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. 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-L1+ Tregs amplified by PD-1 blockade 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 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 overexpression 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.

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

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Mutation subtype</th>
<th>ORR, %</th>
<th>PD rate, %</th>
<th>Median PFS, months</th>
<th>Median OS, months</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET</td>
<td>–</td>
<td>6.3</td>
<td>75</td>
<td>2.1</td>
<td>21.3</td>
<td>IMMUNOTARGET (3)</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>0</td>
<td>62</td>
<td>3.4</td>
<td>NA</td>
<td>Offin et al. (16)</td>
</tr>
<tr>
<td>BRAF</td>
<td>V600E</td>
<td>24.3</td>
<td>45.9</td>
<td>1.8</td>
<td>8.2</td>
<td>IMMUNOTARGET (3)</td>
</tr>
<tr>
<td></td>
<td>Non-V600E</td>
<td>25</td>
<td>58</td>
<td>3.7</td>
<td>NR</td>
<td>Dudnik et al. (17)</td>
</tr>
<tr>
<td>MET</td>
<td>Amplification</td>
<td>15.6</td>
<td>50</td>
<td>1.3</td>
<td>8</td>
<td>IMMUNOTARGET (3)</td>
</tr>
<tr>
<td></td>
<td>Exon 14 mut</td>
<td>16.7</td>
<td>54.2</td>
<td>1.9</td>
<td>18.2</td>
<td>Sabari et al. (18)</td>
</tr>
<tr>
<td>HER2</td>
<td>–</td>
<td>7.4</td>
<td>66.7</td>
<td>2.5</td>
<td>20.3</td>
<td>IMMUNOTARGET (3)</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>6</td>
<td>81</td>
<td>1.8</td>
<td>17.1</td>
<td>Negrao et al. (19)</td>
</tr>
</tbody>
</table>

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.
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

Conflicts of Interest: The authors have no conflicts of interest to declare.

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.

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