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REVIEW

To be, or not to be: the dilemma of immunotherapy for non-small cell lung cancer harboring various driver mutations

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Abstract

Introduction Lung cancer is one of primary cancer type with high incidence and mortality, non-small cell lung cancer (NSCLC) is the most common type of lung cncer. For advanced lung cancer, traditional chemotherapy and targeted therapy become difficult to solve the dilemma of further progress. In recent years, with the clinical application of immunotherapy, the therapeutic strategy of lung cancer has changed dramatically. At present, immunotherapy has shown conspicuous efficacy in NSCLC patients with high expression of programmed death-ligand 1 (PD-L1) and high tumor mutational burden (TMB). The discovery of driver mutations brings delightful hope for targeted cancer therapy. However, it remains controversial whether immunotherapy can be used in NSCLC patients with these specific driver mutations.

Method This article summarized the latest research progresses of immunotherapy in advanced NSCLC. We paid close attention to the relevance of various driver mutations and immunotherapy in NSCLC patients, and summarized the predictive effects of several driver mutations and immunotherapy.

Results The mutations of KRAS, KRAS+TP53, EPHA (especially EPHA5), ZFHX3, ZFHX3+TP53, NOTCH, BRAF and LRP1B+FAT3 have potential to be used as biomarkers to predict the positive effectiveness of immunotherapy. ZFHX3, ZFHX3+TP53, STKII/LKB1+KEAP1+SMARCA4+PBRM1 mutations in LUAD patients get more positive effect in immunotherapy. While the mutations of EGFR, KEAP1, STKII/LKB1+KRAS, EML4-ALK, MET exon 14 skipping mutation, PBRM1, STKII/LKB1+KEAP1+SMARCA4+PBRM1, ERBB2, PIK3CA and RET often indicate poor benefit from immunotherapy.

Conclusion Many gene mutations have been shown to be associated with immunotherapy efficacy. Gene mutations should be combined with PD-L1, TMB, etc. to predict the effect of immunotherapy.

Keywords Non-small cell lung cancer (NSCLC) · Immunotherapy · Driver mutations · Common mutation · Rare mutation

Introduction

Lung cancer is one of the primary cancer types with high incidence and mortality, and non-small cell lung cancer (NSCLC) is the most common pathological type (Molina

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et al. 2008). With the emergence of adverse effects and the toxicity of chemotherapy drugs, the resistance of targeted therapy, immunotherapy has stepped onto the historical stage of NSCLC treatment. Immunotherapy improves the anti-tumor immunity of tumor microenvironment through stimulating or mobilizing immune system. The discovery of programmed cell death 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated protein-4 (CTLA-4) has promoted the development of tumor immunotherapy. Immunotherapy includes immune checkpoint inhibitors (ICIs) (targeting PD-1, PD-L1, TIGIT, Tim-3, Lag-3, etc.) (Anderson et al. 2016; Chauvin and Zarour 2020), immune checkpoint agonists (targeting CD40, TLR7, TLR8) (Freed-Pastor et al. 2021; Byrne et al. 2021; Mullins et al. 2019), cancer vaccines (Enokida et al. 2021), CAR-T therapy and other strategies. These treatments can effectively enhance the anti-tumor immune effect and inhibit the tumor growth. However, the curative effect of immunotherapy varies from patient to patient. How to predict the curative effect of immunotherapy to guide the clinical application of immunotherapy has become a hot research topic.

Recent researches have indicated that the expression of PD-L1 (Herbst et al. 2014), tumor mutation load (TMB) (Rizvi et al. 2018), special gene mutation, tumor-infiltrating lymphocytes (TIL) (Lu et al. 2019), antigen presentation defects (Thompson et al. 2021), gene expression profiles (GEPs) (Wang et al. 2019) could be used as predictive biomarkers of immunotherapy efficacy. Among them, PD-L1 expression, TMB ($\geq$10 mut/Mb), microsatellite instability (MSI-H) and mismatch repair deficient (MMR) have been approved by health regulatory agencies, which can serve as predictive biomarkers for immunotherapy of NSCLC patients (Hellmann et al. 2018a, b; Marabelle et al. 2020; Bodor et al. 2020; Rizvi et al. 2018). In addition, being as the composite biomarkers, PD-L1 and TMB have stronger predictive abilities than alone (Rizvi et al. 2018; Carbone et al. 2017). In recent years, studies have shown that the mutation of *TP53*, one of the tumor suppressor genes, was related to high PD-L1 expression and high TMB (Dong et al. 2017). Besides, patients with *TET1* mutation achieved longer progression-free survival (PFS) and overall survival (OS) after treated by immunotherapy than those without *TET1* mutation in various cancers (Wu et al. 2019). Gene mutations may have some connection with DNA damage and repair (DDR) pathway to improve tumor immunogenicity by accumulating false DNA damage reaction, which shows good curative effect in immunotherapy (Wang et al. 2018; Teo et al. 2018). These findings manifest that some gene mutations can be new promising biomarkers for immunotherapy in NSCLC patients. Therefore, this review summarized the researches of immunotherapy in NSCLC patients with driver mutations in recent years, focusing on their relationship.

Here, we defined mutation rate of more than 5% as common mutation and mutation rate of less than 5% as rare mutation.

Common gene mutations and immunotherapy in NSCLC

TP53

As the most frequently mutant gene with more than 30% incidence in NSCLC (Dearden et al. 2013), the relevance of *TP53* and immunotherapy has been extensively studied. Several researches revealed that *TP53* mutation was regularly in connection with increased PD-L1 expression and TMB (Dong et al. 2017; Herbst et al. 2016). It also facilitated CD8 + T-cell infiltrations (CD8 + TILs) which were the predominant effector population following treatment with anti-PD-1/PD-L1 immunotherapy (Topalian et al. 2015). All these discoveries uncovered that *TP53* mutation played a role in immune checkpoint inhibitor therapies.

Further, *TP53* mutation included missense mutation and nonsense mutation (Bouaoun et al. 2016). Compared with the wild type, *TP53* missense mutation showed significantly higher PD-L1 expression. And *TP53* missense mutation was associated with a superior response to ICIs than *TP53* nonsense mutation (Sun et al. 2020). But no clinical study has validated this outcome.

In addition, a meta-analysis which analyzed 19 studies that involved 6,084 patients with NSCLC found the *TP53* wild type was correlated with a remarkable higher overall survival (OS) than the *TP53* mutant type (Gu et al. 2016). Meanwhile, another analysis also identified that lung adenocarcinoma (LUAD) patients with *TP53* mutation carried a poorer prognosis in contrast with those *TP53* wild type (Wang and Sun 2017).

So, TP53 mutation is related with worse prognosis, but the efficacy with immunotherapy is still unclear.

EGFR

The incidence of *EGFR* mutation was about 27% in NSCLC (Dearden et al. 2013). According to the CheckMate 057, KEYNOTE 010 and POPLAR trials, PD-1 inhibitors prolong the OS compared with docetaxel in NSCLC patients. However, in subgroup analysis, there was no remarkable difference in *EGFR* mutant patients (Borghaei et al. 2015; Herbst et al. 2016; Fehrenbacher et al. 2016). Many studies have reverified above findings. Chee Khoon Lee has indicated that for NSCLC patients with EGFR mutation, those treated by immunotherapy did not possess any more

significant survival benefits than those treated by chemotherapy in second and later lines of therapy (Lee et al. 2018). Namely, in *EGFR* mutant advanced NSCLC patients, there is no significant improvement in OS between immunotherapy and chemotherapy.

Another retrospective analysis has suggested that NSCLC patients with *EGFR* mutation were related with poor immunotherapy efficacy (Gainor et al. 2016). It observed a statistically inferior progression-free survival (PFS) and objective response rate (ORR) for *EGFR* mutant patients received anti-PD-1/PD-L1 immunotherapy compared with the *EGFR* wild type. Further exploring possible mechanisms, we learned that EGFR mutations were relevant with fewer CD8 + TILs (Akbay et al. 2013).

All these studies confirmed that *EGFR* mutation could be regarded as a negative biomarker to immune checkpoint inhibitors.

KEAP1

KEAP1 is a mutated gene with the third frequency in LUAD. Study has found the frequency of *KEAP1* mutation is more than 17% in LUAD (Cancer Genome Atlas Research Network 2014).

A study evaluated the information from TCGA data has shown that *KEAP1* mutation has negative prognostic effect on immunotherapy (Cheng et al. 2021). But it has been found that *KEAP1* mutation showed close association with lower TILs and cytotoxic T lymphocyte. It indicated that *KEAP1* mutation may be associated with lower tumor immunity (Cheng et al. 2021).

Furthermore, other researches have also confirmed that patients with *KEAP1* and *STK11* mutation have poor therapeutic effect with pembrolizumab (Aggarwal et al. 2020).

Based on Impower150 study, Howard Jack West et al. have found compared with the wild type, patients with *KEAP1* mutation treated by atezolizumab and/or bevacizumab with carboplatin/paclitaxel were associated with inferior OS and PFS (West et al. 2022).

KRAS

The incidence of *KRAS* mutation is about 17% in NSCLC (Dearden et al. 2013). ICIs can reduce the death risk of NSCLC patients with KRAS mutation compared with chemotherapy (Lee et al. 2018). Studies found that immunotherapy had a greater therapeutic benefit for *KRAS* mutation than *KRAS* wild type in NSCLC patients (Lee et al. 2018; Mazieres et al. 2019). The research which retrospectively analyzed 88 advanced NSCLC patients receiving immunotherapy disclosed that patients with *KRAS* mutation in immunotherapy had longer PFS and OS than the wild type (Dong et al. 2017). In addition, according to a prospective analysis of Song et al. patients who have higher rates of *KRAS* mutations treated by immunotherapy obtained durable benefit (Song et al. 2020).

The underlying mechanism why patients with *KRAS* mutation might benefit from anti-PD-1/PD-L1 immunotherapy remains unclear. Some researches pointed out that it might because *KRAS*-mutant tumors had more tumor-infiltrating lymphocytes in the microenvironment and were almost always active. On top of this, *KRAS*-mutant NSCLC expressed more PD-L1, and as mentioned above, the high expression of PD-L1 was confirmed to be related to better therapeutic effect (Mazieres et al. 2019; Rizvi et al. 2018).

Generally, tumor suppressor genes, such as *TP53, KEAP1, STK11/LKB1, ATM* and *CDKN2A*, are the most frequently co-mutated genes with *KRAS* (Aredo et al. 2019; Lee et al. 2018; Skoulidis et al. 2015). Studies suggested that the PD-L1 expression in *KRAS* + *TP53* co-mutation are much higher than the single mutation of *KRAS* (Skoulidis et al. 2018; Dong et al. 2017). A recent study which contained 165 patients with *KRAS*-mutant NSCLC undergoing anti-PD-1/PD-L1 immunotherapy demonstrated that the co-mutation of *TP53* might be associated with higher response (Lee et al. 2018). It can be inferred that NSCLC patients with co-mutation of *KRAS* and *TP53* are more sensitive to immunotherapy.

Therefore, it is speculated that *KRAS* mutation and *KRAS* + *TP53* co-mutation will become the predictive biomarkers for immunotherapy in NSCLC.

STK11/LKB1

STK11/LKB1 mutations are prevalent in NSCLC with 9% incidence (Dearden et al. 2013). They are related to lower a PD-L1 expression and an intermediate or high TMB. According to research findings, The *STK11/LKB1*-mutant tumors revealed significantly lower ORR/PFS/OS to anti-PD-1/PD-L1 immunotherapy (Skoulidis et al. 2018). And another research also uncovered that patients who harbored *STK11* mutation treating with immunotherapy showed progress disease and the PFS was only 4.2 weeks (Kauffmann-Guerrero et al. 2020). But another research indicated that there was no direct link to poor ICIs outcomes and *STK11/LKB1* mutation (Di Federico et al. 2021).

As mentioned above, *STK11/LKB1* are particularly prevalent among KRAS-mutant tumors. *STK11/LKB1* loss directly promotes the formation of non-T-cell-inflamed tumor immune microenvironment in immune competent murine models of *KRAS*-mutant LUAD (Skoulidis et al. 2018). Numerous researches found the co-mutation of *KRAS* and *STK11/LKB1* in NSCLC patients receiving immunotherapy has been confirmed to be related to poor therapeutic effect (Di Federico et al. 2021; Skoulidis et al. 2018). Indeed, co-existence of both mutations is associated with

more metastatic sites at diagnosis and a higher risk of brain metastases (Calles et al. 2015).

In conclusion, the co-mutation of *STK11/LKB1* and *KRAS* can be considered as a negative predictive marker for immunotherapy in NSCLC.

EPHA

Ephrin A receptor (*EPHA*) is an important member in receptor tyrosine kinase family, and it is a key regulator of intercellular signal transduction in normal development and diseases. *EPHA3-7* are all common mutant genes in NSCLC (about 5%–15%) (Jamal-Hanjani et al. 2017; Campbell et al. 2016; Hellmann et al. 2018a, b). At present, studies have indicated that *EPHA* mutation is a new predictor that significantly prolonged PFS in NSCLC patients with immunotherapy, which may independently predict the clinical benefits of immunotherapy in NSCLC without being affected by other gene mutations. Like *ZFHX* mutation, the superior clinical efficacy to immunotherapy with EPHA mutation is mostly manifested in LUAD patients (Bai et al. 2020).

EPHA5, as a member of the Eph receptor family, is a common mutation in LUAD (Chen et al. 2020). Chen et al. have found that compared with the wild type, the *EPHA5* mutant significantly changed tumor microenvironment, and the TMB level increased. It was speculated that immunotherapy was an effective treatment to the *EPHA5* mutant patients. And this study also indicated that the survival time of LUAD patients with *EPHA5* mutation who received immunotherapy was more prolonged (Chen et al. 2020). It implies that *EPHA5* mutation is a promising positive biomarker for immunotherapy in NSCLC, especially in LUAD patients. More importantly, this research pointed out that although patients with *EPHA5* mutation and high TMB showed a longer OS than those with low TMB, the OS time of *EPHA5* wild-type patients with high TMB was the same as that of patients with low TMB. Therefore, detecting *EPHA5* mutation may be useful to prevent over-treatment of patients who choose immunotherapy only based on high TMB.

ZFHX3

ZFHX3, namely zinc finger homeobox 3, is an inhibitor of alpha-fetoprotein gene and one of the tumor suppressor genes in many cancers (Hu et al. 2019; Walker et al. 2015). According to the COSMIC database, the mutant rate of *ZFHX3* is about 7–8%. It may be related to brain metastasis in lung cancer (Song et al. 2021). Recently, studies have suggested that NSCLC patients with ZFHX3 mutation had a good prognosis after immunotherapy, and their PFS and OS were significantly longer than those of *ZFHX3* wild-type patients, especially the *ZFHX3* mutated LUAD patients (Zhang et al. 2021b, a). Further analysis suggests that it may be due to the positive correlation between *ZFHX3* mutation and the previously mentioned immunotherapy biomarkers, such as TILs, TMB, DDR pathway in NSCLC, etc. At the same time, the study revealed that activated CD4 + T cells, dendritic cells (DCs) and M1 macrophages were more abundant in *ZFHX3* mutated LUAD patients.

In addition, Zhang et al. have indicated that the *ZFHX3* mutation predicted higher survival rate in NSCLC patients treated with immunotherapy. And patients with the co-mutation of *TP53* and *ZFHX3* had longer OS than those with TP53 mutation after immunotherapy (Zhang et al. 2021a, b).

All the above results indicate that *ZFHX3* mutation can be regarded as a valuable predictive biomarker for immunotherapy in NSCLC, and it shows a positive therapeutic effect, especially for LUAD patients with *ZFHX3* and TP53 co-mutation.

SMARCA4

SMARCA4 alterations include two categories: class 1 are truncating mutations, fusions, and homozygous deletion and class 2 are missense mutations (Chakravarty et al. 2017). According to a large retrospective study gathering data from three institutions, the prevalence of *SMARCA4* mutation in NSCLC is about 6% (Cancer Genome Atlas Research Network 2014). Another study gathered the information of 532 patients from the immunotherapy-treated cohort has found that the ORR/PFS/OS of *SMARCA4* mutant patients had no significant extension with immunotherapy therapeutic efficacy (Alessi et al. 2021).

But previously another large study has indicated that *SMARCA4* mutant tumors tended more to have lower PD-L1 expression and higher TMB. It moved forward to illuminate those patients with *SMARCA4* mutant seemed to obtain benefit from immunotherapy, despite the negative PD-L1 expression (Schoenfeld et al. 2020).

In addition, Alessi et al. have found that *STK11* or *KEAP1* mutation often co-mutated with *SMARCA4* in NSCLC patients (Alessi et al. 2021). But the co-mutations of *STK11*, *KEAP1* and *SMARCA4* were associated with the negative immunotherapy effect (Di Federico et al. 2021; Marinelli et al. 2020).

Therefore, the relationship of immunotherapy and *SMARCA4* mutation remains unclear and further research is needed.

EML4-ALK

The incidence of *EML4-ALK* mutation in NSCLC is about 5.3% (Dearden et al. 2013). The POPLAR and ATLANTIC trails have indicated that anti-PD-1/PD-L1 immunotherapy had lower therapeutic effect on NSCLC patients with *EML4-ALK* mutation than those with wild type (Fehrenbacher et al. 2016; Garassino et al. 2018). And a retrospective analysis also observed a significant shorter PFS and objective response rate (ORR) in *EML4-ALK* mutant patients with anti-PD-1/PD-L1 immunotherapy compared with those with wild type (Gainor et al. 2016). There were a large number of clinical researches proved that ICIs are ineffective in NSCLC patients with *EML4-ALK* mutation. That was likely because *EML4-ALK* mutation was not related with increased effector T cells which adjusted anti-tumor immune responses, despite it was associated with high expression of PD-L1 (Pyo et al. 2020).

However, there was a case report showed that a *EML4-ALK* mutant patient treated twice with ICIs obtained remarkable curative effect which may because of high TMB and abundant CD8 + T-cell infiltration (Song et al. 2019).

Therefore, although *EML4-ALK* mutation was often related with negative immunotherapeutic effect, some patients with that mutation received good survival benefits.

PTEN

PTEN gene mutation in NSCLC is about 5.1% (Dearden et al. 2013). Little research has reported the association between PTEN mutation and immunotherapy in patients with NSCLC. Previously, a study has manifested that *PTEN* mutation was associated with immunotherapy resistance through enhancing the expression of immunosuppressive cytokines and inhibiting autophagy (Peng et al. 2016). Multiple clinical trials have confirmed the relevance of *PTEN* and immunotherapy resistance.

A case report observed that a patient who showed negative effect to Nivolumab was detected *PTEN* mutation by next-generation sequencing. It suggested that *PTEN* mutation in tumors was associated with immunotherapy resistance (Teng et al. 2022). Besides, another case also reported a NSCLC patient with *PTEN* mutation obtained poor immunotherapy efficacy (Ren et al. 2022). So, *PTEN* mutation may be hopefully considered as a new biomarker to predict negative therapeutic effect to immunotherapy in NSCLC.

A retrospective cohort study from the European Thoracic Oncology Platform (ETOP) Lungscape Project found that *PTEN* mutation was related with the expression of PD-L1 $\geq$ 1% cut-off (Kerr et al. 2019). However, another case report revealed a metastatic NSCLC patient with *PTEN* mutation expressed a poor response to the ICIs, although it exhibited high TMB and PD-L1 (Parikh et al. 2018).

In contrast to that, a prospective analysis reported by Peng Song has proved that patients who obtained durable benefit by immunotherapy in NSCLC had higher rates of *PTEN* mutation and *TP53* + *PTEN* co-mutation, suggesting that patients with these gene mutations may achieve positive effect from immunotherapy. But there was no specific statistical correlation between these genetic mutations and long-term benefit outcomes (Song et al. 2020).

Above all, *PTEN* mutation is often associated with negative immunotherapeutic effect, but it still needs more large-scale studies to verify this conclusion.

Rare gene mutations and immunotherapy in NSCLC

NOTCH

NOTCH family consists of four members, including *NOTCH1/ NOTCH2/ NOTCH3/ NOTCH4* (Mumm and Kopan 2000). According to the COSMIC database, the mutant rate of *NOTCH* is just about 5%.

A study has demonstrated that *NOTCH* mutation reduced immune cell infiltration, such as myeloid-derived suppressor cells, tumor-associated macrophages and Tregs. And it also decreased the expression of PD-1, CTLA-4, TIM-3 and LAG-3 (Mao et al. 2018).

Kai Zhang et al. have detected the association between *NOTCH* mutation and positive immunotherapeutic clinical effect. The overall immunotherapy response rate was 20.7% in NSCLC patients with *NOTCH* mutation. In addition, the median PFS and OS were 3.1 months and 16.0 months, respectively (Zhang et al. 2020). It also found patients with *NOTCH1, NOTCH2* or *NOTCH3* mutations exerted longer ORR and PFS than the patients with *NOTCH* wild type, but patients with *NOTCH4* mutation did not have this trend (Zhang et al. 2020). However, another research found *NOTCH4* mutant tumors were characterized by the abundant expressions of TMB and high CD8 T-cell infiltration, which indicated the *NOTCH4* mutation may also be associated with good immunotherapy benefit (Long et al. 2021).

MET

MET gene alteration existed in 3–4% of NSCLC. One of the gene mutations was *MET* exon 14 skipping mutation (Frampton et al. 2015; Awad et al. 2016).

A study enrolled 63 NSCLC patients with *MET* exon 14 skipping mutation, the duration of immunotherapy ranged from 2 weeks to 9.6 months and ORR was only 17%, the effect of immunotherapy was poor compared with that of targeted therapy which ORR was 32% and median PFS was 7.3 months (Drilon et al. 2020). Also, The ImmunoTarget

multicentric worldwide retrospective study showed that 36 NSCLC patients with *MET* mutation reflected 16% ORR and the median PFS and OS were 3.4 months and 18.4 months, respectively (Mazieres et al. 2019). A recent study has also found patients treated with immune checkpoint blockade with *MET* mutation had short median PFS (only 2.69 months) (Negrao et al. 2021).

Another retrospective study recruited 147 patients with *MET* exon 14 skipping mutation in lung cancer has showed that responses of immunotherapy were related to neither high PD-L1 expression nor high TMB (Sabari et al. 2018).

PBRM1

PBRM1 is a tumor suppressor gene which regulates the cell cycle, maintains the stability of the genome and improves centromere cohesion (Mota et al. 2019). It has been found that *PBRM1* mutation was particularly common in renal clear cell carcinoma, and it has been proved that *PBRM1* mutation was considered as a significant biomarker for immunotherapy in renal clear cell carcinoma (Braun et al. 2019).

The relevance of *PBRM1* mutation and immunotherapy in lung cancer is still unclear. Recently, a large retrospective study gathering data from three institutions found the prevalence of *PBRM1* mutation in NSCLC was about 3.04% (Zhou et al. 2020). It also pointed out that the mutation of *PBRM1* often indicated poor efficacy of immunotherapy in NSCLC patients (Zhou et al. 2020). According to this study, patients with *PBRM1* mutation tended to have higher TMB, but in both the high TMB and low TMB groups, patients with *PBRM1* mutation who received immunotherapy had lower OS than those with wild type. Therefore, *PBRM1* is more likely to be a promising biomarker to forecast poor survival benefit of receiving immunotherapy.

Another study combined the date from 240 advanced NSCLC patients to find the relevance between *PBRM1* mutation and the PFS after treating with anti-PD-L1 immunotherapy. It also indicated that *PBRM1* mutant patients in LUAD tended to express higher TMB but a less PFS (Yang et al. 2021).

Moreover, studies have shown that two or more co-mutations often occurred in *KEAP1, LKB1/STK11, PBRM1* and *SMARCA4*, which were related to the decline of immunotherapy effect (Marinelli et al. 2020; Di Federico et al. 2021). This study revealed that the co-mutation of the above four genes showed higher TMB in LUAD. But the survival time is significantly less than those patients without these co-mutations. Therefore, when two or more gene mutations of *KEAP1, STK11, PBRM1* and *SMARCA4* coexist in NSCLC patients, especially in LUAD patients, it is still necessary to use immunotherapy with caution.

ERBB2

ERBB2 mutation occurs in 2–4% of NSCLC patients, more frequently in LUAD and never-smokers (Ekman 2019). Most of patients with *ERBB2* mutation were with in-frame insertions in exon 20 (*ERBB2-ex20ins*) mutation, which were found about 1.7% incidence in NSCLC patients (Mazières et al. 2013). Nowadays, the therapeutic effect of immunotherapy in NSCLC patients with *ERBB2* mutation was still unclear. What we already learned is that *ERBB2* amplified tumors were associated with higher TMB (Dudnik et al. 2018a, b), but PD-L1 expression was low (Guisier et al. 2020). Some researchers have speculated the negative efficacy of ICIs in *ERBB2-ex20ins* mutant patients might be attributed to lower cytotoxic CD8 + T-cell infiltration and lower PD-L1 expression (Gainor et al. 2016).

The ImmunoTarget multicentric worldwide retrospective study showed a negative therapeutic effect of anti-PD-1/PD-L1 immunotherapy in *ERBB2* mutation subgroups (Mazieres et al. 2019). A study which performed genomic profiling of 78 NSCLC patients has indicated that patients with *ERBB2* mutation manifested lower PFS than those with wild type (Fang et al. 2019). Another large retrospective analysis indicated that patients with *ERBB2* mutation have showed poor response to immunotherapy (Guisier et al. 2020).

However, a case report showed a patient with *ERBB2-ex20ins* mutation significantly benefited from anti-PD-1 therapy plus chemotherapy treatment and showed more than half of tumor reduction (Tian et al. 2021).

BRAF

The incidence of *BRAF* mutation is about 2.5% in NSCLC (Dearden et al. 2013). *BRAF V600E* is uniformly considered as the most common type. It consists in more than half of the patients in *BRAF* mutation (Ding et al. 2017). At present, the

significantly potential efficacy of *BRAF* mutation in immunotherapy in melanoma has already been suggested (Welsh et al. 2016).

According to a retrospective analysis, *BRAF* mutation in NSCLC is connected with higher PD-L1 expression, lower TMB and lower MS-Stable status. And ICIs are effective in NSCLC patients with both *BRAF V600E* and *non-V600E* mutations (Dudnik et al. 2018a, b). A large retrospective study indicated that *BRAF* mutation was related to a better immunotherapy effect. It has been found that patients with *BRAF* mutation might be considered for immunotherapy after targeted therapy and first-line chemotherapy (Mazieres et al. 2019). Another large retrospective analysis also proved that patients with *BRAF* mutation in immunotherapy have showed effective responses (Guisier et al. 2020).

PIK3CA

The prevalence of *SMARCA4* mutation in NSCLC is about 2%. Many researches showed patients with *PIK3CA* mutation had poor immunotherapy effect.

A retrospective study including 84 NSCLC patients who were treated with immunotherapy analyzed the correlation of molecular findings and immunotherapy response. It indicated that all 5 patients existing *PIK3CA* mutation expressed low PFS to immunotherapy and showed minimal or even no PD-L1 expression (Kauffmann-Guerrero et al. 2020).

Besides, *PIK3CA* mutant LUSC exhibited substantially low expression of PD-L1 and its surrounding immune cells reduced the expression of PD-1 receptor compared with wild-type tumors (Choi et al. 2017). Meanwhile, Kadara et al. found the expression of PD-L1 was also significantly decreased in *PIK3CA* mutant LUAD (Kadara et al. 2017). Since objective response to atezolizumab was found to be remarkably associated with high expression of PD-L1, this tended to show that *PIK3CA* mutation might be a biomarker for negative response to immunotherapy (Herbst et al. 2014).

ROS1

ROS1 rearrangement was initially identified from the cell of glioblastoma (Birchmeier et al. 1987), and was first identified in NSCLC in 2007(Rikova et al. 2007). The incidence of *ROS1* rearrangement was about 1%–2% in NSCLC patients (Gainor and Shaw 2013).

There were fewer studies investigate the relationship of this gene mutation and immunotherapy. In a retrospective study, only one NSCLC patient treated with ICIs harboring *ROS1* rearrangement, and the PFS and OS were both only 0.1 month (Dudnik et al. 2018a, b).

According to a recent study, patients treated with immune checkpoint blockade with *ROS1* rearrangement had short PFS, although they expressed high PD-L1 (up to 55%) (Negrao et al. 2021). This suggested that there were oncogene-specific factors apart from PD-L1 expression influenced clinical immunotherapeutic effect. Thus, PD-L1 might not be independent predictors to immunotherapy effect (Negrao et al. 2021).

Therefore, ROS1 rearrangement was correlated with negative immunotherapeutic effect. But large-scale researches were needed to verify that.

RET

RET fusion was also identified less than 5% (at approximately 1%-2%) frequency in NSCLC. And it was more prevalent among LUAD never-smokers (Takeuchi et al. 2012; Kohno et al. 2012). Multiple studies have evaluated that NSCLC patients with *RET* fusion had negative effect in ICIs.

Jiyun Lee et al. have found the median PFS of NSCLC patients with *RET* fusion treated by immunotherapy was only 2.1 months, and the ORR was just 7.7%. On the contrary, the ORR among patients treated with pemetrexed-based regimens was 63.0%, and the median PFS was 9.0 months (Lee et al. 2020). Besides, this study also found patients with *RET* fusion were more likely to develop intracranial metastases.

Meanwhile, a large retrospective multicenter study indicated that patient with *RET* mutation was only one and had showed negative response in immunotherapy (Guisier et al. 2020). And Marcelo V Negrao et al. have also found patients with RET fusion treated with immune checkpoint blockade had short PFS (Negrao et al. 2021).

FBXW7

The *FBXW7* gene, lies at chromosome 4q31q.3, is also one of the tumor suppressor genes. No study has counted the incidence of *FBXW7*.

The clinical significance of its mutation is obvious in various cancers, such as lung, hematopoietic, colon, esophageal, gastric, etc., and it is closely associated with the occurrence of cancer, tumor metastasis, poor prognosis and drug resistance of adjuvant therapy (Fan et al. 2022; Yeh et al. 2018). Little is known as regards the treatment effect of immunotherapy in NSCLC patients with *FBXW7* mutation.

At present, another research has found if *FBXW7* mutation existed in malignant melanoma, it would become resistant to immunotherapy (Gstalder et al. 2020).

The latest clinical research shows that the expressions of TMB and CD8 + T cells and macrophages in NSCLC patients with *FBXW7* mutation are significantly higher than those of patients with wild type. Patients can get better clinical benefits from immunotherapy (Liu et al. 2022). However, further research is needed to prove or overturn this conclusion.

LRP1B and FAT3 co-mutation

LRP1B is one of the tumor suppressor genes which encodes low-density lipoprotein (LDL) family receptor (Liu et al. 2001). *FAT3* is also one of tumor suppressor genes, which is a part of *FAT* family genes encoding large proteins with extracellular Cadherin repeats, EGF-like domains, and Laminin G-like domains (Katoh 2012). At present, it has been found that *FAT3* often co-mutates with *LRP1B*. And the expression of TMB and CD8A in co-mutation showed higher level than single mutation (Zhu et al. 2021).

Table 1 The relationship of gene mutations, PD-L1 expression and TMB

Driver mutations	Incidence	PD-L1 expression	TMB
TP53	30%	High	High
EGFR	27%	–	–
KEAP1	17%	–	–
KRAS	17%	High	–
STK11 /LKB1	9%	Low	Intermediate or high
EPHA	5–15%	–	High
ZFHX3	7–8%	–	High
SMARCA4	6%	Low	High
EML4-ALK	5.3%	High	High
PTEN	5.1%	High	High
NOTCH	5%	–	High
MET	3–4%	High	High
PBRM1	3.04%	–	High
ERBB2	2–4%	Low	High
BRAF	2.5%	High	Low
PIK3CA	2%	Low	–
ROS1	1–2%	High	–
RET	1–2%	–	–
FBXW7	No count	–	High
LRP1B and FAT3 co-mutation	No count	–	High

1. High or low is compared to the wild type in the cited literature

2. "-" means not mentioned in the cited literature in this article

On the basis of TCGA dataset, a study has found *LRP1B* evidently had much more than 5% mutation frequency (34.78%, 176/506) in LUAD patients. And the frequency of *FAT3* mutation was 21.34% (108 out of 506) in LUAD. Co-mutation of *FAT3* and *LRP1B* happened in 10.87% (55 out of 506) LUAD patients (Zhu et al. 2021). Most importantly, this study also indicated that patients with co-mutation of *FAT3* and *LRP1B* showed remarkably longer PFS with immunotherapy than patients with single mutation. Therefore, the co-mutation of *FAT3* and *LRP1B* genes can become another promising biomarker for NSCLC with immunotherapy. However, there is no research to prove whether LUAD patients with only *FAT3* or *LRP1B* mutation can benefit from immunotherapy yet.

Conclusion and perspectives

In conclusion, as these clinical studies mentioned in this article, several gene mutations have shown potential as biomarkers for immunotherapy in NSCLC (Table 1). The mutations of *KRAS, KRAS + TP53, EPHA* (especially *EPHA5*), *ZFHX3, ZFHX3 + TP53, NOTCH, BRAF* and *LRP1B + FAT3* have potential to be used as biomarkers to predict the positive effectiveness of immunotherapy. More importantly, *ZFHX3, ZFHX3 + TP53, STKII/LKB1 + KEAP1 + SMARCA4 + PBRM1* mutations in LUAD patients get more positive effect in immunotherapy. While the mutations of *EGFR, KEAP1*, *STKII/LKB1 + KRAS, EML4-ALK, MET exon 14 skipping mutation, PBRM1, STKII/LKB1 + KEAP1 + SMARCA4 + PBRM1, ERBB2*, *PIK3CA* and *RET* often indicate poor benefit from immunotherapy. It is well known that the guidelines have clearly stated that *EGFR* mutant patients with NSCLC generally did not use immunotherapy. However, the current researches have not made a clear judgment on the predictive significance of the following common or rare mutant genes. The predicting significancy of mutations like *TP53, STKII/LKB1, PTEN, SMARCA4, ROS1, FBXW7, LRP1B* and *FAT3* with immunotherapy is still controversial, further studies are needed to find out the relationship between these mutations and immunotherapy. In addition, the co-mutation of *TP53 + ZFHX3* and *FAT3 + LRP1B* showed better effect in immunotherapy than single mutation (Tables 2 and 3).

This paper may provide guidance for the appliance of immunotherapy in NSCLC patients. Except *EGFR* mutation which is fully studied in various researches, more large-scale clinical studies for positive mutations are needed to guide clinical treatments. Furthermore, gene mutations should be combined with PD-L1, TMB, TILs, etc. to predict the effect of immunotherapy. There should not only consider one factor.

Table 2 The relationship of common gene mutations and immunotherapy

	Driver mutations	Medicines	Sample size	Representative reference
Positive	*KRAS*	Pembrolizumab	179	Dong et al. (2017)
	KRAS + *TP53*	Nivolumab/pembrolizumab/atezolizumab	174	Skoulidis et al. (2018)
	EPHA	Anti-PD-(L)1 monotherapy	239	Chen et al. (2020)
	ZFHX3	Anti-PD-(L)1 monotherapy or in combination with anti-CTLA-4	350	Zhang et al. (2021a, b)
	ZFHX3 + *TP53*	Anti-PD-(L)1 monotherapy or in combination with anti-CTLA-4	329	Zhang et al. (2021a, b)
	EGFR	Nivolumab/pembrolizumab/atezolizumab	3025	Lee et al. (2018)
Negative	*KEAP1*	Atezolizumab and/or bevacizumab with carboplatin/paclitaxel	1694	West et al. (2022)
	STKII/LKB1 + *KRAS*	Nivolumab/pembrolizumab/atezolizumab	174	Skoulidis et al. (2018)
	EML4-ALK	Atezolizumab	142	Fehrenbacher et al. (2016)

Table 3 The relationship of rare genes and immunotherapy

	Driver mutations	Medicines	Sample size	Reference
Positive	*NOTCH*	Anti-PD-(L)1 monotherapy	58	Zhang et al. (2020)
	BRAF	Nivolumab/ pembrolizumab/ atezolizumab	39	Dudnik et al. (2018a, b)
	LRP1B + *FAT3*	Immune checkpoint inhibitors	506	Zhu et al. (2021)
Negative	*MET exon 14* skipping mutation	Pembrolizumab/ nivolumab/ durvalumab/ atezolizumab/ ipilimumab + nivolumab	147	Sabari et al. (2018)
	PBRM1	Anti-PD-(L)1 monotherapy	240	Yang et al. (2021)
	ERBB2	Anti-PD-(L)1 monotherapy	78	Fang et al. (2019)
	STKII + *KEAP1* + *SMARCA4* + *PBRM1*	Anti-PD-(L)1 monotherapy	1269	Marinelli et al. (2020)
	PIK3CA	Nivolumab/atezolizumab/pembrolizumab	84	Kauffmann-Guerrero et al. (2020)
	RET	Nivolumab/pembrolizumab/atezolizumab/ durvalumab/tremelimumab	59	Lee et al. (2020)

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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