that patients with non-V600E mutations had numerically (but not significantly) longer PFS than those with V600E mutations. In the study by Dudnik *et al.*, patients with a ≥50% TPS tended to survive longer than those with a 0–49% TPS, and *BRAF*-mutated NSCLC was associated with high PD-L1 expression (TPS ≥50%: 44.8%; TPS 1–49%: 24.1%) (17). It is thus likely that elevated PD-L1 expression is an essential predictor of ICI efficacies in NSCLC patients with *BRAF* mutations. We previously found that siRNA-mediated BRAF knockdown and inhibition of BRAF or MEK resulted in a decrease in PD-L1 expression levels in PD-L1-overexpressing H2087 NSCLC cells with *BRAF* L597V mutations, suggesting that oncogenic BRAF induces PD-L1 overexpression through activation of the MEK-ERK pathway in NSCLC cells (7). Considering that no effective targeted drugs are available for NSCLC with *BRAF* non-V600E mutation, PD-1/PD-L1 axis blockage could be a therapeutic option for PD-L1-overexpressed and *BRAF*-mutated NSCLC.

Regarding the patients with alterations in *MET* or *HER2*, the clinical efficacies of ICIs are disappointing (*Table 1*). Sabari *et al.* investigated the clinical outcomes of patients harboring *MET* exon 14 mutations and found similar ORRs and PD rates but shorter PFS compared to the IMMUNOTARGET results (18). Notably, the responses to ICIs were not enriched in patients with either high PD-L1 expression or in those with high TMB (18), which is supported by a recent report describing that two patients with *MET* exon 14-mutated NSCLC failed to respond to pembrolizumab, irrespective of a ≥50% PD-L1 TPS (22). With regard to NSCLC patients with *HER2* alterations, a retrospective study evaluated 16 NSCLC patients with *HER2* exon 20 mutations, and a low ORR, a high PD rate and poor PFS were observed (19), consistent with the IMMUNOTARGET result (3). In the IMMUNOTARGET cohort, it is noteworthy that none of the *HER2*-mutated tumors had a ≥50% PD-L1 TPS. These observations suggest that the PD-L1 expression status is irrelevant to the efficacy of ICIs for NSCLCs carrying alterations in *MET* or *HER2*.

The IMMUNOTARGET study demonstrated that smoking history was correlated with longer PFS in the entire cohort, whereas the clinical impact of smoking was inconsistent according to the type of oncogenic driver (3). In patients with *EGFR*, *BRAF* and *HER2* alterations, smokers experienced longer PFS than never smokers, whereas PFS was prolonged in never smokers compared with smokers in patients with *ALK/ROS/RET* fusions, and the smoking status did not affect clinical outcomes in patients with *KRAS* and *MET* alterations. Thus,

cigarette smoking may have differential roles in immune microenvironments relevant to the efficacy of ICIs among oncogene-driven NSCLC tumors.

To overcome NSCLC tumors with oncogenic drivers, the combined use of anticancer drugs plus ICIs may be an optional therapeutic strategy. For instance, a subgroup analysis of the IMpower150 trial revealed that the combination therapy of ICIs plus chemotherapy with an anti-VEGF antibody (atezolizumab plus carboplatin plus paclitaxel plus bevacizumab) appeared effective for *EGFR*-mutated or *ALK*-rearranged NSCLC patients (23). The anti-VEGF antibody has immunomodulatory effects of reprogramming the tumor microenvironment from 'cold' to 'hot' (24), suggesting that the combination therapy of ICIs plus anti-VEGF may be compatible for oncogene-driven NSCLC. The efficacy of the therapeutic strategy of ICIs plus EGFR tyrosine kinase inhibitors (EGFR-TKIs) has also been evaluated by clinical trials (12). Intriguingly, a recent case report showed a drastic response to EGFR-TKIs administered within one month after treatment with the PD-1 antibody nivolumab in *EGFR*-mutated NSCLC patients acquiring resistance to EGFR-TKIs (25). This suggests that the immediate use of EGFR-TKIs after ICIs may be effective for NSCLC patients who have acquired resistance to EGFR-TKIs, although we need to pay careful attention to immune-related adverse event-related interstitial lung disease.

Currently, a molecular targeted therapy is the first-choice treatment for advanced NSCLC patients with driver oncogenes. However, most oncogene-driven tumors ultimately acquire resistance to the targeted drugs, and the survival benefit of chemotherapy is limited for relapsed patients. Thus, other treatment options are indispensable for achieving the long-term survival of such patients. In this regard, the effective use of ICIs is highly attractive. Therapeutic strategies such as the combination of ICIs with chemotherapy, molecular targeted drugs and anti-VEGF drugs may be promising. Further studies are warranted to explore a single biomarker or biomarker combinations predictive of the response to ICIs and novel immune therapy drugs for NSCLC with driver oncogenes.

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Footnote

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References

1. Singal G, Miller PG, Agarwala V, et al. Association of patient characteristics and tumor genomics with clinical outcomes among patients with non-small cell lung cancer using a clinicogenomic database. JAMA 2019;321:1391-9.
2. Miura Y, Sunaga N. Role of immunotherapy for oncogene-driven non-small cell lung cancer. Cancers (Basel) 2018. doi: 10.3390/cancers10080245.
3. Mazières J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol 2019;30:1321-8.
4. Lee CK, Man J, Lord S, et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma: a systematic review and meta-analysis. JAMA Oncol 2018;4:210-6.

5. Miao D, Margolis CA, Vokes NI, et al. Genomic correlates of response to immune checkpoint blockade in microsatellite-stable solid tumors. Nat Genet 2018;50:1271-81.
6. Jeanson A, Tomasini P, Souquet-Bressand M, et al. Efficacy of immune checkpoint inhibitors in KRAS-mutant non-small cell lung cancer (NSCLC). J Thorac Oncol 2019;14:1095-101.
7. Miura Y, Sunaga N, Bao P, et al. PD-L1 overexpression induced by oncogenic KRAS and BRAF mutations through MAPK pathway activation in non-small cell lung cancer. Cancer Research 2018;78:abstr 5740.
8. Skoulidis F, Goldberg ME, Greenawalt DM, et al. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. Cancer Discov 2018;8:822-35.
9. Skoulidis F, Byers LA, Diao L, et al. Co-occurring genomic alterations define major subsets of KRAS-mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. Cancer Discov 2015;5:860-77.
10. Sato S, Nagahashi M, Koike T, et al. Impact of concurrent genomic alterations detected by comprehensive genomic sequencing on clinical outcomes in east-asian patients with EGFR-mutated lung adenocarcinoma. Sci Rep 2018;8:1005.
11. Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: a retrospective analysis. Clin Cancer Res 2016;22:4585-93.
12. Yu S, Liu D, Shen B, et al. Immunotherapy strategy of EGFR mutant lung cancer. Am J Cancer Res 2018;8:2106-15.
13. Kamada T, Togashi Y, Tay C, et al. PD-1+ regulatory T cells amplified by PD-1 blockade promote hyperprogression of cancer. Proc Natl Acad Sci U S A 2019;116:9999-10008.
14. Hastings K, Yu H, Wei W, et al. EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small cell lung cancer. Ann Oncol 2019. [Epub ahead of print].
15. Bylicki O, Paleiron N, Margery J, et al. Targeting the PD-1/PD-L1 immune checkpoint in EGFR-mutated or ALK-translocated non-small-cell lung cancer. Target Oncol 2017;12:563-9.
16. Offin M, Guo R, Wu SL, et al. Immunophenotype and response to immunotherapy of RET-rearranged lung cancers. JCO Precis Oncol 2019. doi: 10.1200/PO.18.00386.
17. Dudnik E, Peled N, Nechushtan H, et al. BRAF mutant lung cancer: programmed death ligand 1 expression, tumor mutational burden, microsatellite instability status, and response to immune check-point inhibitors. J Thorac Oncol 2018;13:1128-37.
18. Sabari JK, Leonardi GC, Shu CA, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncol 2018;29:2085-91.
19. Negrao MV, Reuben A, Robichaux JP, et al. Association of EGFR and HER-2 exon 20 mutations with distinct patterns of response to immune checkpoint blockade in non-small cell lung cancer. J Clin Oncol 2018;36:abstr 9052.
20. Jain A, Fujioka N, Patel M. Immune checkpoint inhibitors in ros1-rearranged non-small cell lung cancer: a report of two cases. J Thorac Oncol 2019;14:e165-7.
21. Yamasaki M, Saito N, Hada Y, et al. Nivolumab therapy for synchronous ALK-positive lung cancer and gastric cancer. Case Rep Oncol 2017;10:361-7.
22. Reis H, Metzenmacher M, Goetz M, et al. MET expression in advanced non-small-cell lung cancer: effect on clinical outcomes of chemotherapy, targeted therapy, and immunotherapy. Clin Lung Cancer 2018;19:e441-63.
23. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
24. Hegde PS, Wallin JJ, Mancao C. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. Semin Cancer Biol 2018;52:117-24.
25. Kaira K, Kagamu H. Drastic response of re-challenge of EGFR-TKIs immediately after nivolumab therapy in EGFR-TKI-resistant patients. J Thorac Oncol 2019;14:e135-6.

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