Front. Med. 2023, 17(1): 18−42
https://doi.org/10.1007/s11684-022-0976-4

REVIEW

Treatment of advanced non-small cell lung cancer with driver mutations: current applications and future directions

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Abstract **With the improved understanding of driver mutations in non-small cell lung cancer (NSCLC), expanding the targeted therapeutic options improved the survival and safety. However, responses to these agents are commonly temporary and incomplete. Moreover, even patients with the same oncogenic driver gene can respond diversely to the same agent. Furthermore, the therapeutic role of immune-checkpoint inhibitors (ICIs) in oncogene-driven NSCLC remains unclear. Therefore, this review aimed to classify the management of NSCLC with driver mutations based on the gene subtype, concomitant mutation, and dynamic alternation. Then, we provide an overview of the resistant mechanism of target therapy occurring in targeted alternations ("target-dependent resistance") and in the parallel and downstream pathways ("target-independent resistance"). Thirdly, we discuss the effectiveness of ICIs for NSCLC with driver mutations and the combined therapeutic approaches that might reverse the immunosuppressive tumor immune microenvironment. Finally, we listed the emerging treatment strategies for the new oncogenic alternations, and proposed the perspective of NSCLC with driver mutations. This review will guide clinicians to design tailored treatments for NSCLC with driver mutations.**

Keywords non-small cell lung cancer; driver mutations; treatment strategy; resistant mechanism; immune-checkpoint inhibitors

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Improved understanding of driver mutations of non-small cell lung cancer (NSCLC) has led to more biomarker-directed treatment for patients with advanced stages. The expanding number of drugs targeting these driver mutations offers more opportunity to improve patient's survival benefit.

To date, NSCLCs, especially those with non-squamous histology, are recommended for testing epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) gene rearrangements, ROS proto-oncogene receptor tyrosine kinase 1 (*ROS-1*) rearrangements, B-raf proto-oncogene (*BRAF*) mutations, rearranged during transfection (*RET*) fusions, Met proto-oncogene (*MET*) amplification and exon 14 skipping alterations, neurotrophic receptor tyrosine kinase (*NTRK*) gene fusions, and immunohistochemistry (IHC) testing for the programmed death receptor-ligand 1 (PD-L1) expression.

EGFR-activating mutations are the most common driver mutations in NSCLC. Targeted therapies included first-generation epidermal growth factor inhibitor tyrosine kinase inhibitors (*EGFR*-TKIs), erlotinib, gefitinib, and icotinib; second-generation pan-human epidermal growth receptor (*HER*) family inhibitor, afatinib and dacotinib; and third-generation *EGFR*-TKI, osimertinib, that inhibits both *EGFR*-sensitive mutations and resistant mutation *EGFR* T790M [1–3]. *ALK* inhibitors included first-generation, crizotinib; second generation, ceritinib, alectinib, and brigatinib; and third-generation, lorlatinib, with increasing capacity for *ALK* inhibition generation-by-generation [4,5]. The resistance caused by secondary *ALK* mutations can be overcome by next-generation *ALK*-TKIs [6]. Moreover, alectinib, brigatinib, and lorlatinib are all recommended as first-line treatment choice for *ALK*-rearranged NSCLC for their superior survival compared with crizontinb [7–9]. Crizotinib, ceritinib, brigatinib, and lorlatinib can also inhibit *ROS-1* [10,11]. *BRAF* inhibitor dabrafenib combined with *MEK* inhibitor

Received August 22, 2022; accepted December 5, 2022
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trametinib is now the recommended treatment for *BRAF* V600E-mutated NSCLC attributing to improved outcomes compared with vemurafenib or dabrafenib monotherapy [12]. Drugs targeting *MET* aberrations with different binding modes included type Ia, crizotinib; type Ib, tepotinib, capmatinib, and savolitinib; and type II, cabozantinib. Entrectinib and larotrectinib are the current standard treatment for *NTRK* fusion-positive NSCLC [13]. Kirsten ratsarcoma viral oncogene homolog (*KRAS*) mutations occur in ~20%–30% of patients with NSCLC. Recently, several small molecules including sotorasib (AMG510), adagrasib (MRTX-849) have been developed to specifically target *KRAS* G12C [14].

Although drugs targeting oncogenic driver mutations have significantly improved survival but their long-term responses are still uncommon for most patients, the emergence of acquired drug resistance is inevitable. Therefore, exploration and understanding of the resistance mechanism of target therapy are important to enhance the clinical outcomes and ultimately increase the treatment rate of NSCLC. Meanwhile, improved understanding of biological characteristics in various molecular subtypes of each driver mutation helps explore new classified treatment strategies. Until recently, multiomics analysis has ushered in a new era of precision targeted therapy in lung cancer and led to a deeper understanding of the underlying resistant mechanism. All these scientific and clinical progresses ultimately lead to improved survival in NSCLC and achieve more refined individualized treatment.

We searched PubMed for articles describing clinical trials and reviews of medical therapies for NSCLC with driver mutations form January 1, 2013 to April 1, 2022. The guidelines from major professional societies were also reviewed.

Classified management of NSCLC with driver mutation

Stratification by gene subtypes

EGFR mutations are the most common driver mutations in NSCLC, contributing to approximately 50% of patients with NSCLC in Asians and 15% in Caucasians [15]. Exon 19 deletion (19del) and L858R mutation in exon 21 (L858R) are the major subtypes of *EGFR*-sensitive mutations. *EGFR* exon 19 deletion was associated with better response to *EGFR*-TKI treatment than L858R mutation [16]. A meta-analysis including studies comparing *EGFR*-TKIs with chemotherapy as the first-line treatment revealed that the benefit of *EGFR*-TKI versus chemotherapy was 50% higher for patients with exon 19 deletion (hazard ratio (HR) 0.24, 95% confidence interval (CI) 0.20–0.29) than those with exon 21 L858R alternation (HR 0.48, 95% CI 0.39–0.58, *P* interaction < 0.001) [17]. In the pooled analysis of the LUX-Lung-3 and 6 studies, two phase 3 trials comparing afatinib and chemotherapy, the overall survival (OS) improvement was significant in patients with exon 19 deletion but not in those with exon 21 L858R mutation [18]. In the FLAURA study, the median OS was significantly prolonged in the first-line osimertinib group than the first-generation *EGFR*-TKI comparator. However, the magnitude of OS benefit varied among the two *EGFR* mutation subtypes, with the HRs close to 1.00 (95% CI 0.71–1.40) in the L858R subgroup and 0.68 (95% CI 0.51–0.90) in the 19-deletion subgroup [19]. JO22567 and NEJ026 showed that the bevacizumab plus erlotinib significantly improved progression-free survival (PFS) than erlotinib alone in patients with *EGFR*-positive NSCLC. Subgroup analyses by *EGFR* mutation subtype suggested that median PFS was longer in patients with L858R mutations in the combination therapy group than those in the erlotinib group (HR 0.57, 95% CI 0.33–0.97). No differences were found between treatment groups in patients with *EGFR* exon 19 deletions (HR 0.69, 95% CI 0.41–1.16) [20]. Similar results were verified in CTONG 1509, a similar design study in the Chinese population [21]. The INCRESE study showed that double-dose icotinib improved the median PFS (12.9 vs. 9.2 months, HR 0.75, 95% CI 0.53–1.05) and overall response rate (ORR) (73% vs. 48%) in patients with NSCLC harboring 21-L858R mutation compared with the routine dose with acceptable tolerability [22]. All of these findings suggest fundamental differences in biological characteristics and treatment responsiveness between these two subtypes of activating *EGFR* mutations. Therefore, for patients with *EGFR* exon 19 deletion, second- or third-generation *EGFR*-TKI monotherapy is sufficient; however, for patients with *EGFR* L858R mutation, more aggressive treatments including *EGFR*-TKIs combined with anti-angiogenesis therapy or dose increase might better extend the PFS and OS.

Most prospective clinical trials of *EGFR*-TKIs enrolled NSCLC patients with common (19del or L858R) mutations. However, 10%–20% of *EGFR* mutant NSCLC harbor uncommon mutations, which are less sensitive to *EGFR*-TKIs treatment. Second- and third-generation *EGFR*-TKIs have a broader activity profile across uncommon *EGFR* mutations [23]. A combined analysis of LUX-Lung 2/3/6 indicated that afatinib was active in NSCLC with uncommon *EGFR* mutations, especially G719X, L861Q, and S768I but less active in *de novo* T790M and exon 20 insertions [24]. A recent clinical trial indicated that patients harboring uncommon *EGFR* mutations including exon 20 insertion were also sensitive to osimertinib. Early clinical activity in *EGFR/HER2* exon 20 has been observed with the dual *EGFR/HER2*-TKIs, poziotinib, and TAK-788 [25]. Amivantamab, a monoclonal bispecific anti-EGFR-MET antibody, showed

an ORR of 40% and PFS of 8.3months for patients with *EGFR* exon 20 insertion mutant NSCLC with prior platinum-based chemotherapy in the phase I clinical trial, which was certified by the United States Food and Drug Administration as breakthrough therapy for *EGFR* exon 20 insertion mutant NSCLC [26,27]. A recent study also found that NSCLC with uncommon EGFR mutations associated with a significantly lower incidence of acquired T790M mutation and benefited significantly less from subsequent osimertinib treatment than common *EGFR* mutations [28].

The mutation abundance also affects the therapeutic efficacy of *EGFR*-TKI. Studies indicated both tissue and plasma abundance of *EGFR* driver mutation affected clinical response and PFS of *EGFR*-TKIs [29,30]. Meanwhile, the mutation abundance of *EGFR* T790M could also predict the efficacy of osimertinib [31].

Besides *EGFR*, other gene alternations also need to stratify patients according to gene subtypes, such as *ALK* rearrangement. Currently, eight *EML4-ALK* variants (V) have been identified with a number (1, 2, 3a/b, 4', 5a/b, 5′, 7, 8), among them *EML4-ALK* variants 1 and 3 being the two predominant variants. Different clinical response to *ALK*-TKIs between the "short" (V3 and V5) and "long" (V1, V2, V5′, V7, and V8) *EML4-ALK* variants has been reported. According to clinical data concerning crizotinib or lorlatinib, patients with V3a/b seem to have had significantly shorter PFS than did patients with V1. However, these results conflict with those of other studies with crizotinib or alectinib that report insignificant differences in PFS among patients with V1, V2, and V3 [32]. Meanwhile, V3 was associated with worse overall survival in *ALK*-positive NSCLC [33]. Additionally, *ALK* G1202R is more prone to develop among *EML4-ALK* V3 after use of *ALK* TKIs [34].

Generally, *BRAF* alterations can be categorized into three classes. Class I *BRAF* mutations including *BRAF* V600 mutations function as RAS-independent monomers, which represent most of *BRAF* alterations observed in cancer; non-V600 *BRAF* mutants can be divided into two categories, class II mutations, including K601E, L597Q, and G469A, signal as RAS-independent activated dimers, and class III mutations, including D594 and G466 mutants, which are kinase impaired but increase signaling through enhanced RAS binding and signal as dimers [35,36]. Class I *BRAF* mutation well response to *BRAF* and *MEK* dual inhibition. However, the treatment of NSCLC harboring non-V600 mutations is challenging because of functional heterogeneity and lack of clinical data, though few study indicated that certain non-V600 *BRAF* alternations (such as L597R mutation, class II mutation) also have durable response to *MEK* and *BRAF* inhibitors [37]. These distinct responses of different classes of *BRAF* mutations have important implications for future classified management of *BRAF* mutant NSCLC.

RET rearrangements are an emerging targetable driver mutation in NSCLC. The most common fusion partner was the kinesin family 5B gene (*KIF5B*), followed by coiled-coil domain containing 6 (*CCDC6*). Due to the low prevalence of *RET* fusions, there is only limited data about the clinical characteristics and outcomes of *RET*-rearranged NSCLC. Patients with *CCDC6-RET* fusion may have a better prognosis [38] and longer PFS for chemotherapy [39] compared with *KIF5B-RET* and other subtypes. For target therapy, ORR was similar with *KIF5B* and *CCDC6*, but lower in other *RET* fusions in ARROW study [40].

Alterations in *MET* include MET protein overexpression, *MET* gene amplification, and *MET* exon 14 skipping mutations or activating mutations. MET overexpression is related to poor clinical outcome in NSCLCs but its role as a therapeutic marker remains controversial. *MET* amplification has been regarded as a therapeutic biomarker, with clinical data demonstrating that the high *MET* gene copy number indicated a high response rate to targeted therapies. *MET* exon 14 skipping mutations also indicate poor outcomes in NSCLC and are presently the most promising driver mutation for the use of *MET*-TKIs. As we mentioned before, there are three subtypes of *MET*-TKIs and response differently to the *MET* mutations: type I *MET* inhibitors bind to the activated ATP-pocket of MET, and are subdivided into Ia and Ib; type II inhibitors bind the ATP-pocket in the inactive state; type III inhibitors bind to allosteric sites distinct from the ATP binding site. Mutations in the MET activation loop D1228 and Y1230 confer resistance to type Ia *MET*-TKIs while sensitive to type II kinase inhibitors. The solvent front mutation G1163R mediates resistance only to type Ia inhibitor crizotinib but not to type Ib or type II *MET* inhibitors. Conversely, mutations in residues L1195 and F1200 confer resistance to type II *MET* inhibitors. These findings provide rationality for sequential or combination therapy to avoid resistance to *MET* TKIs [41–43].

Stratification by concomitant mutation

EGFR is a member of the ErbB family of receptor tyrosine kinases. Its downstream pathways include PI3K-AKT-mTOR, JAK-STAT, RAF-MEK-ERK, and other pathways. Co-mutations in downstream and other ErbB family members can spur the cell growth through signal transduction, eventually resulting in tumor proliferation and even metastasis [44]. Clinical data also indicated the concomitant genetic alterations associated with poorer response to *EGFR*-TKI treatment among the *EGFR* mutant NSCLC [45]. Some co-mutations such as *TGFBR1*, *MTOR*, and *RNF43* might indicate primary

resistance to *EGFR*-TKIs [46]. In the BENEFIT study [47], a prospective study using circulating tumor DNA (ctDNA) as direct first-line *EGFR*-TKI treatment, patients with tumor suppressor co-mutations and tumors with other driver mutations had shorter PFS (9.3 (7.6–10.5) vs. 4.0 (2.4–9.3) months vs. 13.2 (11.3–15.2)) and OS (21.7 (19.3–27.0)) vs. 15.5 ((10.5–33.7) months vs. 32.0 (29.2–41.5)) than those with pure *EGFR*-sensitive mutation [48]. Preclinical data suggest that *EGFR*-TKIs combined with chemotherapy may act synergistically to restrict the development of acquired resistance [49]. Meanwhile, clinical data also indicated that the adverse events are manageable [50]. For patients with concomitant mutation, the treatment mode like that of the NEJ009 study, *EGFR*-TKIs combined with chemotherapy [51], might improve the prognosis of patient with concomitant mutations. Some clinical trials aiming to assess the efficacy of combined *EGFR*-TKIs and chemotherapy in NSCLC with co-mutations are ongoing (ChiCTR2000032354).

Occasionally, tumors have T790M coexistence with *EGFR*-activating mutations at the time of diagnosis. Using more sensitive methods such as DNA mass array, the occurrence of T790M in TKI-naïve patients was higher than that in direct sequencing (25.2% vs. 2.8%, $P < 0.001$) [52]. Naturally, third-generation *EGFR*-TKIs are the recommended choice of patients with *de novo* T790M.

Besides *EGFR* concomitant mutations, *EGFR* amplification was also regarded as an *EGFR*-dependent resistant mechanism to *EGFR*-TKIs [53]. *EGFR* amplification is more likely to arise in cases with resistance to third generation of *EGFR*-TKIs [54], and accounts for approximately 20% of the resistant mechanism. The EGFR-MET bispecific antibody amivantamab in combination of third-generation *EGFR*-TKIs might improve the outcome of patient with *EGFR* amplification and *EGFR* sensitive mutations. The clinical trial that is called the MARIPOSA study (NCT04487080) to compare the antitumor activity of amivantamab + lazertinib versus osimertinib alone in patients with *EGFR* mutant NSCLC first line treatment is ongoing [55].

The concomitant sensitive mutations rarely occurred. The frequency of *EGFR*/*ALK* or *EGFR*/*ROS-1* co-alternations was about 1% [56]. Based on the published data and case report, *EGFR*/*ALK* co-altered NSCLC still showed response to *EGFR*-TKIs [57,58], though the *EGFR*-sensitizing mutant NSCLC with other driver mutations exhibited shorter PFS (4.0 versus 13.2 months) and OS (15.5 versus 32.0 months) compared with those with *EGFR*-sensitive mutation alone [48,59]. The co-mutation of *EGFR* and *MET* (2% prevalence) or *ERBB2* (4% prevalence) amplification was also associated with significantly shorter progression-free survival with first-line 1st or 2nd generation *EGFR*-TKIs therapy [60]. Generally, the first-line *EGFR*-TKIs might be a reasonable care for the NSCLC with *EGFR* and other driver mutations. The frequency of the co-alterations, the sensitivity of the detection methods, and the phosphorylation levels of the driver gene and its downstream proteins should be considered when making treatment choice [61].

Like *EGFR* mutations, concomitant mutations in the non-*EGFR* mutation-driven NSCLC also mostly indicated poor duration of response. For *ALK* fusion NSCLC, the presence of *TP53* mutations is a poor predictive and prognostic factor. Though lacks of clinical data, pre-clinical study provided insight that the combination of *ALK*-TKIs and proteasome potentially leads to *TP53*-independent apoptosis [34]. The co-occurrent *PIK3CA* E542K and *EML4-ALK* V3 was also reported to be resistant to *ALK*-TKIs [62]. For *RET*-rearranged NSCLC, patient with concomitant *TP53* mutation showed shorter overall survival than those without [63]. Specially, patient with *STK11* mutation, *KRAS* G12C mutation and wild type *KEAP1* benefit more from the sotorasib therapy [64].

Stratification by dynamic alternation

The dynamic gene mutation changes are also key predictive factors for target therapy. Liquid biopsy identifying molecular alterations in plasma ctDNA makes the dynamic monitoring possible. In the BENEFIT study, 147 (88%) patients exhibited *EGFR* mutation clearance in ctDNA at week 8, and the median PFS was longer for these patients than those with *EGFR* mutations that persisted at week 8 (11.0 months (95% CI 9.43–12.85) vs. 2.1 months (1.81–3.65); HR 0.14, 95% CI 0.08–0.23; $P < 0.0001$) [47]. Patients with persistent activating *EGFR* mutations in plasma ctDNA after osimertinib initiation also indicated worse prognosis, either in the first-line setting [65] or T790M-positive patients as the second-line treatment [66]. Patients without detectable *EGFR* mutation in the pretreatment ctDNA possessed the best prognosis from the sequential TKI treatment [67].

Patients with ctDNA nonclearance at the first visit might require combined therapy because of the limited survival benefit of *EGFR*-TKI monotherapy. A clinical trial that investigates the efficacy and safety of osimertinib plus carboplatin/pemetrexed versus osimertinib monotherapy in metastatic *EGFR* mutant NSCLC patients with *EGFR* mutation persistence in ctDNA 3 weeks after the first-line osimertinib is ongoing (NCT04769388).

Therefore, for *EGFR*, the target therapy should be stratified based on diverse mutation subtypes, concomitant mutations, and dynamic ctDNA changes. With the in-depth understanding of other driver mutations, this stratified treatment mode can be an effective reference to other target therapy.

Stratification by special metastasis site

Brain or leptomeningeal metastasis is a generally negative prognostic factor and is refractory to treatment due to the blood–brain barrier. Second- or third-generation *EGFR*-TKIs [52] or *ALK*-TKIs are better options for those patients. Second- or third-generation *EGFR* and *ALK* inhibitors had higher intracranial ORR and disease control rate (DCR) in patients refractory to first-generation TKIs; thus, the next-generation *EGFR/ALK*-TKIs are currently replacing first-generation TKIs as the first-line treatment, especially for NSCLC with central nerve system (CNS) metastasis [68]. Stereotactic radiosurgery and whole-brain radiotherapy are also the treatment options for patients with CNS metastasis.

Oligo-metastatic disease represents a special subtype of metastatic NSCLC that required local treatment [69]. A series of phase II clinical trials confirmed that local consolidative therapy for patients with oligo-metastatic NSCLC did not progress after initial systemic therapy, which more significantly improved PFS than those without local therapy [70,71]. Moreover, for oligo-progressive conditions during target therapy, local ablation of these resistant lesions using either surgery or radiation can prolong the long-term response of the existing target therapy, with an average time to next progression of 6–7 months [72,73].

Stratification by multinomic profiles

With the advent of new genomics, transcriptomics, metabolomics, and proteomics technology, integrated genomic studies have fundamentally contributed to the definition of multinomics landscape of NSCLC. Copy number alterations represent one of the key genetic alterations and included two types: large-scale copy number gain or loss and focal events of gene amplification or loss [74]. The large-scale copy number gain or loss is consistent in most lung adenocarcinoma [75], whereas some focal events were associated with negative outcomes, such as *KRAS* gene amplification and *MET* focal gains [74]. A previous study also indicated the use of DNA-sequencing, RNA-sequencing, and immunological biomarkers for patients matched to targeted therapies and to identify new potential cancer driver genes [76,77]. Mutational signature may also help identify patients. The APOBEC signature was associated with early-onset EGFR wild-type lung cancer in women, which is in line with the finding that the APOBEC signature was associated with better immunotherapeutic response [78].

Resistance mechanisms and coping strategies

Although the target therapy improves survival in NSCLC with driver mutations, only a part of patients respond to these agents and the benefit is temporary. Recognition of the resistance complexity to targeted therapeutics is necessary to understand the tumor biological behavior and to design optional therapeutic strategies.

Based on the duration of disease control, resistance to targeted agents can be classified into intrinsic and acquired resistance [79]. Primary resistance is defined as resistance in NSCLC with sensitive mutations that progressed within 90 days (3 months) and without showing any evidence of objective responses while receiving target therapy [80]. The intrinsic resistance

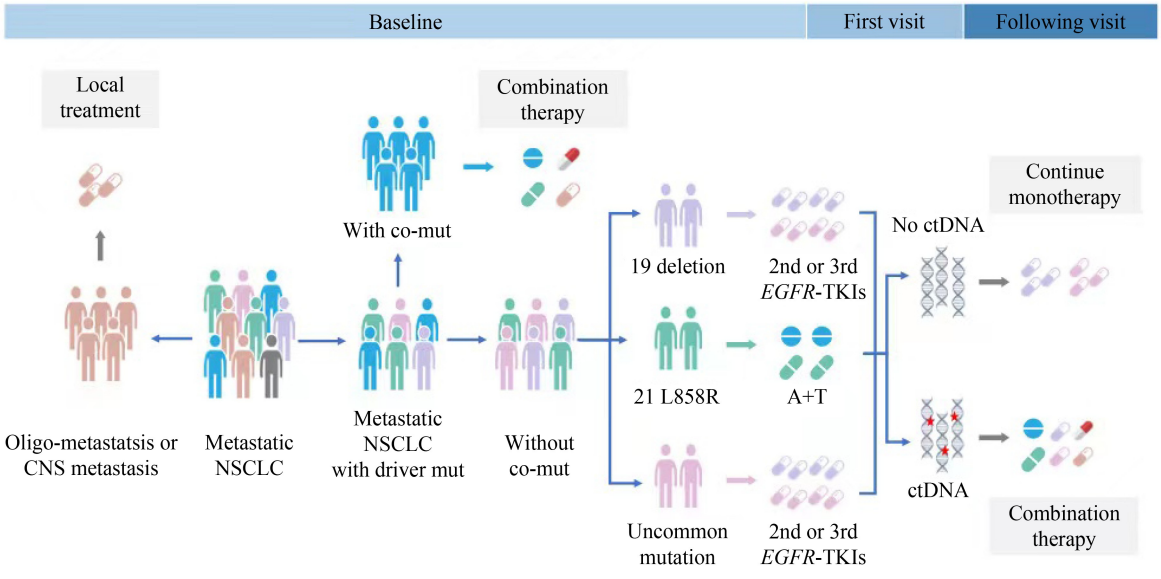

Fig. 1 Stratified management of NSCLC with driver mutations (take *EGFR* mutation as an example).

might be associated with insensitive driver mutations. For *EGFR*-TKIs, intrinsic-resistant mechanisms include *EGFR* uncommon mutations, co-mutations that activate downstream or bypass signaling pathways, the presence of germline *Bcl-2*-interacting mediator of cell death (*BIM*, also known as *BCL2L11*), or activation of *NF-κB* (nuclear factor-κB) that impairs the apoptosis process in *EGFR*-TKI treatment. Acquired resistance refers to tumors that initially responded to the target therapy (usually > 6 months) but ultimately progressed based on Response Evaluation Criteria in Solid Tumors [81]. Acquired resistance increases both from the selection for pre-existing genetic alterations within a heterogeneous tumor and from the acquisition of new mutations under the therapeutic selective pressure [79].

Based on the disease failure mode, disease progression in the target therapy can be classified into three subgroups: dramatic, gradual, and local progression. Patients with NSCLC with gradual progression have longer PFS and OS compared with those with local and dramatic progression, and the TKI continuation is superior to switching to chemotherapy in a subsequent setting for patients with gradual progression. For patients with local progressive disease, continued use of the target therapy plus local therapy is recommended. Conversely, studies demonstrated a better survival with chemotherapy instead of continued TKIs for patients with dramatic progression [82].

Depending on the resistant mechanism, the two major pathways of therapeutic failure are additional genomic mutations in the targeted oncogene (target-dependent resistance) and alternations leading to bypass or downstream activation (target-independent resistance) [83].

Target-dependent resistance

The target-dependent resistance mutations include second-site mutations, oncogene amplification or loss, limiting the ability of a drug to inhibit the target activity. The second-site mutations include T790M mutation that leads to acquired resistance to first- and second-generation *EGFR*-TKIs and C797S mutation that mediates the resistance to third-generation *EGFR*-TKIs. A recent study separated *EGFR* mutations into four distinct subgroups based on sensitivity and structural changes, indicating that the on-target mutation might cause EGFR structural changes, thus causing different outcomes following treatment with *EGFR* inhibitors [84]. The on-target mutation is the most common resistant mechanism for third-generation *EGFR*-TKIs, such as C797S, G796S, and L792F/H mutations that abolish the covalent binding or confer structural steric hindrance of osimertinib to the EGFR protein. “Fourth-generation” *EGFR*-TKIs such as EAI045, JBJ-04-125-02, and BLU-945 are being developed to inhibit these triple mutations (i.e., del19 or L858R/T790M/C797S), yet remain at the early clinical stages of development [85]. The EGFR/MET bispecific antibody amivantamab has demonstrated activity against a myriad of compound *EGFR* mutations [86].

Meanwhile, *ALK* L1196M [87] and *ROS1* L2026M [88] that sterically hinder TKI binding also lead to resistance to first-generation *ALK*-TKIs. Similarly, *RET* G810X mutation is responsible for resistance to *RET*-selective inhibitors, such as selpercatinib (LOXO-292) and pralsetinib (BLU-667) [89]. Both *KRAS* R68S and Y96C/D/S drug binding resistance mutations show high-level resistance to both sotorasib and adagrasib [90–92]. *EGFR* amplification and loss of *EGFR* T790M mutation have been reported to be resistant to third-generation *EGFR*-TKIs [93]. Similarly, *ALK* amplification and copy number gain mediate resistance to crizotinib [94]. *KRAS* G12C amplification has been reported at resistance to adagrasib (Table 1) [91].

Moreover, for NSCLC with *EML4-ALK* fusion, the eight *EML4-ALK* variants also demonstrate a differential clinical response to *ALK*-TKIs, with variants 3 and 5, indicating poor responses and short PFS [95].

Target-independent resistance

Target-independent resistance occurs through the parallel activation or downstream signaling pathways using the driver oncoprotein [96]. Taking *EGFR* (also known as *ERBB1*) for example, the alternation in other *ERBB* family members such as *HER2*, *HER3*, and *HER4* all results in the activation of three downstream pathways including PI3K-AKT, JAK-STAT, and MAPK pathways [97].

In *EGFR*-mutated tumors, the MAPK pathway reactivation can occur by acquiring a *BRAF* mutation (V600E), loss of *NF1* gene, and activation of *NRAS* mutations [98,99]. In preclinical studies, this resistance to third-generation *EGFR*-TKIs was reversed by combination treatment with *MEK* and *EGFR* inhibitors [98]. The *PTEN* loss and *PIK3CA* mutations are the most common resistant mechanisms in the PIK3CA-AKT pathway. Inhibitors targeting the PI3K-AKT-mTOR pathway are now in clinical trials and have shown potent efficacy. Autocrine interleukin-6 (IL-6) signaling by tumor cells increases JAK-STAT3 activity, which can be activated as an adaptive response to the *EGFR*-TKI treatment.

SRC is an oncoprotein implicated in tumor survival and differentiation. SRC activation was reported in *EGFR*-TKI-resistant NSCLC cell lines, and the addition of SRC inhibitor dasatinib to erlotinib showed early signs of clinical efficacy in patients with *EGFR* mutant NSCLC [100]. MET and its ligand, hepatocyte growth factor

Table 1 Summary of resistant mechanisms for target therapy in lung cancer

Drugs	Resistant mechanism		Possible solutions	References
EGFR				
First- or second-generation *EGFR*-TKIs	Target-dependent resistance	T790M	Third generation *EGFR*-TKIs	Cross *et al*. [121]
	Target-independent resistance	*MET* amplification/ skip mutation	*EGFR*-TKIs + MET inhibitor	Giroux-Leprieur *et al*. [122]
		RET fusion	*EGFR*-TKIs + RET inhibitor	Piotrowska *et al*. [123]
		BRAF mutation, *HER-2* mutation and amplification	*EGFR*-TKIs + BRAF/HER-2 inhibitor	Wu *et al*. [124]
	Other resistant mechanisms	Histologic transformation	Etopside + platinum	Marcoux *et al*. [125]
Third-generation *EGFR*-TKIs	Target-dependent resistance	C797S in *trans*	Osimertinib + first generation *EGFR*-TKIs	Arulananda *et al*. [126]
		C797S in *cis*	Osimertinib + bevacizumab + brigatinib	Zhao *et al*. [127]
		EGFR amplifications and mutations	*EGFR/MET* bispecific monoclonal antibody (amivantamab)	Shah *et al*. [86], Scalvini *et al*. [128]
	Target-independent resistance	*MET* amplification	Osimertinib + MET inhibitors, or amivantamab	Giroux-Leprieur *et al*. [122], Neijssen *et al*. [129]
		BRAF mutation or *NF1* mutation that leads to activation of *MAPK* pathway	Combined *MEK* and *EGFR*-TKIs	Tricker *et al*. [98]
		Loss of *PTEN* and *PIK3CA* mutation	PI3K-AKT-mTOR pathway inhibitors	Sato *et.al*. [130]
		Her-2 mutation and amplification	HER-2 inhibitors	Zhou *et.al*. [131]
		SRC activation	*SRC* inhibitor dasatinib	Watanabe *et al*. [132]
		AXL overexpression	*AXL*-TKIs	Okura *et al*. [133]
		Cell cycle alternations (*CCND1* amplification, *CCND2* amplification, *CKD6* amplification, *CCKE1* amplification)	No evidence	Cho *et al*. [134]
	Other resistant mechanisms	SCLC/SCC transformation	Etopside + platinum/chemotherapy for SCC	Yin *et al*. [135,136]
ALK				
First generation *ALK*-TKIs	Target-dependent resistance	*ALK* copy number gain	Second generation *ALK*-TKIs	Russo *et al*. [137]
		L1196M, C1156Y, 1151Tins, L1152R, G1202R, D1203N, S1206 Y, G1269A, G1128A, I1171T, E1210K, C1156S, F1245V	Second generation *ALK*-TKIs (G1202R only sensitive to brigatinib and lorlatinib)	Russo *et al*. [137]
	Target-independent resistance	*KIT* amplification, *KRAS* mutations, *EGFR* mutation and/or amplification, *IGF-1R* activation, *RAS/MEK* activation	No evidence	Russo *et al*. [137]
	Other resistant mechanisms	SCLC/EMT transformation	Etopside + platinum	Russo *et al*. [137]
Second generation *ALK*-TKIs	Target-dependent resistance	G1202R, I1171; F1174 (resistant to ceritinib but sensitive to alectinib)	Lorlatinib	Shaw *et al*. [138]
	Target-independent resistance	*MET* amplification, *RAS/MEK* activation, protein kinase C (*PKC*) activation, *SRC* activation, activation of *EGFR* and *HER4* pathways, *SHP2* activation, and *NF2* loss	No evidence	Russo *et al*. [137]

(*Continued*)

Drugs	Resistant mechanism		Possible solutions	References
Third generation *ALK*-TKIs	Target-dependent resistance	Compound mutations such as G1202R + L1196M, D1203N + F1174C, D1203N + E1210K	Rechallenge with 1st/2nd generation *ALK*-TKIs 4th generation TKI: TPX0131 has potency against wild-type (WT) *ALK* and a spectrum of acquired resistance mutations	Russo *et al*. [137], Yoda *et al*. [137], Takahashi *et al*. [137], Murray *et al*. [139]
	Target-independent resistance	*MET* amplification	*ALK*-TKI + MEK inhibitors	Dagogo-Jack *et al*. [140]
ROS-1				
Crizotinib	Target-dependent resistance	L2026M	No evidence	Mccoach *et al*. [141]
		ROS1-G2032R,D2033N, S1986F/Y	G2032R mutation tumors was inhibited by repotrectinib, S1986F/Y mutation tumors was inhibited by lorlatinib [142]	Katayama *et al*. [143], Drilon *et al*. [144], Gainor *et al*. [145]
	Target-independent resistance	*KRAS* G12C and *NRAS* Q61K	No evidence	Cui *et al*. [146]
		Kit mutation (D816G)	No evidence	Cui *et al*. [146]
RET				
Selpercatinib/pralsetinib	Target-dependent resistance	*RET* G810R/S/C/V	No evidence	Lin *et al*. [89]
	Target-independent resistance	*MET* amplification	No evidence	Subbiah *et al*. [147]
		KRAS amplification/*PIK3CA* mutation	No evidence	Nelson-Taylor *et al*. [148]
Vandetanib/cabozantinib	Target-dependent resistance	*RET* V804M	Selpercatinib	Drusbosky *et al*. [149]
BRAF				
Dabrafenib + trametinib	Target-dependent resistance	*BRAF* splice variants or *BRAF* amplification	No evidence	Shimizu *et al*. [150]
		BRAF fusion genes	No evidence	Kulkarni *et al*. [151]
	Target-independent resistance	Reactivation of RAS-RAF-MEK-ERK pathway, such as *NRAS/KRAS* or *MEK 1/2* mutations	No evidence	Johnson *et al*. [152]
		Activation of PI3K-AKT pathway, such as *AKT* activating mutations and *PTEN* loss of function	No evidence	Proietti *et al*. [153]
		TP53, *CDKN2A*, *KRAS* G12D	No evidence	Rudin *et al*. [154]
MET				
Type Ia (crizotinib)	Target-dependent resistance	V1092I/L, G1163R, D1164G, L1195V, D1228X, Y1230X	No evidence	Fujino *et al*. [154], Ou *et al*. [154]
	Target-independent resistance	*HER-2* amplification, *KRAS* amplification. *EGFR* amplification	No evidence	Ding *et al*. [155], Bahcall *et al*. [156], Dagogo-Jack *et al*. [157]
Type Ib (topotinib, savolitinib, capmatinib)	Target-dependent resistance	D1228H/N, Y1230C/H/S	*MET* V1092L, D1228G or Y1230H can benefit from type II MET inhibitors	Yu *et al*. [158], Shen *et al*. [159]
	Target-independent resistance	*KRAS*, *NRAS*, *BRAF*, *PIK3CA*, *FGF19*, *TP53*	No evidence	Guo *et al*. [160]

(*Continued*)

Drugs	Resistant mechanism		Possible solutions	References
Type II (cabozantinib)	Target-dependent resistance	D1133V, Y1159H, L1195F, F1200I/L	No evidence	Fujino *et al*. [106]
HER2 20 insertion				
Poziotinib	Target-dependent resistance	C805S	HSP90 inhibitors	Koga *et al*. [161]
	Target-dependent resistance	*HER2* copy number gain	*HER2* targeted therapy: trastuzumab, afatinib, ado-trastuzumab emtansine	Chuang *et al*. [162]
EGFR-TKIs (elotinib, afatinib, osimertinib)	Target-dependent resistance	*HER2* mutations A775_G776insYVMA (YVMA)	Poziotinib	Koga *et al*. [161]
Lapatinib	Target-dependent resistance	L755P/S, T798M mutation in *HER2*	No evidence	Yu *et al*. [163]
KRAS G12C				
Sotorasib	Target-dependent resistance	*KRAS* Y96C/D/S, R68S/M, G12D/R/V/W, G13D, A59S, A59T	The G13D, R68M, A59S, and A59T mutation is sensitive to adagrasib. Combination of BI-3406 (SOS1 inhibitor) and trametinib had potent activity against Y96D/S mutation. Novel KRAS inhibitor RM-018 overcomes *KRAS* G12C/Y96D	Tanaka *et al*. [90], Awad *et al*. [91], Koga *et al*. [92]
	Target-independent resistance	*NRAS* (Q61K or G13R), *MRAS* (Q71R), *BRAF* (G596R), *EGFR* (amplification, P1108L and S1046R), *FGFR2* (amplification, A68T and D304N)	No evidence	Zhao *et al*. [103]
		MET amplification	A combination of sotorasib and MET inhibitors such as crizotinib and capmatinib	Zhao *et al*. [103], Suzuki *et al*. [105]
		HER2 amplification	A combination of sotorasib and SHP2 inhibitors	Ho *et al*. [104]
Adagrasib	Target-dependent resistance	*KRAS* Y96C/D/S/, R68S	Combination of BI-3406 and trametinib had potent activity against Y96D/S. RM-018 overcomes *KRAS* G12C/Y96D	Tanaka *et al*. [90], Awad *et al*. [91], Koga *et al*. [92]
		KRAS G12C amplification	No evidence	Awad *et al*. [91]
	Target-independent resistance	*NRAS* Q61L/R/K, *BRAF* V600E, *MAP2K1* Q56P, *MAP2K1* E102_103/104del, *PIK3CA* H1047R, *RET* M918T, *MET* amplification, *EML4-ALK* and *FGFR3- TACC3*, etc.	No evidence	Awad *et al*. [91]
	Other resistant mechanism	Squamous cell transformation	No evidence	Awad *et al*. [91]
NTRK fusion				
Larotrectinib or entrectinib	Target-dependent resistance	Solvent front, gatekeeper residue and xDFG motif	No evidence	Russo *et al*. [137], Cocco *et al*. [191]
	Target-independent resistance	*KRAS* mutation, *MET* amplification, *BRAF* mutation	No evidence	Cocco *et al*. [191]

(HGF), can activate MAPK and PI3K-AKT-mTOR signaling. *MET* amplification and exon 14 skip mutation account for 10%–20% of *EGFR*-TKI-resistant NSCLC. A series of clinical trials concerning combined EGFR and MET inhibitors are ongoing. Meanwhile, *MET* variations are also responsible for *ALK*-TKI resistance in *ALK*-rearranged NSCLC.

The receptor tyrosine kinase AXL also activates MAPK and PI3K-AKT signaling. The overexpression of *AXL* in NSCLC resulted in resistance to both *EGFR*-TKIs and *ALK*-TKIs [101]. The *AXL*-TKI is also at the early phase clinical trials. *HER2* gene amplification/ overexpression and *HER2* exon 20 insertion mutations can also lead to bypass activation. Poziotinib and pyrotinib have shown potent inhibitory abilities against *HER2* mutant NSCLC; however, patients with *HER2* overexpression have shown limited responses to *HER2* inhibitors [96,102].

The "Target-independent resistance" mechanism can be subdivided into tumor suppressor gene, other driver gene, cell cycle related gene and others. Acquired bypass resistance mechanisms of *KRAS* G12C inhibitors included *MET* and *HER2* amplification; activating mutations in *NRAS*, *BRAF*, *MAP2K1*, and *RET*; oncogenic fusions involving *ALK*, *RET*, *BRAF*, *RAF1*, and *FGFR3*; and loss-of-function mutations in *NF1* and *PTEN* [91,103–105]. The majority of resistance to selective *RET* inhibition may be driven by *RET*-independent resistance, such as acquired *MET* or *KRAS* amplification (Table 1) [106].

Other resistant mechanisms

Phenotype transformation

Phenotype transformation is a less common mechanism of *EGFR*-TKI resistance and other target therapies, encompassing the histological transformation of adenocarcinoma to small cell lung cancer (SCLC) and to squamous cell carcinoma (SCC) [83]. The transformed derivatives manifest a more aggressive subtype that can escape from anticancer-targeted therapies. Epithelial-to-mesenchymal transition (EMT) is another phenotypic transformation as a resistance change to both *EGFR* and *ALK*-TKI therapies [107], indicating a more invasive phenotype. *RB1* and *TP53* deficiencies indicated a higher incidence of SCLC transformation [108], and the classical chemotherapy for SCLC is also sensitive to the transformed SCLC [109].

EMT is a cause of both intrinsic and acquired resistance of *KRAS* G12C inhibitors by activating the PI3K pathway [110]. Moreover, histological transformation from adenocarcinoma to squamous cell carcinoma was observed in patients resistant to adagrasib without determining any genomic resistance mechanisms [90].

Tumor microenvironment (TME)

TME refers to the tumor-surrounded stromal components, including fibroblasts, immune cells, blood vessels, and cytokines, influencing the response to targeted therapy. Coculture of cancer-associated fibroblasts (CAFs) can induce both EMT and resistance to *EGFR*-TKIs in NSCLC cells [111]. Cytokines, such as HGF, activate the ERK signaling and consequently result in *EGFR*-TKI resistance [112]. The HGF secretion by CAFs can also lead to *ALK*-TKI resistance by inducing MET-dependent signaling activation [113]. Furthermore, the VEGF pathway is a key mediator of tumor angiogenesis. *In vitro* studies have found that VEGF and EGFR pathways share common oncogenic downstream signaling and elevated VEGF contributing to the emergence of *EGFR*-TKI resistance. In clinical trials, the addition of anti-VEGF therapy to *EGFR*-TKIs significantly improved the clinical outcomes [114]. Angiogenic factors such as the Tie2 receptor also regulated EGFR downstream signaling PI3K/AKT and/or MAPK pathways [115].

Impaired apoptosis

Germline *BIM* (also known as *BCL2L11*) deletion polymorphism impairs the apoptotic response to *EGFR*-TKI therapy, thus leading to drug resistance [116]. Activation of NF-κB weakens the apoptosis and rescues *EGFR* mutant NSCLC from *EGFR*-TKI treatment. The inactivation of NF-κB pathway enhances cell death induced by *EGFR*-TKIs [117]. A recent study has found that YES-associated protein (YAP) activation mediates resistance to combined *EGFR/MEK* inhibition. The combination of drugs targeting the YAP pathway, such as transcriptional enhancer associate domain (TEAD) inhibitor, promotes apoptosis of resistant cancer cells [52].

Barriers and drug–drug interactions (DDIs)

Further challenges beyond the former factors include overcoming barriers, such as blood–brain barriers that limit effective drug delivery to CNS metastases. Increasing drug exposure by dose escalation or exploring new-generation TKIs is a possible solution to overcome body barriers. DDIs should also be under consideration. The combination of drugs interacting with cytochrome P450 and P-glycoprotein should be avoided. Proton pump inhibitors also impair the pH-dependent solution, thus reducing drug absorption [118].

Resistant mechanism based on multiomics analysis

By analyzing the adaptive-resistant tumor cells using transcriptomic and metabolomics profiling, drug resistance was found to be correlated with cells in

proliferative-metabolic quiescence and susceptible to glutamine deprivation and TGFβ2 inhibition [119]. This study and others [120] support the co-targeting of bioenergetics and mitochondrial priming to suppress the onset of early drug resistant to *EGFR*-TKIs.

ICIs in NSCLC with driver mutations

Immune-checkpoint inhibitors show limited effectiveness in NSCLC with driver mutations

Patients with *EGFR* mutation poorly respond to PD-1/PD-L1 inhibitors. In the PACIFIC trial of patients with unresectable, stage III NSCLC, the consolidative durvalumab failed to significantly improve the PFS and OS compared with the placebo group in 6.0% patients with *EGFR* mutations [164–166]. A meta-analysis, including CheckMate 017/057, KEYNOTE-010, POPLAR, and OAK found that nivolumab, pembrolizumab, and atezolizumab, was associated with prolonged OS, compared with docetaxel in the *EGFR* wild-type subgroup but not in the *EGFR* mutant subgroup [167]. ATLANTIC is a phase 2, open-label, single-arm trial concerning durvalumab as third-line or later treatment for advanced NSCLC. Although *EGFR* mutant NSCLC with PD-L1 expression of ⩾ 25% had a higher response rate than the low expression group (12.2% vs. 3.6%), it still responded worse than the *EGFR/ALK* wild-type cohorts [168]. The WJOG8515L study is a randomized phase II trial comparing nivolumab with carboplatin and pemetrexed treatment in *EGFR* mutant NSCLC resistant to *EGFR*-TKIs due to mechanisms other than T790M. The PFS of nivolumab was shorter than chemotherapy (1.7–5.6 months), although OS was similar between the two arms [169].

The reasons for *EGFR* mutant NSCLC showed little benefits to ICIs are as following. *EGFR* activation induces CD73 expression, which can subsequently reduce the expression of interferon γ mRNA signature [170]. Meanwhile, high CD73 expression in NSCLC and other tumors is associated with low PD-L1 expression and densities of $CD8^+$ tumor-infiltrating lymphocytes (TIL) [171]. Simultaneously, tumor mutational burden (TMB) is positively associated with ICI effectiveness and is lower in the *EGFR* mutant tumors compared with *EGFR* wild-type tumors (median 3.77 vs. 6.12 mutations/Mb, $P < 0.0001$) [172].

Retrospective studies or subgroup analyses revealed that the limited evidence indicates the characteristics of *EGFR* mutant tumor that can possibly benefit from ICIs:

(1) Tumors with inflammatory TME. In a study concerting nivolumab monotherapy in tumors with *EGFR* mutation, nivolumab responders had a significantly higher $CD8^+$ TIL density and nonsynonymous mutation burden [173]. The PFS of anti-PD-1 agents in the *EGFR* mutant tumor was longer in patients with high PD-L1 expression and high TMB [172,174]. Although patients with *EGFR* mutant NSCLC tend to have lower TMB and PD-L1 expression [172], studies indicated that *EGFR*-TKI treatment can change the unfavorable TME. In a cohort of 138 patients with *EGFR* mutant NSCLC, the proportion of PD-L1 high expression (⩾ 50%) and the TMB level both significantly increased after *EGFR*-TKI treatment. Moreover, in this cohort, patients with PD-L1 expression increasing from low to high after that *EGFR*-TKI treatment achieved a PFS of > 6 months [174]. In another cohort of 153 patients with *EGFR* mutant lung cancer, TMB also increased at resistance (median 3.42 vs. 6.56 mutations/Mb, $P = 0.008$) [172].

(2) Short PFS to EGFR-TKIs. A study including 58 patients with *EGFR* mutant NSCLC that received ICI treatment after *EGFR*-TKI treatment found that patients with shorter TKI-PFS (PFS of *EGFR*-TKIs was shorter than 10 months) had a significantly prolonged PFS and higher ORR of ICI treatment than those with longer TKI-PFS. Patients with shorter TKI-PFS harbored a higher proportion of $CD8^+$ T cells and a lower ratio of M1 and M2-like macrophages [175].

(3) EGFR L858R mutation. A retrospective study reported that patients with *EGFR* L858R mutation showed similar clinical outcomes compared with the *EGFR* wild-type cohort in anti-PD-1/PD-L1 inhibitor treatment. However, the outcomes were poorer in patients with *EGFR* exon 19 deletion [176].

(4) T790M-negative patients. Clinical data indicated that the PFS of nivolumab after *EGFR*-TKIs treatment failure was longer for T790M-negative than T790M-positive patients (2.1 vs. 1.3 months, $P = 0.099$) [173].

For the driver mutation other than *EGFR*, the current National Comprehensive Cancer Network (NCCN) guidelines also recommended the use of target therapy as the first-line treatment for advanced NSCLC, such as *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET* ex14 skipping, and *RET*. After the disease progression, systematic therapy is recommended. By reviewing the IMMUNOTARGET registry and other published data considering ICIs in NSCLC with oncogenic driver alteration, we found that the ORR and PFS for NSCLC harboring the *KRAS*, *BRAF*, and *c-MET* alterations were comparable to non-mutant NSCLC in ICI registration trials, whereas the ORR in *ALK*, *ROS-1* and *RET* fusion and NSCLC were relatively low. In the IMMUNOTARGET study, PD-L1 expression was relatively high in those *ALK*, *ROS-1* and *RET* translocation cases [177,178]. Limited data showed variable ORRs of *HER2*, *ROS1*, and *NTRK*-altered NSCLCs, leaving an unclear efficacy of ICIs. Generally, patients with actionable tumor alternations show limited benefit form ICI monotherapy, combination of ICIs and chemotherapy and/or antiangiogenic agents is an option. New relevant biomarkers besides PD-L1 expression

should be explored for these oncogenic addicted tumors.

Furthermore, the benefits to ICIs in *KRAS* mutant NSCLCs may vary depending on co-mutations. Co-occurring *KRAS* mutations and *TP53* inactivation are associated with favorable responses to ICI monotherapy. Conversely, *KRAS* mutation co-occurred with liver kinase B1 (LKB1)/STK11 or Kelch-like ECH-associated protein 1 (KEAP1)-nuclear factor erythroid 2-related factor 2 (NRF2) pathway function loss will lead to immuno-suppressed phenotypes, thus resulting in resistantance to PD-1/PD-L1 inhibitors [179–181].

Potential mechanisms of low ICI efficacy in *EGFR* mutant NSCLC

EGFR mutations promote an immunosuppressive TME. First, *EGFR* mutant cancer downregulates CXC-chemokine ligand 10 (CXCL10) via phosphatidylinositol-3 kinase (PI3K)–AKT pathways, resulting in low infiltration of $CD8^+$ T cells. Second, EGFR signaling upregulates the CC-chemokine ligand 22 (CCL22) expression through the JNK–JUN activation, thus recruiting the T-regulatory cells (Tregs). Treg cells can secrete IL-10, IL-35, and TGF-β that reduce antitumor immune responses mediated by natural killer (NK) cells and $CD8^+$ T cells. Third, the activation of EGFR downstream pathways produces pro-tumoral cytokines and EGFR ligands that promote the macrophages 2 (M2) polarization of tumor-associated macrophages (TAMs), which are associated with suppressed cytotoxic T cell function. Fourth, CD39/CD73 are overexpressed in *EGFR*-mutated NSCLCs, which triggers the de-phosphorylation of adenosine triphosphate (ATP) to adenosine diphosphate (ADP), and subsequently results in adenosine monophosphate (AMP) and adenosine (ADO). ADO functions as an immunosuppressive mediator in the TME. The CD73-ADO axis promotes the Treg efficacy and myeloid-derived suppressor cell (MDSC). ADO combined with A2A adenosine receptor (A2AR) also inhibits T cell signal transduction by enhanced immunosuppressive activity of Treg cells and MDSCs [182–184].

The immunosuppressive TME induced by *EGFR* mutation enables tumors to escape from antitumor immune responses. Thus, directly targeting EGFR or upregulating the tumor antigen presentation, inactivating immunosuppressive cells, and downregulating immunosuppressive molecules may lead to antitumor immunity in *EGFR* mutant tumors.

Strategies for ICI treatment in NSCLC with driver mutations

NSCLC with driver mutations generally showed limited ICI responses. Strategies for immunotherapy (IO) in NSCLC with driver mutations include the following.

IO + target therapy

A series of studies explored the combination of immunotherapy and target therapy [185–187]. However, nearly all clinical trials were discontinued due to severe adverse events and failed to increase the efficacy compared with the target monotherapy. Combination of durvalumab and gefitinib failed to increase PFS and had higher hepatic toxicity than either agent alone [188]. Pembrolizumab plus gefitinib was also reported to have liver toxicity and failed to increase ORR [189]. Pembrolizumab or nivolumab plus erlotinib seems tolerable though still does not improve the ORR compared with monotherapy [189,190]. TATTON and CAURAL trial explored the combination use of osimertinib plus durvalumab. Both studies showed high incidence of interstitial lung disease (ILD) [185]. Immunotherapy in combination with first-generation seems prone to cause hepatic toxicity while third-generation *EGFR*-TKI with higher incidence of ILD. The mechanisms to explain the synergistic toxicity include that *EGFR*-TKIs might enhance T cell-mediated killing of tumor cells by promoting the MHC-I presentation [192]. In that case, *EGFR*-TKIs might also have immunomodulatory effects. EGFR signaling also has an impact on the microenvironment, suppressing immune-mediated anti-tumor responses via cytokines such as IL-6, TGF-β1, and progranulin [193]. The abnormality of these cytokines may also result in adverse effect.

IO + chemotherapy ± angiogenesis therapy

The IMpower150 study included 124 patients with *EGFR* mutant NSCLC. In this *EGFR* mutation cohort, the median PFS (10.2 vs. 6.9 months) and response duration (DOR, 11.1 vs. 4.7 months) were significantly improved in the atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP) group versus the standard-of-care bevacizumab plus carboplatin plus paclitaxel in chemotherapy-naive patients. The difference was not significant when ABCP is compared with atezolizumab plus carboplatin plus paclitaxel group, indicating that the angiogenesis therapy is essential in the combination IO therapy in *EGFR*-mutant NSCLC [194]. ORIENT-31 (NCT03802240) compared sintilimab ± IBI305 plus chemotherapy (pemetrexed + cisplatin) for patients with *EGFR* mutant locally advanced or metastasis non-squamous NSCLC after the *EGFR*-TKI treatment failed. With a median follow-up time of 9.8 months, ORIENT-31 met its primary end-point of PFS with sintilimab + IBI305 + chemotherapy, achieving a median PFS of 6.9 months versus 4.3 months for chemotherapy alone (HR = 0.464, 95% CI 0.337–0.639) [195]. Two randomized

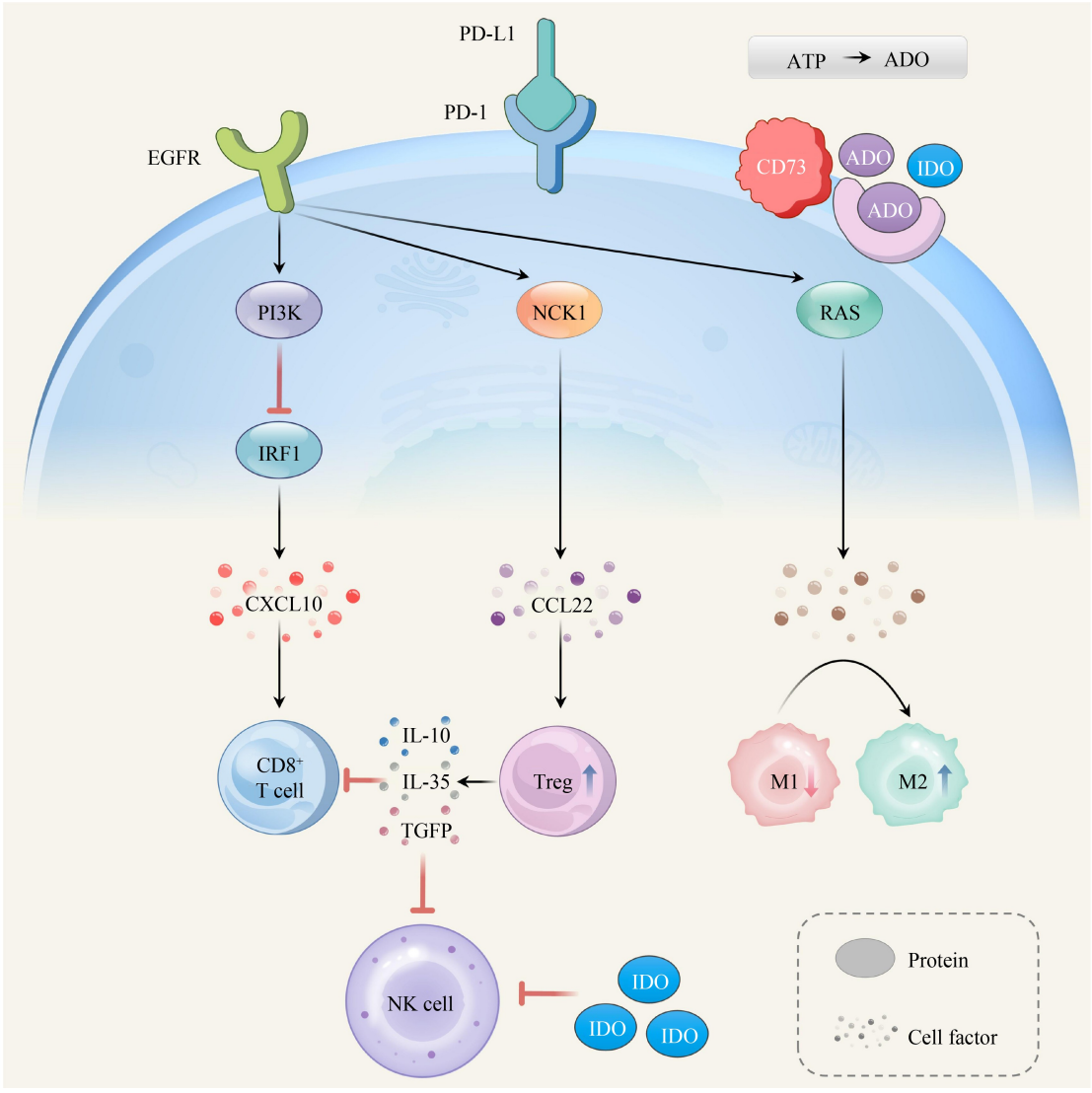

Fig. 2 Potential mechanisms of low ICI efficacy in EGFR mutant NSCLC. Abbreviations: CXCL10, CXC-chemokine ligand 10; PI3K, phosphatidylinositol-3 kinase; CCL22, CC-chemokine ligand 22; Treg, T-regulatory cell; NK cell, natural killer cell; M1, macrophages 2; M2, macrophages 2; ATP, adenosine triphosphate; ADO, adenosine.

phase 3 trails, Keynote-789 (NCT03515837) and CT25 (NCT03924050), were designed to assess the beneficial role of the addition of ICIs to chemotherapy in the *EGFR*-TKI-resistant setting. CheckMate722 (NCT02864251) evaluated the efficacy of nivolumab + chemotherapy and nivolumab + ipilimumab compared with chemotherapy in patients with *EGFR* mutation that progressed on the first-line *EGFR*-TKI therapy. These results have not been published.

Several early-stage studies showed promising antitumor activity of IO + chemotherapy in patients with NSCLC who progressed on *EGFR*-TKIs. A phase II study evaluated the efficacy of pembrolizumab combined with carboplatin and pemetrexed in recurrent *EGFR/ALK* + NSCLC, and results showed that IO + chemotherapy led to a response rate of 42% and a median OS of 22.2 months in *EGFR* mutant NSCLC; however, the combination had limited activity in seven patients with recurrent *ALK*-positive disease [196]. Similarly, in a phase II study that evaluated the efficacy of tislelizumab plus chemotherapy in patients with *EGFR*-mutated advanced non-squamous NSCLC who failed to *EGFR*-TKI therapies, the initial analysis showed that ORR and DCR were 59.4% (95%CI 40.6%–76.3%) and 90.6% (95%CI 75.0%–98.0%), respectively [197].

IO + angiogenesis therapy

In the phase I study that evaluated the efficacy and safety of TQB2450 (a PD-L1 inhibitor) combined with anlotinib in patients with advanced NSCLC after *EGFR*-TKI resistance, the results showed that the combination

therapy was well tolerated with potential clinical antitumor activity, with a DCR rate of 77.8% and a median PFS of 9.1 months. Combined apatinib and camrelizumab in a phase II cohort study also exhibited encouraging antitumor activity and acceptable toxicity in *EGFR* mutant NSCLC after the TKI resistance, demonstrating an ORR of 18.6% and a median PFS of 2.8 months [198].

Emerging immunotherapies

NSCLC with driver mutations generally respond poorly to PD-1/PD-L1 inhibitors. The immunosuppressive TME mainly composed by Treg, MDSC, and M2-TAM is a limitation for the T cell-induced antitumor activity. To change the immunosuppressive TME, increasing evidences sustain the role of new additional inhibitory immune checkpoint molecules, such as T cell immunoglobulin and mucin-containing molecule 3 (TIM-3), lymphocyte activation gene-3 (LAG-3), and T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) to overcome the resistance to traditional ICIs [199–201]. The CD39/CD73/adenosine signaling-mediated dysregulation of energy metabolism in TME is suggested as a potential mechanism involved in the immune escape process. Hence, there is a strong rationale of the combination therapy of ICIs with adenosine signaling inhibitors to overcome immunotherapy resistance in EGFR-mutated NSCLC [202,203]. Several clinical trials evaluating the efficacy of several A2AR inhibitors and anti-CD73 monoclonal antibodies for EGFR mutant NSCLC are in progress. Other novel immunotherapy approaches such as the T cell transfer therapy, TIL therapy, and chimeric antigen receptor-modified T (CAR-T) cell therapy, also have potency to control tumor growth in the presence of an appropriate immune context in NSCLC with driver mutations (Table 2) [204,205].

New target therapies for NSCLC with driver mutations

Multiple novel oncogenic drivers have been identified in NSCLC. SHP2 (Src homology 2-containing phosphotyrosine phosphatase 2) plays an important role in regulating multiple cascade signaling pathways, including the Ras-Raf-MEK-ERK, PI3K-AKT, JAK-STAT, and PD-1/PD-L1 pathways. SHP2 inhibitors might be a promising drug that could synergistically sensitize the antitumor activity of target drugs in the oncogenic-

Table 2 Emerging treatment for NSCLC with driver mutations

Target	Genomic alternation	Treatment	NCT number
EGFR	Mutation	Bispecific antibody targeting EGFR and MET (amivantamab, etc.)	NCT02609776
		Fourth generation *EGFR*-TKIs (BLU-945, etc.)	NCT04862780
		CD73-adenosine axis blocked + PD-(L)1	NCT05431270
			NCT03454451
			NCT05221840
		CD73-adenosine axis blocked + *EGFR*-TKIs	NCT03381274
		EGFR CAR-T cells	NCT03198052
ALK	Fusion	Double mutant active fourth generation *ALK*-TKIs (TPX-0131 and NVL-655)	NCT04849273
			NCT05384626
KRAS	Mutation	KRAS inhibitor sotorasib or adagrasib combination therapy (PD-(L)1/EGFR antibody, etc.)	NCT03785249
			NCT04185883
		KRAS inhibitor + RAF/MEK inhibitor (VS-6766)	NCT05375994
RET	Fusion	RET/SRC inhibitor (TPX-0046)	NCT04161391
ROS-1, NTRK	Fusion	Target solvent-front mutations (repotrectinib)	NCT04772235
MET	Mutation and amplification	MET ADC (ABBV-399)	NCT03539536
			NCT02099058
		Bispecific antibody targeting EGFR and MET (amivantamab, etc.)	NCT02609776
HER2	Mutation and overexpression	HER2 ADC (TDM1, DS-8201) + PD-(L)1 + chemotherapy	NCT04686305
			NCT04042701
HER3	Overexpression	HER3 ADC (patritumab deruxtecan) + *EGFR*-TKIs	NCT04676477
SHP-2	Overexpression	SHP-2 inhibitor + PD-(L)1/KRAS inhibitor	NCT05375084
			NCT05480865
NRG1	Fusion	HER2×HER3 bispecific antibody (zenocutuzumab)	NCT02912949

addicted NSCLC [206]. To date, several small-molecule SHP2 inhibitors have advanced into clinical trials for mono- or combined therapy of cancers [207]. Fusions involving the neuregulin-1 (*NRG1*) gene result in ErbB pathway activation and therefore can be a candidate for targeted treatment [208]. Pan-HER tyrosine kinase inhibitor afatinib has reported the activity in NRG1 fusion NSCLC [208,209]. Another potential strategy is the use of HER3 inhibitors (GSK2849330) that showed the antitumor activity for *CD74-NRG1* gene fusion tumor in a phase I trial [210].

Receptor tyrosine-protein kinase ERBB3 (HER3) is wildly expressed in NSCLC. *HER3* overexpression is associated with metastatic progression and disease relapse in NSCLC. Increased *HER3* expression has been observed in EGFR-resistant cell lines, indicating that *HER3* overexpression contributed to drug resistance. HER3 antibody–drug conjugate (ADC) has shown clinical activity in *EGFR* TKI-resistant cancers, regardless of resistance mechanisms [211]. However, many new target agonists or inhibitors and ADCs with new antibodies or payloads are in clinical or preclinical studies that will considerably help the oncogene-driven personalized treatment of NSCLC (Table 2).

Conclusions and perspectives

First, the discovery of oncogenic driver alterations and target therapy have brought significant clinical benefits and established an individualized treatment approach. The management of advanced NSCLC has shifted from a histology based on a biomarker-driven process.

Second, the treatment landscape of oncogenic-addicted NSCLC has become complex. On the one hand, more individualized treatment based on fine stratification has become the focus of research nowadays. The choice of optimal treatment strategy should consider gene subtype, concomitant mutation, dynamic gene alternation, and metastasis site. On the other hand, understanding primary and acquired resistance to targeted therapy provides an insight into the molecular evolution of tumor development. The recognition of resistant mechanisms is the basis to design new drugs or combinatorial therapeutic strategies.

Lastly, combination strategies require integration with immunotherapy, and the immunosuppressive microenvironment should be reversed to improve the sensitivity of ICIs by the drug combination. We should also be aware of the possible risk of combined toxicity and thereby explore the optimal timing and combined regimen of immunotherapy. Meanwhile, the interaction between driver mutations and immune-microenvironment is essential to uncover after drug resistance and to establish robust predictive biomarker for the NSCLC with driver mutations, in order to identify specific oncogenic driving patients with NSCLC who can benefit from immunotherapy.

Acknowledgements

This work was supported by Beijing Natural Science Foundation (No. 7222144), National Key Research and Development Project (No. 2019YFC1315700), CAMS Key Laboratory of Translational Research on Lung Cancer (No. 2018PT31035).

Compliance with ethics guidelines

Jia Zhong, Hua Bai, Zhijie Wang, Jianchun Duan, Wei Zhuang, Di Wang, Rui Wan, Jiachen Xu, Kailun Fei, Zixiao Ma, Xue Zhang, and Jie Wang declare no potential conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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