Oncologie

Tech Science Press

DOI: 10.32604/oncologie.2022.027545

check for updates

REVIEW

Advances in Targeted Therapy Against Driver Mutations and Epigenetic Alterations in Non-Small Cell Lung Cancer

Jiajian Shi[1], Yuchen Chen[1,*], Chentai Peng[1], Linwu Kuang[2], Zitong Zhang[1], Yangkai Li[2,*] and Kun Huang[1]

[1]Tongji School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China

[2]Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China

*Corresponding Authors: Yuchen Chen. Email: chenyc93@hust.edu.cn; Yangkai Li. Email: doclyk@163.com

Received: 03 November 2022 Accepted: 13 December 2022

ABSTRACT

The incidence and mortality of lung cancer rank top three of all cancers worldwide. Accounting for 85% of the total number of lung cancer, non-small cell lung cancer (NSCLC) is an important factor endangering human health. Recently, targeted therapies against driver mutations and epigenetic alterations have made encouraging advances that benefit NSCLC patients. Druggable driver mutations, which mainly occur in *EGFR*, *KRAS*, *MET*, *HER2*, *ALK*, *ROS1*, *RET* and *BRAF*, have been identified in more than a quarter of NSCLC patients. A series of highly selective mutant targeting inhibitors, such as EGFR tyrosine kinase inhibitors and KRAS inhibitors, have been well studied and applied in clinical treatments, which greatly promote the overall survival of NSCLC patients. However, drug resistance has become a major challenge for targeted treatment, and a variety of methods to overcome drug resistance are constantly being developed, including inhibitors against new mutants, combination therapy with other pathway inhibitors, etc. In addition, epigenetics-based therapy is emerging. Epigenetic regulators such as histone deacetylases and non-coding RNA play a crucial role in the development of cancer and drug resistance by affecting multiple signaling pathways. Epigenetics-based therapeutic strategies combined with targeted drugs show great clinical potential. Many agents targeting epigenetic changes are being investigated in preclinical studies, with some already under clinical trials. This article focuses on driver mutations and epigenetic alterations in association with relevant epidemiological data. We introduce the current status of targeted inhibitors and known drug resistance, review advances in major targeted therapies with recent data from preclinical and clinical trials, and discuss the possibility of combination therapy against driver mutations and epigenetic alterations in overcoming drug resistance.

KEYWORDS

NSCLC; targeted therapy; driver mutation; epigenetics; resistance

1 Introduction

Lung cancer is an important threat to human health. In China, in 2020, the number of new cases of lung cancer reached 0.82 million, and the number of lung cancer deaths reached 0.71 million; the incidence and mortality rate ranked first among all cancers, accounting for 17.9% and 23.8%, respectively [1]. In the United States, about 350 lung cancer deaths per day are projected to occur in 2022 [2]. As surveyed by the World

Health Organization, in 2020, approximately 2.21 million people worldwide were diagnosed with lung cancer (11.4% of 19.29 million new cancer cases), and about 1.8 million people died of lung cancer (18% of 9.96 million cancer deaths) [3] (Fig. 1). Regardless of gender, lung cancer ranks among the top three most common cancers and cancer death causes, while men seem to suffer from a higher risk of lung cancer deaths since lung cancer is the most common cause of cancer deaths among men in 93 of 183 countries [2,4].

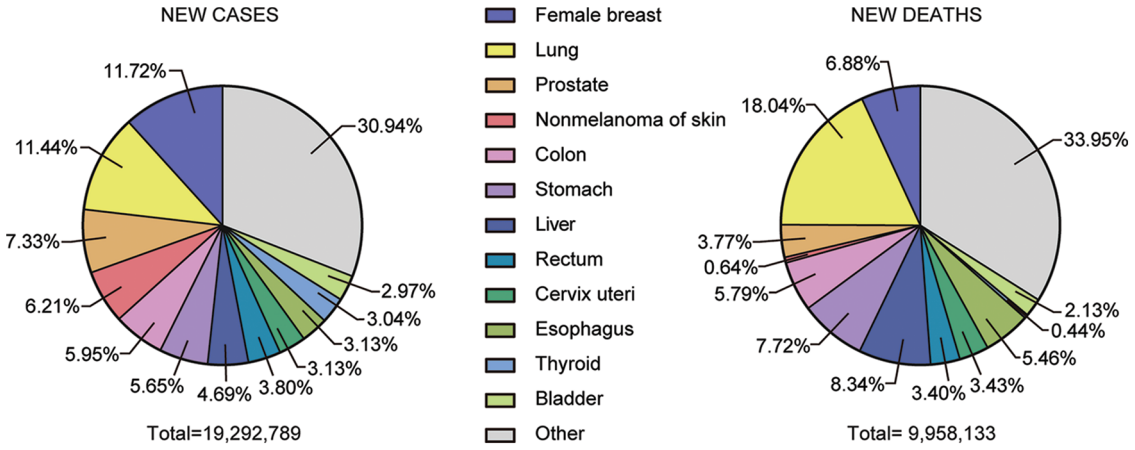

Figure 1: Global data of new cases and deaths for 12 common cancers in 2020. Top 12 in new cases list are included. Source: GLOBOCAN 2020

Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer; accumulating studies have revealed diverse driver mutations as key causes and promising therapeutic targets for NSCLC. Over the past decades, many targeted drugs against driver mutations have been clinically applied and effectively prolonged progression-free survival (PFS), including inhibitors against EGFR, ALK, MET, BRAF, ROS1, HER2, KRAS, RET, etc. [5] (Table 1). In the United States, the incidence-based mortality of NSCLC patients continued to decline from 2006 to 2016, especially between 2013 and 2016 (during which targeted drugs were widely used), while the 2-year relative survival rate continued to rise from 34% in 2010 to 42% in 2015. Among men, the mortality rate decreased by 6.3% annually from 2013 to 2016; among women, it fell by 5.9% annually from 2014 to 2016 [6,7]. Ten years ago, the average survival time of NSCLC patients with EGFR-activating mutations was less than two years [8]; nowadays, the median PFS of these patients has been significantly improved to over three years with EGFR-TKIs (epidermal growth factor receptor tyrosine kinase inhibitors) [9]. However, these targeted drugs only benefit patients with specific mutations, and drug resistance occurs almost inevitably; in this regard, efforts to develop new targeted drugs and combination strategies never stop.

Recent studies show that apart from driver mutations, epigenetic alterations also play a crucial role in the development of lung cancer. Aberrant DNA methylation, histone modification, nucleosome remodeling and changes in microRNA (miRNA) levels *in vivo* are closely related to the occurrence, proliferation and metastasis of tumour cells [7,10]. A variety of epigenetic drugs, including DNMT (DNA methylation transferase) inhibitors and HDAC (histone deacetylase) inhibitors, have shown good anti-cancer effects in preclinical studies and entered clinical trials [11,12]; preclinical data also indicates the therapeutic potentials of some non-coding RNAs [13]. Moreover, epigenetic drugs combined with classic targeted drugs show great potential in overcoming drug resistance [14]. In this article, we summarize recent advances in targeted drugs against driver mutations and epigenetic alterations in NSCLC treatment, focusing on noteworthy progress in preclinical and clinical studies of new drugs and exploration of combination therapy.

2 Common Druggable Driver Mutations in NSCLC

More than a quarter of NSCLC patients harbor druggable driver mutations. The frequency of driver mutations varies greatly among different populations. EGFR mutations occur in a much larger proportion in Asian (~46.5%) compared with Western NSCLC populations (~17.7%), while KRAS mutations show higher prevalence in Western (~26.0%) than in Asian NSCLC cases (~11.0%); no significant difference was observed regarding population distribution of mutated MET, RET, ROS1, etc. (Fig. 2A). EGFR mutation is one of the earliest oncogenic mutations studied. Seven targeted drugs against mutant EGFR have been approved, and the number of EGFR-targeting drugs in the clinical trial stage far exceeds that of the other mutations in NSCLC (Fig. 2B). Recent years have witnessed the rapid development of targeted drugs against other mutations, especially for the "undruggable" KRAS, with sotorasib being the first approved drug for the treatment of KRAS G12C mutant NSCLC in 2021 (Fig. 2B). Compared to cytotoxic chemotherapy, these targeted drugs have shown great advantages in improving PFS with reduced side effects. The response rate of targeted therapy for patients carrying EGFR, ALK, ROS1 and BRAF mutations ranges from 50% to 80%, and the overall survival (OS) is between 18 and 38.6 months [9,15]. Here, advances in targeted therapies against these oncogenic mutations are introduced (Fig. 2B; Table 1), with focus on the most frequent EGFR and KRAS mutations.

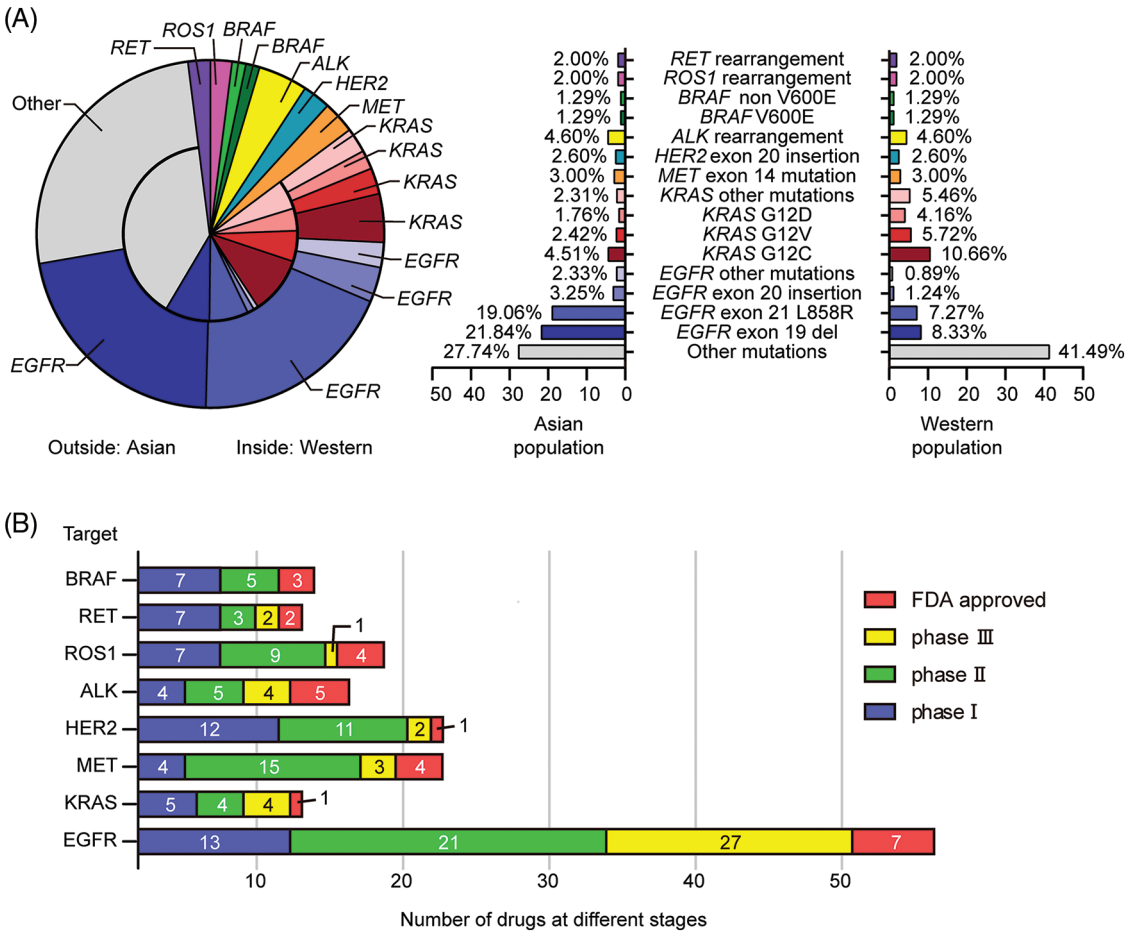

Figure 2: Frequency of common oncogenic driver molecular alterations and relevant targeted drug development in NSCLC. (A) Incidences of oncogenic driver mutations in NSCLC; data extracted from the studies by Midha et al. [16], Harrison et al. [17], Friedlaender et al. [18], Adderley et al. [19], Awad et al. [20], Pillai et al. [21], Gainor et al. [22], Lin et al. [23], Cardarella et al. [24]. (B) Summary of drugs targeting the indicated common driver mutations under different drug development stages as of October 2022; clinical trial data was derived from ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home), search terms include "NSCLC" and corresponding targets "EGFR", "KRAS", etc.

2.1 EGFR Mutations

EGFR-activating mutation occurs in 47% of Asian patients, 15% of European patients, 21% of African patients and has a higher mutation frequency in female patients [16]. Exon 19 deletion (EX19del) and exon 21 L858R mutation (L858R) are the main types of EGFR mutations, accounting for 47% and 41%, respectively. There are more than ten known rare mutations, including exon 19 insertion (EX19ins), exon 20 insertion (EX20ins), and point mutations S768I, L861Q, G719X, G709X [17,25].

So far, three generations of EGFR-TKIs have been approved for first-line treatment of NSCLC (Table 1), with favorable response rate (56%–83%) and progression-free survival (8.4–18.9 months) [26,27]. The first-generation EGFR-TKIs, such as gefitinib and erlotinib, are mainly used to treat EGFR EX19del and L858R mutant NSCLC by reversible interaction with tyrosine kinase [28]. Although the treatment showed a good positive clinical response (50%–80%), secondary drug resistance occurs after about one year, mostly caused by T790M mutation that was observed in ~60% of patients with acquired resistance [29–31]. The second-generation EGFR-TKIs are mainly irreversible ErbB family blockers, such as afatinib, dacomitinib and neratinib, which produce longer-lasting inhibitory effects than first-generation TKIs and more complete blockade of EGFR signaling pathway [32]. However, 40%–50% of patients treated with second-generation TKIs still develop drug resistance due to T790M mutation; and indiscriminate blockade of the EGFR signaling pathway may result in more severe side effects [33,34]. At present, represented by osimertinib, the third-generation EGFR-TKIs are in full bloom (Table 1) and mainly applied to treat NSCLC patients with T790M mutation-related secondary resistance [35]. These drugs selectively and irreversibly target EGFR L858R/EX19del/T790M mutations with about 200 times higher potency than targeting wild-type EGFR [36]. According to the AURA phase III clinical trial, the median PFS of osimertinib treatment was significantly higher than that of platinum plus pemetrexed therapy (10.1 *vs*. 4.4 months; HR, 0.30; 95% CI, 0.23–0.41; $p < 0.001$) in patients with T790M-positive NSCLC after first-generation EGFR-TKIs treatment [37]. When applied as first-line treatment, osimertinib compared with first-generation EGFR-TKIs significantly prolonged PFS (18.9 *vs*. 10.2 months; HR, 0.80; 95% CI, 0.37–0.57; $p < 0.001$) in patients with EGFR EX19del/L858R mutations [9,38]. Moreover, third-generation EGFR-TKIs also exhibited lower epithelial toxicity, with fewer adverse events of grade 3 or higher in osimertinib group *vs*. the second-generation EGFR-TKI group (40% *vs*. 48%) [39,40].

Currently, resistance mutations to third-generation drugs, bypass activations and some rare undruggable point mutations remain challenges for treating EGFR-mutant NSCLC; fourth-generation EGFR-TKIs and new therapeutic strategies are thus developed [41]. The mechanisms of resistance to third-generation EGFR-TKI treatment are heterogeneous. C797X, a point mutation at position 797 in exon 20 that is covalently linked to osimertinib, occurs in 22%–25% of T790M-positive patients treated with osimertinib, but is found in only 2% of patients treated with another third-generation EGFR-TKI rociletinib [42,43]. C797S is the main type of C797X mutation. Among osimertinib-treated patients with C797X mutations, the prevalence is 82% for C797S/T790M mutations in cis and 10% for C797S/T790M mutations in trans [44]. Interestingly, when C797S and T790M are mutated in trans but not in cis, lung cancer cells with ternary mutations (EGFR-activating mutation/T790M/C797S) retain sensitivity to first- and second-generation EGFR-TKIs [44,45]. In addition, cells with EGFR-activating mutation/C797S are sensitive to the first- and second-generation EGFR-TKIs [44]. Therefore, different generations of EGFR-TKIs can be combined to overcome resistance [41]. Meanwhile, allosteric drug designs for C797X mutation are ongoing [46]. An allosteric small-molecule inhibitor, JBJ-04-125-02 showed high inhibitory activity and low toxicity against EGFR L858R/T790M/C797S mutation [47,48]. BI-4020, a non-covalent triple mutant EGFR targeting inhibitor, effectively induced EGFR EX19del/T790M/C797S mutant tumour regression in a mouse xenograft model [49]. A growing number of fourth-generation EGFR-TKIs against C797X are in clinical trials (Table 1). In addition to the frequent C797X mutation, other causes of third-generation EGFR-TKI resistance include EGFR mutations like L718Q/V (4%), L792H (2%) and G796S

(1%), other alterations like MET amplification (20%) and HER2 amplification (10%), as well as aberrant activation of RAS-MAPK pathway, PI3K pathway, etc. [50,51]. Studies have shown that the combination of MET inhibitors (such as crizotinib) and osimertinib overcame drug resistance in osimertinib-resistant EGFR-mutant NSCLC cell lines with MET amplification, suggesting that simultaneous targeting MET and EGFR may be an effective strategy [51]. The combination of anti-VEGF (vascular endothelial growth factor) therapy and EGFR-TKIs is also proposed as a promising strategy, yet further assessment is warranted because the combination of different anti-VEGF strategies and different generations of EGFR-TKIs had different outcomes. The PFS of erlotinib plus ramucirumab (a VEGFR2 inhibitor) group was superior to that of erlotinib plus placebo group in a phase III trial (median PFS: 19.4 *vs*. 12.4 months; HR, 0.59; $p < 0.001$) [52]. In 2020, ramutuzumab combined with erlotinib was approved for first-line treatment of NSCLC [25]. However, for NSCLC patients with acquired T790M mutations after failure on previous EGFR-TKI therapy, bevacizumab (a VEGF inhibitor) combined with osimertinib did not improve median PFS compared to osimertinib alone (15.4 *vs*. 12.3 months, stratified log-rank $P = 0.83$; HR, 0.96; 95% CI, 0.68–1.37), with a similar ORR (objective response rate) of 55% in both groups [25,53].

Efforts have also been made to develop EGFR-TKIs targeting rare EGFR mutations, such as EX20ins mutation which accounts for 4%–9% of EGFR mutations [54]. A phase II trial of mobocertinib, a TKI targeting both EGFR EX20ins and HER2 EX20ins, showed a confirmed ORR of 43% and a median PFS of 7.3 months [54]. Poziotinib as an irreversible pan-HER inhibitor inhibited the growth of EGFR EX20ins mutant cells with approximately ~100 times higher potency than osimertinib; however, it showed obvious toxic side effects in a phase II trial during which 60% of patients experienced grade 3 toxicity and 45% required dose reduction [55]. The preliminary efficacy of another inhibitor CLN-081 is being evaluated in a multi-center phase I–II study among NSCLC cases harboring EGFR EX20ins (NCT04036682). Moreover, amivantamab have been approved in 2021 for the treatment of locally advanced or metastatic NSCLC adult patients with EGFR EX20ins mutation [56] (Table 1) .

2.2 KRAS Mutations

KRAS (Kirsten rat sarcoma oncogene homologue) mutation as another frequent driver mutation occurs in 20%–25% of NSCLC patients, with a higher incidence in Western populations than in Asian populations (26% *vs*. 11%) [18,19] (Fig. 2A). KRAS mutation frequency is closely related to smoking, ranging from 25% to 35% in smokers and 5% in non-smokers [57]. Of all KRAS mutations, 83% were located at codon 12 and 14% at codon 13; G12C is the most common alteration at codon 12 (41%), followed by G12V (22%) and G12D (16%) [58–60].

KRAS is a membrane-regulatory small guanine nucleoside bound protein (G protein), which has a smooth surface and lacks binding pockets, making it difficult to target. Belonging to the guanosine triphosphatase (GTPase) family, KRAS exists in two different states (GDP binding-inactivation state, GTP binding-activation state). The high concentration of GTP *in vivo* and the high affinity of GTP to KRAS are also difficulties in developing competitive inhibitors for KRAS [61,62]. Therefore, indirect strategies are adopted, with focus on reducing KRAS expression, blocking the membrane position of KRAS, interfering with the signal transduction of KRAS; however, none of these efforts has achieved clinical application [63]. For example, salirasib, as a farnesyltransferase inhibitor, inhibited the modification of KRAS protein to hinder its binding to the membrane but showed insufficient therapeutic activity in phase II clinical trials [64].

The emergence of small molecules directly targeting KRAS mutants changed this situation. KRAS G12C mutant has a binding pocket near the 12th cysteine residue when binding to GDP in an inactivation state, which can be utilized for drug design to stabilize this inactivation state [65,66]. This notion led to the development of sotorasib (AMG-510) [67]. NSCLC patients treated with sotorasib showed ORR of 37.1% (95% CI, 28.6–46.2), DCR (disease control rate) of 80.6% (95% CI, 72.6–87.2),

and median PFS of 6.8 months (95% CI, 5.1–8.2); moreover, the drug has a tolerable safety profile: 19.8% of patients experienced grade 3 adverse events, and 0.8% experienced grade 4 adverse events [68]. In 2021, sotorasib was approved for the treatment of NSCLC patients with KRAS G12C mutation who have undergone at least one systemic treatment [69]. Patients treated with another oral KRAS G12C inhibitor adagrasib (MRTX849) showed ORR of 42.9%, DCR of 79.5%, median DOR (duration of response) of 8.5 months and median PFS of 6.5 months in phase I/II trial (NCT03785249) [70,71]. Recently, PROTACs (proteolytic targeting chimeras) comprising of ligands targeting proteins of interest, E3 ligase recruiting elements and linkers, show game-changing potential in treating cancers driven by mutant proteins without deep binding pockets via selectively mediating ubiquitin-proteasome degradation of target proteins [72]. LC-2, the first-in-class endogenous KRAS G12C degrader, combines adagrasib warhead and a E3 ligase ligand VHL to form a ternary complex with KRAS G12C and induce proteasome degradation [73]. Another example is KRAS G12C degrader YF135, which induces VHL-mediated KRAS G12C degradation and attenuates pERK signaling in a reversible manner [74]. In addition, KRAS G12D inhibitors achieved a breakthrough recently. The first non-covalent selective KRAS G12D inhibitor MRTX1133 showed a 1000-fold higher potency against KRAS mutants than wild-type KRAS *in vivo* [75]. It is also demonstrated that selective targeting of KRAS G12D can be achieved by cyclic peptides in the GTP-bound state, suggesting that peptides may be an option for targeting KRAS G12D beyond small chemical molecules [76]. Currently, inhibitors of KRAS G12V and other KRAS mutations have not been reported.

In clinical practice, poor clinical efficacy occurred in 50%–60% of patients receiving KRAS inhibitors. A possible reason is that some KRAS mutant cells have low KRAS dependency, due to the activation of other pathways, such as AKT and mTORC1 pathways, that lead to intrinsic resistance; while the investigation is warranted to further interpret the mechanism [77]. Acquired resistance to KRAS inhibitors also occurs, possibly due to abnormal compensatory activation of bypass pathways [78]. The reactivation of the adaptive KRAS feedback pathway is mediated by multiple RTKs (receptor tyrosine kinases) after treatment with sotorasib and another KRAS G12C inhibitor ARS-1620, while SHP2 inhibitor can serve as a blocker of multiple RTK signal transduction to suppress KRAS feedback pathway and be applied with KRAS G12C inhibitor in combination [79]. Activation of PI3K pathway is also responsible for acquired resistance to KRAS G12C inhibitor by promoting epithelial-mesenchymal transition (EMT) [80]. Additionally, treating KRAS G12C mutant cells with sotorasib and adagrasib, respectively resulted in totally 142 resistant clones, of which 124 (87%) harbored secondary KRAS mutations. In sotorasib resistant clones, KRAS G13D was the most common secondary mutation (23%), followed by R68M (21.2%) and A59S (21.2%). In adagrasib resistant clones, KRAS Q99L was the most common secondary mutation (52.8%), followed by Y96D (15.3%) and R68S (13.9%) [69,81]. Acquired resistance to KRAS G12C inhibitors and underlying mechanisms have received great attention nowadays and has been systematically reviewed [82–84].

To overcome drug resistance and maximize the potential of KRAS inhibitors, multiple combination strategies are designed. As mentioned above, the combination of KRAS inhibitors and SHP2 inhibitors showed stronger efficacy. Co-treatment of ARS-1620 and a SHP2 inhibitor SHP-099, compared to mono treatment, led to a more significant reduction of tumour volume *in vivo*; the combination of adagrasib and another SHP2 inhibitor RMC-4550 also showed higher anti-tumour activity in adagrasib-resistant cells [80,85]. The therapeutic effect of combining KRAS G12C inhibitors with SHP2 inhibitors is under evaluation in ongoing clinical trials (NCT04330664 and NCT04185883). Combined use of KRAS inhibitors and inhibitors targeting SOS1 (another common downstream effector in multiple RTK signaling pathways), such as BAY293, have shown synergistic anti-tumour effects [86]. The combination of KRAS inhibitors with tumour metabolism therapy or immune therapy is also of great concern [63].

2.3 MET Mutations

Mesenchymal-epithelial transition (MET) encoded by MET proto-oncogene is a tyrosine kinase receptor that binds to hepatocyte growth factor (HGF). MET gene amplification and exon 14 skipping (EX14ski) are main categories of MET mutations. Mutations in MET exon 14 are found in about 3% of NSCLC patients. Importantly, MET amplification is significantly increased in patients with EGFR-TKI resistance, accounting for 5%–20% of patients with first-generation TKI resistance and up to 25% of patients with third-generation TKI resistance [20,51]. MET mutations and amplification cause activation of a series of pathways, including RAS, ERK/MAPK, PI3K/AKT, Wnt/beta-catenin, JAK/STAT pathway, thereby promoting the proliferation and migration of cancer cells [87]. Currently, several MET inhibitors have been approved. Capmatinib, a highly selective oral MET inhibitor, was approved in 2020 for the treatment of metastatic NSCLC patients harboring MET EX14ski. Patients treated with capmatinib showed ORR of 41% (95% CI, 29–53) and DOR of 9.7 months (95% CI, 5.5–13.0) [88]. Another MET EX14ski inhibitor tepotinib received FDA approval in 2021, with ORR of 54.4%, median DOR of 18.5 months, median PFS of 12.1 months, and median OS of 20.4 months [89,90]. Other MET targeting drugs in clinical practice include savolitinib, which is applied for the treatment of metastatic NSCLC carrying MET EX14ski mutation who progresses after chemotherapy or cannot tolerate platinum-based chemotherapy; and amivantamab, a bispecific monoclonal antibody targeting EGFR and MET, is recently approved for treating NSCLC patients with EGFR EX20ins mutation, and its effect on those with MET amplification warrants further evaluation [91,92]. In addition, different types of MET inhibitors are under development worldwide, including chemicals, monoclonal antibodies, polyclonal antibodies, and ADCs (antibody-drug conjugates), among which glumetinib (NCT05507294), telisotuzumab vedotin (NCT03539536), Gb263T (NCT05332574), MCLA-129 (NCT04868877) have entered clinical trials (Table 1).

2.4 HER2 Mutations

Human epidermal growth factor receptor 2 (HER2; eRBB2) is a member of the tyrosine kinase receptor family, which also includes EGFR, HER1, HER3 and HER4 [93]. HER2 mutations occur in about 2%–4% of NSCLC cases, the most common of which is exon 20 insertion mutation; other point mutations have also been reported, including G776C, L755S, etc. HER2 amplification, as previously described as a mechanism of EGFR-TKI resistance, occurs in approximately 3% of patients who have not been treated with EGFR-TKIs, with a significant increase of incidence (approximately 10%) among patients with EGFR-TKI resistance [21,94,95]. In 2022, enhertu became the first drug approved by the FDA for NSCLC with HER2 mutation. According to data from its phase II trial (NCT03505710), the median DOR was 9.3 months (95% CI, 5.7–14.7), median PFS was 8.2 months (95% CI, 6.0–11.9), and median OS was 17.8 months (95% CI, 13.8–22.1) [96,97]. In addition, another HER2 inhibitor XMT-1522, an auristatin-derivative molecule conjugated to a novel compound dolaflexin, was well tolerated in a phase I trial and showed early signs of anti-tumour activity with DCR of 83%, partial remission of 17% and stable disease of 67% [15]. Current clinical trials about HER2-targeting ADCs are overall encouraging, bringing hope for the NSCLC patients with HER2 mutations and those with acquired HER2-related TKI resistance [98].

2.5 ALK Fusions/Rearrangements

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase receptor, and its rearrangement is reported in 3%–7% of global NSCLC cases [22]. Echinoderm microtubule-associated protein-like 4 (EML4) is ALK's most common fusion partner. In addition, there are at least 20 other fusion genes, such as TGF-ALK, KIF5B-ALK, and STRN-ALK [99]. Crizotinib was the first ALK-TKI drug approved as a second-line treatment for ALK-positive NSCLC in 2011 and approved by European Medicines Agency to be applied in first-line NSCLC treatment in 2015. The second-generation ALK-TKI drugs alectinib, ceritinib, brigatinib, and ensatinib achieve greater curative effects, yet acquired resistance and recurrence are

inevitable [100]. ALK mutation is a common cause for ALK-TKI resistance; frequently seen resistant mutations to crizotinib include L1196M, G1269A, C1156Y, G1202R, I1171T/N/S, S1206C/Y, E1210K, L1152P/R, V11180L, I1151T, G1128A, and F1174V [101]. The most known ALK G1202R mutation occurred in 21%, 29% and 43% of patients resistant to treatment of ceritinib, alectinib, and brigatinib [102]. A noteworthy fact is that patients carrying ALK-rearranged NSCLC with a prior history of ALK inhibitors have a high incidence (45%–70%) of central nervous system (CNS) metastases, indicating that brain metastasis is a common failed form of ALK targeted therapy [103]. Compared with second-generation inhibitors, third-generation ALK-TKI lorlatinib is designed to overcome known secondary resistance mutations in the ALK tyrosine kinase domain and to penetrate the CNS [104]. Preclinical studies demonstrate that lorlatinib is effective against most known single ALK-resistant mutations, including the highly refractory ALK G1202R [104,105]. Consistently, in a phase II study, lorlatinib showed beneficial activity in patients treated with first- or second-generation ALK inhibitors [106].

2.6 ROS1 Fusions/Rearrangements

The ROS1 gene belongs to the subfamilies of tyrosine-kinase insulin-receptor genes. ROS1 fusions produce defective genes that act as tumour drivers, leading to excessive proliferation of tumour cells. ROS1 fusions occur in about 1%–2% of NSCLC patients [23]. This change is most common in patients with NSCLC who have adenocarcinoma and are also negative for ALK, KRAS, and EGFR mutations. The kinase domains of ROS1 and ALK share about 70% homology. Crizotinib, which is approved for the ALK-positive NSCLC, is also an inhibitor of ROS1 and improves survival in NSCLC patients with ROS1 fusions [107]; in 2016, Crizotinib was approved for the treatment of ROS1-positive NSCLC. Ceritinib, a second-generation ALK inhibitor, also benefit patients with ROS1-positive NSCLC [108]. In 2019, entrectinib that targets ROS1 and ALK was approved for adults with metastatic ROS1-positive NSCLC [109]. Entrectinib can pass through the blood-brain barrier and is clinically proven effective against primary and metastatic brain diseases [110]. Moreover, preclinical studies suggested that the third-generation ALK-TKI lorlatinib can effectively inhibit ROS1 mutants [111]. Acquired resistance to ROS1-TKIs can be mediated by secondary mutations within the ROS1 kinase domain (E1935G, L1947R, L1951R, G1971E, L1982F, S1986F/Y, L2026M, G2032R, D2033N, C2060G, V2098I and L2155S and L2086F), or by activation of alternative signaling pathways (KRAS, NRAS, EGFR, HER2, MET, BRAF and MEK) [112]. ROS1 G2032R, the most common resistance substitution found in approximately one-third of the cases, is highly resistant to crizotinib as well as entrectinib and lorlatinib [113]. A new selective ROS1 inhibitor DS-6051b may overcome G2032R drug resistance as demonstrated in a preclinical study [114].

2.7 RET Fusions/Rearrangements

The RET gene is located on human chromosome 10 and encodes a single-pass transmembrane RTK. RET fusion, as an independent oncogenic driver, occurs in 1%–2% of NSCLC. Chromosomal fusions between the RET gene and its fusion partners lead to RET overexpression [115]. The most common gene fusion partners are KIF5B and CCDC6, accounting for about 70%–90% and 10%–25% of RET-positive cases, respectively. The chimeric fusion proteins can activate the ligand-independent activation of RET and promote the growth and survival of cancer cells [116]. Recently, the development of highly selective RET inhibitors, such as an oral small-molecule inhibitor selpercatinib (LOXO-292), has greatly improved the outcome of RET fusion-positive NSCLC patients [117,118]. Selpercatinib actively against not only RET fusions (KIF5B-RET, CCDC6-RET, etc.) but also some RET-activating point mutations (V804L, V804M, and M918T) [119]. The ORR of selpercatinib treatment was 64% (95% CI, 54–73) in RET fusion-positive NSCLC patients who previously received at least platinum-based chemotherapy and was 85% (95% CI, 70–94) in those untreated [120]. Moreover, another approved highly selective RET inhibitor pralsetinib (BLU-667) was able to overcome acquired resistance to EGFR-TKIs, including osimertinib, according to data from cell studies and the clinic [121].

2.8 BRAF Mutations

BRAF is a cytosolic serine/threonine kinase belonging to the RAF kinase family, serving as an important step of signal transmission from the cell surface to the nucleus after EGFR activation [122]. As a part of MAPK pathway, BRAF is involved in cell growth, proliferation, survival, and differentiation [123]. BRAF mutations occur in 1.5%–3.5% of NSCLC cases. BRAF-activating mutations are divided into BRAF V600E and BRAF non-V600E mutation; the former accounts for more than 50% of BRAF mutated NSCLC cases [124] and appears more common in female patients with lung adenocarcinoma, while the latter is more common in smokers [24,125]. The PFS of NSCLC patients with BRAF V600E mutation is shorter than those without [126]. Inhibitors have been developed to specifically bind to the ATP binding pocket of mutant BRAF, especially BRAF V600E, such as vemurafenib or dabrafenib [127]. Vemurafenib was the first MAPK inhibitor tested in BRAF mutant lung cancer. however, resistance eventually develops, mostly due to MAPK pathway reactivation [128]. Combined use of MEK inhibitors such as binimetinib can maximally block MAPK pathway and delay the emergence of drug resistance. In 2017, a combination therapy of dabrafenib and a MEK inhibitor trametinib received FDA approval for the treatment of metastatic NSCLC carrying BRAF V600E mutation [129]. In addition, cancer cells carrying BRAF V600E showed resistance to osimertinib, while a BRAF V600E inhibitor encorafetnib restored osimertinib sensitivity, suggesting its potential to promote the therapeutic effect of the third-generation EGFR-TKIs [130].

Table 1: Drugs targeting driver mutations in NSCLC

Target	Drug		Status	Preclinical study/clinical trial data
EGFR EX19del and L858R	First generation	Gefitinib (Iressa)	Approved by the FDA	1,217 patients with metastatic NSCLC showed a significant improvement in PFS (median PFS: 10.9 months [gefitinib] *vs*. 7.4 months [platinum-doublet chemotherapy]), ORR (67% *vs*. 41%) and DOR (median DOR: 9.6 *vs*. 5.5 months) [131].
EGFR EX19del and L858R		Erlotinib (Tarceva)	Approved by the FDA	Among 174 patients, erlotinib significantly improved PFS time compared with platinum-based chemotherapy in the patients with EGFR-activating mutations (9.7 *vs*. 5.2 months; HR, 0.37; 95% CI, 0.25–0.54; $p < 0.001$) [132]. (NCT00446225)
EGFR EX19del and L858R		Icotinib	Phase III	Among 296 patients, the PFS time of the icotinib group was significantly longer than that of the pemetrexed plus cisplatin chemotherapy group following the 1st-line treatment of *EGFR*-mutated NSCLC (11.2 *vs*. 7.9 months; HR, 0.61; 95% CI, 0.43–0.87; $p = 0.006$) [133]. (NCT01719536)
EGFR EX19del and L858R	Second generation	Afatinib	Approved by the FDA	Afatinib significantly improved outcomes in treatment-naive patients with *EGFR*-mutated NSCLC compared with gefitinib, with PFS (median 11.0 months [10.6–12.9] with afatinib *vs*. 10.9 months [9.1–11.5] with gefitinib) and time-to-treatment failure (median 13.7 months [11.9–15.0] with afatinib *vs*. 11.5 months [10.1–13.1] with gefitinib) [134]. (NCT01466660)
EGFR EX19del and L858R		Dacomitinib	Approved by the FDA	Among 452 patients, median PFS according to masked independent review was 14.7 months (95% CI, 11.1–16.6) in the dacomitinib group and 9.2 months (9.1–11.0) in the gefitinib group (HR, 0.59, 95% CI, 0.47–0.74; $p < 0.001$). Dacomitinib significantly improved PFS over gefitinib [135]. (NCT01774721)
EGFR EX19del and L858R		Neratinib	Phase II	Among 167 patients after neratinib treatment, 24% required discontinuation, 20% required dose reduction, and 11 patients (7%) discontinued the study due to adverse events [136]

(Continued)

Table 1 (continued)

Target	Drug		Status	Preclinical study/clinical trial data
EGFR EX19del and L858R and T790M	Third generation	Osimertinib	Approved by the FDA	Among 419 patients, Osimertinib group showed significantly longer median PFS time than that with platinum therapy plus pemetrexed (10.1 *vs*. 4.4 months; HR, 0.30; 95% CI, 0.23–0.41; $p < 0.001$) [37]. (NCT02151981) Among 566 patients, the median PFS time of untreated patients with *EGFR* mutation was significantly longer following osimertinib administration compared with that following gefitinib or erlotinib administration (18.9 *vs*. 10.2 months; HR, 0.80; 95% CI, 0.37–0.57; $p < 0.001$) [38]. (NCT02296125)
EGFR EX19del and L858R and T790M		Rociletinib	Phase II	After independent analysis ($n = 130$), the maturation confirmation response rate was updated to 45% and the median PFS time to 6.1 months [137]. (NCT02186301) The development of rociletinib was terminated due to efficacy and safety including diarrhea (2.7%), hyperglycemia (24.0%), corrected QT prolongation (6.7%) and cataracts [138]. (NCT02322281)
EGFR EX19del and L858R and T790M		Almonertinib	Phase III	Among 429 patients, the median PFS time was significantly longer with almonertinib than that with gefitinib, the median PFS was 19.3 months (17.8–20.8) and 9.9 months (8.3–12.6). The ORR was 73.8% (67.4%–79.6%) [almonertinib] and 72.1% (65.6%–78.0%) [gefitinib]. (NCT03849768)
EGFR EX19del and L858R and T790M		Lazertinib	Phase III	Among 127 patients, the ORR was 57.7% (45/78) (95% CI, 44.7-67.6), the median DOR of the 76 centrally-confirmed *EGFR* T790M patients (n = 76) was 13.8 months (95% CI; 9.6-NR) and the median PFS was 11.0 months (95% CI; 5.6-16.4) [139]. (NCT03046992) Phase III clinical trials of Lazertinib in NSCLC are ongoing. (NCT04248829, NCT04077463)
EGFR EX19del and L858R and T790M		Abivertinib	Phase III	Among 227 patients, the ORR was 52.2% (109/209) (95% CI, 45.1–59.1), the median PFS was 7.5 months (95% CI, 6.0–8.8) and the median DOR was 7.6 months (95% CI, 6.1–9.2) [140]. (NCT02330367) A randomized phase III trial comparing efficacy and safety of abivertinib to gefitinib in NSCLC was planned and registered. (NCT03856697)
EGFR EX19del and L858R and T790M		Alflutinib	Phase III	Among 220 patients, the ORR was 74.1% (95% CI, 67.8–79.7) (163/220), the median PFS was 9.6 months (95% CI, 8.2–9.7) [141]. (NCT03452592) A phase III trial comparing alflutinib with gefitinib in treatment of EGFR positive NSCLC patients is on-going. (NCT03787992)
EGFR EX19del and L858R and T790M and C797S	Potential fourth generation	BLU-945	Phase I–II	A phase I-II, open-label, first-in-human study is designed to evaluate the safety, tolerability, PKs, PDs, and anticancer activity of BLU-945, as monotherapy or in combination with osimertinib. (NCT04862780)
EGFR EX19del and L858R and T790M and C797S		BLU-701	Phase I–II	A phase I-II, open-label, first-in-human study is designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumour activity of BLU-701 as monotherapy or in combination with either osimertinib or platinum-based chemotherapy in patients with EGFR-activating NSCLC. (NCT05153408)

(Continued)

Table 1 (continued)

Target	Drug	Status	Preclinical study/clinical trial data
EGFR EX19del and L858R and T790M and C797S	JIN-A02	Phase I–II	A phase I–II, open-labeled, multicenter clinical study is designed to evaluate the safety, tolerability, PKs, and preliminary efficacy of JIN-A02, the 4th generation of orally administered EGFR-TKI, in patients with *EGFR* mutation advanced NSCLC after standard anti-tumour treatment including the currently approved EGFR-TKIs and platinum-based chemotherapy up to once. (NCT05394831)
EGFR EX19del and L858R and T790M and C797S	BBT-176	Phase I–II	The first-in-human study of BBT-176 is to investigate the safety and tolerability of BBT-176 and to evaluate the anti-tumour activity of BBT-176. (NCT04820023)
EGFR EX19del and L858R and T790M and C797S	U3-1402	Phase I	A phase I study is designed to evaluate safety and anti-tumour activity of U3-1402 in two parts: dose escalation and dose expansion. (NCT03260491)
EGFR EX20ins	Mobocertinib	Approved by the FDA	Among 210 patients, confirmed ORR was 28%, including 1 CR; DCR was 78% (95% CI, 69–85); median DOR was 17.5 months. Mobocertinib demonstrated clinically meaningful benefit for patients with *EGFR* EX20ins NSCLC with a manageable safety profile [142]. (NCT02716116) A phase III clinical trial of mobocertinib is ongoing to compare the effectiveness of TAK-788 as first-line treatment with that of platinum-based chemotherapy in NSCLC. (NCT04129502)
EGFR EX20ins	Rybrevant (Amivantamab)	Approved by the FDA	The purpose of this study is to assess the feasibility of subcutaneous administration of amivantamab based on safety and pharmacokinetics and determine a dose, dose regimen and formulation for amivantamab subcutaneous delivery. (NCT04606381) More combination therapies in NSCLC are ongoing. (NCT04487080; NCT04538664; NCT04077463)
EGFR EX20ins	Poziotinib	Phase II	Among 88 patients, the ORR in the as-treated population was 14.8% (95% CI 8.9–22.6), and the DCR was 68.7% (95% CI 59.4–77.0) with a median DOR of 7.4 months, 65% patients had tumour size reductions and the median PFS was 4.2 months [143]. (NCT03318939)
EGFR EX20ins	CLN-081	Phase I–II	A phase I-II, open label, multi-center study of CLN-081 in patients with NSCLC harboring an *EGFR* EX20ins mutation, is designed to determine the MTD and recommended phase II dose, as well as to evaluate preliminary efficacy. (NCT04036682)
KRAS G12C	Sotorasib (AMG-510)	Approved by the FDA	Among 126 patients, the median DOR was 11.1 months (95% CI, 6.9-could not be evaluated), disease control occurred in 100 patients (80.6%; 95% CI, 72.6–87.2), the median PFS was 6.8 months (95% CI, 5.1–8.2), and the median OS was 12.5 months (95% CI, 10.0 to could not be evaluated) [68]. (NCT03600883) Other clinical trials in NSCLC: NCT05118854; NCT05054725; NCT05400577; NCT05311709

(Continued)

Table 1 (continued)

Target	Drug	Status	Preclinical study/clinical trial data
KRAS G12C	Adagrasib (MRTX849)	Phase III	Among 116 patients, the ORR was 42.9% (48/112), the DCR was 79.5% (89/112), the median DOR was 8.5 months (95% CI 6.2–13.8), the median PFS was 6.5 months (95% CI 4.7–8.4), the median OS was 12.6 months (95% CI 9.2-NE) [70]. (NCT03785249) A phase III study will evaluate the efficacy of the investigational agent adagrasib (MRTX849) *vs*. docetaxel in patients who have been previously treated for metastatic NSCLC with a *KRAS* G12C mutation. (NCT04685135)
KRAS G12C	JDQ443	Phase III	A phase III open label study is designed to compare JDQ443 as monotherapy to docetaxel in participants with advanced non-small cell lung cancer (NSCLC) harboring a *KRAS* G12C mutation who have been previously treated with a platinum-based chemotherapy and immune checkpoint inhibitor therapy either in sequence or in combination. (NCT05132075)
KRAS G12C	JAB-21822	Phase I–II	Among 53 patients, the ORR and DCR were 70% (7/10) and 100% (10/10), respectively, including 5 non-confirmed PR [144]. (NCT05009329)
KRAS G12C	GFH925	Phase I–II	Phase I: To evaluate the safety and tolerability of GFH925 in subjects with KRAS G12C mutant advanced solid tumours and estimate the MTD and/or a recommended phase II dose. Phase II: To evaluate the efficacy of GFH925 in subjects with KRAS G12C mutant advanced non-small cell lung cancer (NSCLC). 128 patients demonstrated the preliminary efficacy signal of GFH925 in previously treated advanced NSCLC and CRC [145]. (NCT05005234)
KRAS G12C	D-1553	Phase I–II	A phase I–II study (n = 144) is designed to evaluate the safety, tolerability, pharmacokinetics and efficacy of D-1553 combination therapy in subjects with *KRAS* G12C-mutated locally advanced or metastatic non-small cell lung cancer. (NCT05492045)
MET EX14ski	Savolitinib	Approved by the FDA	Among 76 patients, the ORR was 47.5% (95% CI, 34.6–60.7), DCR 93.4% (95% CI, 84.1–98.2) and the median PFS was 6.8 months (95% CI, 4.2–13.8) among all treated patients [145]. (NCT02897479)
MET EX14ski	Capmatinib	Approved by the FDA	Among 69 previously treated *MET* EX14ski patients receiving capmatinib in the second- or third-line setting, the an ORR was 41% (95% CI, 29–53) and median DOR was 9.7 months (95% CI, 5.6-13.0) [146]. (NCT02414139)
MET EX14ski	Tepotinib	Approved by the FDA	79 Asian patients were assessed for efficacy (38% female, 42% smoking history, 34% treatment-naïve [1L] and 82% adenocarcinoma), ORR was 54.4% (42.8, 65.7), median DOR was 18.5 months (8.3, ne), median PFS was 12.1 months (6.9, ne) and median OS was 20.4 months (19.1, ne) [89]. (NCT02864992)

(Continued)

Table 1 (continued)

Target	Drug	Status	Preclinical study/clinical trial data
MET EX14ski	Crizotinib	Approved by the FDA	Crizotinib, a multi-kinase inhibitor approved by FDA for *ALK* or *ROS1* rearranged advanced NSCLC, also has activity against MET kinase. Among 65 patients, the ORR was 32% (95% CI, 21–45) and the median DOR was 9.1 months (95% CI, 6.4–12.7) [146]. (NCT00585195)
MET EX14ski	Amivantamab	Phase II	43 patients showed amivantamab demonstrates anti-tumour activity in primary *MET* EX14ski NSCLC including after prior MET inhibitor treatment. Enrollment is ongoing in NSCLC and updated data will be shown [147]. (NCT02609776)
MET EX14ski	Glumetinib	Phase II	Among 18 patients, only one patient among 6 evaluable patients at 400 mg cohort reported one DLT of grade 3 vomiting. Treatment-related adverse events mostly were grade 1 or 2 nausea, vomiting, elevated alkaline phosphatase, elevated conjugated bilirubin, edema, headache, asthenia and decreased appetite [147]. (NCT03466268) A phase Ib/II, pen-label, study to valuate the efficacy and safety of glumetinib (SCC244) is ongoing. (NCT04270591)
MET over-expressing	Telisotuzumab vedotin	Phase III	Among 43 patients, the ORR was 36.5% in the EGFR WT cohort (52.2% in c-Met high group and 24.1% in c-Met intermediate group) [148]. A phase III open-label, randomized trial is to determine if telisotuzumab vedotin works better than docetaxel and to assess how safe telisotuzumab vedotin is in adult participants with NSCLC who have previously been treated. (NCT04928846)
MET over-expressing	GB263T	Phase I–II	A phase I–II study of GB263T in participants with advanced NSCLC and other solid tumour will consist of a dose-escalation and expansion stage to determine recommended phaseII dose (Phase I), and an extension stage (Phase II) where participants will be enrolled into indication-specific cohorts. (NCT05332574)
HER mutation	Enhertu	Approved by the FDA	Among 91 patients, the median DOR was 9.3 months (95% CI, 5.7–14.7), median PFS was 8.2 months (95% CI, 6.0–11.9), and median OS was 17.8 months (95% CI, 13.8–22.1) [96]. (NCT03505710)
HER mutation	Neratinib	Phase II	A phase II, open-label study is designed to evaluate neratinib monotherapy and neratinib plus temsirolimus combination therapy in patients with NSCLC who have documented somatic *HER2* mutations. (NCT01827267)
HER mutation	XMT-1522	Phase I	Among 19 patients, there have been no DLTs nor serious adverse events attributed to study drug, the DCR was 5/6 (83%) for patients dosed at 16 mg/m^2 or 21.3 mg/m^2 with 1 PR and 4 SD [149]. (NCT02952729)
ALK fusion	Crizotinib	Approved by the FDA	Among 343 patients, the PFS was significantly longer with crizotinib than with chemotherapy (median, 10.9 *vs.* 7.0 months; HR, 0.45; 95% CI, 0.35–0.60; $p < 0.001$) [150]. (NCT01154140)

(Continued)

Table 1 (continued)

Target	Drug	Status	Preclinical study/clinical trial data
ALK fusion	Ceritinib	Approved by the FDA	Among 231 patients, ceritinib had a significant improvement in median PFS compared with chemotherapy (5.4 months [95% CI, 4.1–6.9] for ceritinib *vs*. 1.6 months [95% CI, 1.4–2.8] for chemotherapy; HR, 0.49; $p < 0.001$) [151]. (NCT01828112)
ALK fusion	Alectinib	Approved by the FDA	Among 303 patients, the PFS significantly prolonged PFS with alectinib (HR, 0.43; 95% CI, 0.32–0.58; median PFS 34.8 *vs*. 10.9 months crizotinib) [152]. (NCT02075840)
ALK fusion	Brigatinib	Approved by the FDA	Among 275 patients, the PFS assessed by Bio-integral resource cente, brigatinib showed consistent advantages over cozotinib, median, 24.0 *vs*. 11.0 months (HR, 0.49; 95% CI, 0.35–0.68; $p < 0.0001$) [153]. (NCT02737501)
ALK fusion	Lorlatinib	Approved by the FDA	Among 296 patients, the PFS was improved with lorlatinib *vs*. crizotinib in patients with and without brain metastases at baseline (12-month PFS rates: 78% *vs*. 22% and 78% *vs*. 45%, respectively) [154]. (NCT03052608)
ALK fusion	Ensartinib	Phase III	Among 343 patients, the median PFS was significantly longer with ensartinib than with crizotinib (25.8 *vs*. 12.7 months; HR, 0.51; 95% CI, 0.35–0.72; $p < 0.001$) [154]. (NCT02767804)
ROS1 fusion	Crizotinib	Approved by the FDA	Among 129 patients, the ORR was 71.7% (95% CI, 63.0–79.3), median PFS was 15.9 months (95% CI, 12.9–24.0) [155]. (NCT01945021) A phase III clinical trial study comparing the efficacy and safety of entrectinib with crizotinib in participants with advanced or metastatic ROS1 NSCLC. (NCT04603807)
ROS1 fusion	Ceritinib	Phase II	The ORR was 62% (95% CI, 45–77). The median PFS was 9.3 months (95% CI, 0–22) for all patients and 19.3 months (95% CI, 1–37) for crizotinib-naïve patients. The median OS was 24 months (95% CI, 5–43) [108]. (NCT01964157)
ROS1 fusion	Lorlatinib	Phase II	Among 364 patients, 13 (62%; 95% CI, 38–82) of 21 TKI-naive patients and 14 (35%; 95% CI, 21–52) of 40 patients previously treated with crizotinib as their only TKI had an objective response [156]. (NCT01970865)
RET fusion	Selpercatinib (LOXO-292)	Approved by the FDA	Among 105 consecutively enrolled patients with RET fusion-positive NSCLC who had previously received at least platinum-based chemotherapy, the ORR was 64% (95% CI, 54–73). The median DOR was 17.5 months (95% CI, 12.0 to could not be evaluated), and 63% of the responses were ongoing at a median follow-up of 12.1 months. Among 39 previously untreated patients, with an ORR was 85% (95% CI, 70–94), and 90% of the responses were ongoing at 6 months [120]. (NCT03157128) A phase III clinical trial is ongoing to compare selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab as initial treatment of advanced or metastatic RET fusion-positive NSCLC. (NCT04194944)

(Continued)

Table 1 (continued)

Target	Drug	Status	Preclinical study/clinical trial data
RET fusion	Pralsetinib (BLU-667)	Approved by the FDA	Among 79 patients with advanced RET fusion + NSCLC, ORR among 57 response-evaluable patients with measurable disease and at least one follow-up disease assessment was 56% (95% CI, 42–69; 32 PR, 9 PR pending confirmation, 20 SD, 5 progressive disease). 91% (29/32) of responding patients remain on treatment; 6 have achieved response duration ≥ 6 months. DCR was 91% (52/57) [157]. (NCT03037385)
BRAF V600E mutation	Dabrafenib and Trametinib	Approved by the FDA	Among 177 patients showed the proportion of patients with investigator-assessed confirmed overall response was 23 (64%; 95% CI, 46–79), with two (6%) patients achieving a complete response and 21 (58%) a partial response [158]. (NCT01336634)
BRAF V600E mutation	Vemurafenib	Approved by the FDA	In the cohort (n = 208) with NSCLC, the response rate was 42% (95% CI, 20–67) and median PFS was 7.3 months (95% CI, 3.5–10.8) [159]. (NCT01524978) A phase II–III, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in combination in participants with unresectable, advanced or metastatic NSCLC. (NCT04591431)

Abbreviations: CI, confidence interval; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; EX14ski, exon 14 skipping; EX19del, exon 19 deletion; EX20ins, EX20ins; FDA, U.S. Food and Drug Administration; HR, hazard ratio; MTD, maximum tolerated dose; NSCLC, non small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; SD, stable disease.

3 Epigenetic Targets in NSCLC

Cancer was considered a genetic disease, while recent studies reveal epigenetic alterations are also important participants in cancer development [160–162]. Epigenetic alterations, as the main cause of transcriptional heterogeneity, lead to changes in the expression of key oncogenes and tumour suppressor genes and thus affect multiple signaling pathways [160,163–165]. Epigenetic regulation mainly includes DNA methylation, histone modification, non-coding RNA regulation and chromatin remodeling [166,167]. Various inhibitors targeting epigenetic alterations are being investigated and some of them entered clinical trials (Tables 2 and 3). Studies also suggest that epigenetic changes contribute to initial response heterogeneity and acquired drug resistance of driver mutation targeting therapy in NSCLC patients [168–171]. Therefore, it is of great clinical significance to consider epigenetic network targets for NSCLC treatment [172].

3.1 DNA Methylation

DNA methylation mainly occurs in CpG dinucleotides (concentrated in high-density regions called CpG islands), which inhibits the binding of RNase to gene fragments and thereby silences related genes [172,173]. DNA methyltransferases (such as DNMT1, DNMT3A and DNMT3B) and DNA demethylases (such as TET1, TET2 and TET3) are mainly responsible for the regulation of DNA methylation [168,174]. The functions of DNMT members in NSCLC vary; DNMT1 knockdown inhibits the growth of lung cancer cells *in vitro* and *in vivo*, whereas low expression of DNMT3A is associated with poor prognosis, and knockout of DNMT3A in Kras mutant mouse models promotes tumour growth and progression [175,176]. DNMT inhibitors, including azacitidine and decitabine, have not shown obvious efficacy on NSCLC in early clinical trials. However recent preclinical studies demonstrated that they could restore cancer cell sensitivity to EGFR-TKIs. Combined treatment of azacitidine and gefitinib lead to growth

inhibition and apoptosis of drug-resistant cancer cells [177,178]. Loss-of-function mutations of TET can promote cancer development, and these mutations often co-occur with oncogenic *KRAS* mutations. In a Kras G12D NSCLC mouse model, deletion of TET promoted tumour development by up-regulating Wnt signaling pathway [179]. In addition, gefitinib repressed TET1 through the C/EBPα transcription factor, and knockdown of TET1 resulted in resistance to gefitinib. TET1 expression was also lower in gefitinib-resistant patients than in sensitive patients [180]. More recently, a correlation between DNA methylation and EGFR-TKI response was found in 79 patients with NSCLC. Transcription factor enrichment analysis showed that the hypermethylation in the enhancer region of HOXB9 mainly occurred in patients with poor EGFR-TKI response [181]. Although some agents targeting DNA methylation are under clinical trial (Table 2), more trials are warranted to further evaluate whether inhibition of DNA methylation can be applied to fight against EGFR-TKI resistance. Moreover, challenges remain in dealing with the low specificity and high side effects of DNA methylation drugs. These drugs can be a double-edged sword, up-regulating tumour suppressor genes while also activating proto-oncogenes [182]. Preclinical studies demonstrated that combination therapy could help overcome this limitation by countering the dependency on the activated oncogene or synergistically strengthening tumour-suppressing effect. For example, upregulation of oncofetal protein SALL4 was induced in SALL4-negative cancer cells treated with azacytidine, while this also provides a vulnerability to entinostat, which can suppress SALL4; azacytidine in combination with entinostat significantly repressed tumour growth [183]. Combination of azacytidine with histone deacetylase inhibitors also exhibited a robust anti-tumour effect in NSCLC cells and mouse models by reversing tumour immune evasion [184]. Appropriate dosage is also important for using DNA methylation drugs in clinical practice since adverse events caused by high doses were observed in earlier clinical trials [11,172].

3.2 Histone Modifications

Histones are key components of chromatin, and their post-translational modification plays a crucial role in regulating gene expression and developing lung cancer [185,186]. Chromatin modification enzymes are classified into histone methyltransferases (HMTs), histone demethylasehistone (HDMs), histone acetyltransferases (HATs) and histone deacetylases (HDACs) [187,188]. HMTs play a key role in many cellular processes and are typically dysregulated in cancer, with diverse consequences. One of the most well-studied HMTs in NSCLC is EZH2. Overexpression of EZH2 promotes lung cancer progression through multiple signaling pathways, including VEGF-A, AKT, E2F/Rb and TGF-β, which are also associated with resistance to chemotherapy and poor survival [189,190]. EZH2 inhibitors such as JQEZ5 and GSK126 showed anti-tumour effects against NSCLC in preclinical studies, yet further evaluation in clinical trials is warranted [191,192]. In contrast, the absence of another HMT called SETD2 leads to accelerated tumour progression in a Kras G12D NSCLC mouse model [193]. These contrary results indicate heterogeneous roles of HMTs in NSCLC development. In addition, a histone lysine methyltransferase SMYD3 is up-regulated in Ras-driven lung cancer cells. It enhances the activation of Ras/Raf/MEK/ERK signaling module through methylating a non-histone protein MAP3K2, suggesting the potential of epigenetic regulators as a therapeutic target for NSCLC patients with KRAS inhibitor resistance [194].

Inhibition of HDACs alone lacks specific efficacy in clinical trials, but its combination with targeted drugs has great potential in overcoming TKI resistance. HDAC inhibitors help to overcome EGFR-TKI resistance by suppressing EMT [12,195] and inhibiting the self-renewal of cancer stem cells [196]. Preclinical studies have shown that vorinostat, which selectively inhibits HDAC3, increases EGFR-mutant cellular sensitivity to osimertinib *in vitro* and *in vivo* [197]. Moreover, vorinostat combined with ALK-TKI brigatinib showed more potent anti-tumour activity in lung adenocarcinoma cells carrying EGFR L858R/T790M/C797S mutations [198]. In a phase II trial, patients with high E-cadherin levels treated with erlotinib combined with an HDAC inhibitor entinostat had longer OS than those treated with erlotinib alone (9.4 *vs*. 5.4 months) [199]. More combination therapies, including HDAC inhibitors and

EGFR-TKIs (NCT02151721, NCT02520778), HDAC inhibitors and DNMT inhibitors (NCT00387465) are under clinical trials, providing ideas for overcoming targeted resistance and enhancing TKI efficacy in NSCLC [7] (Table 2). In addition, dual inhibitors against driver mutations and HDAC are being developed. Compound 9E, a dual inhibitor based on osimertinib and vorinostat, showed superior antiproliferative activity against several tumour cell lines [200].

Similar to DNA methylation, the adverse reactions of HDAC inhibitors also raised broad concern. The use of nanocarrier technologies (such as polymeric nanoparticles, PEG-coated nanoparticles, and colloid carrier systems) can deliver HDAC inhibitors with enhanced solubility, tumour specificity and less toxicity [201,202]. Developing HDAC inhibitors with higher tumour selectivity, exploring proper timing for administration, and identifying predictive biomarkers to better select patients will also be helpful in improving HDAC-based therapy [12].

Table 2: Drugs targeting epigenetic alterations in NSCLC

Target	Drug	Status	Preclinical study/Clinical trial data
DNMT	Decitabine	Phase I–II	Phase I dose-escalation study of decitabine with a fixed dose of genistein to treat advanced solid tumour was followed by a phase II study in advanced lung cancer patients [203]. (NCT01628471)
DNMT	Azacitidine	Phase II	This phase II clinical trial is studying how well azacitidine works in treating patients with previously treated advanced NSCLC. (NCT01281124)
DNMT	Azacitidine + Entinostat	Phase II	Among 25 patients, the combination of 5-azacitidine and entinostat is safe and well tolerated in advanced NSCLC patients. Two patients have had durable benefit from treatment, including a complete response. Pharmacodynamic and pharmacokinetic analyses are being conducted to identify characteristics of the subset of patients responding to this novel therapy [204]. (NCT00387465)
DNMT	Deoxycytidine + Tetrahydrouridine	Phase II	This phase II clinical trial is designed to determine if 5-Fluoro-2′-Deoxycytidine and tetrahydrouridine can work together to control lung cancer growth and to evaluate the safety and tolerability of 5-Fluoro-2′-Deoxycytidine and tetrahydrouridine when given together. (NCT00978250)
HDAC	Vorinostat	Phase I–II	Seven of the 12 patients in the trial experienced SD (median 4.2 months, range 2–10.7). Median TTP: 2.8 months (range 1–10.7+); median OS 6.5 months (range 1.4–10.7+); estimated 6 months OS rate 50% [205]. Other combination therapies are ongoing. (NCT01413750; NCT00503971; NCT02151721)
HDAC	Vorinostat + Bortezomib	Phase II	Among 18 patients, SD was observed in 5 patients (27.8%). Median PFS was 1.5 months, 3-month PFS rate was 11.1%, and median OS was 4.7 months. The most common grade 3/4 toxicities were thrombocytopenia and fatigue. Two patients who had baseline taxane-related grade 1 peripheral neuropathy developed grade 3 neuropathy. Bortezomib and vorinostat displayed minimal anti-tumour activity as third-line therapy in NSCLC [206]. (NCT00798720)
HDAC	Vorinostat + Gefitinib	Phase I	Among 12 patients with *EGFR*-mutated NSCLC with the BIM deletion, no dose-limiting toxicity was observed in all patients. The median PFS was 5.2 months (95% CI, 1.4–15.7) and the 6-week DCR was 83.3% (10/12) [207]. (NCT02151721)

(Continued)

Table 2 (continued)

Target	Drug	Status	Preclinical study/Clinical trial data
HDAC	Romidepsin	Phase I	Among 15 patients, romidepsin 8 mg/m^2 plus erlotinib appears well tolerated, has encouraging evidence of disease control, and exhibits effects on relevant molecular targets in an unselected advanced NSCLC population [208]. (NCT01302808)
HDAC	Pivanex	Phase I	Pivanex, at doses up to 2.5 g/m^2 can be administered safely in combination with 75 mg/m^2 of docetaxel in the regimen described above. This dose is being used in an ongoing Phase IIb trial [209].
HDAC	Entinostat + Erlotinib	Phase II	Among 132 patients, the 4-month PFS rate was comparable for both groups (EE, 18% *vs*. EP, 20%; $p = 0.7$). In the subset of patients with high E-cadherin levels, OS was longer in the EE group compared with the EP group (9.4 *vs*. 5.4 months; HR, 0.35; 95% CI, 0.13–0.92) with a corresponding trend toward increased PFS [210]. (NCT00602030)
HDAC	Vorinostat + Sorafenib	Phase I	A phase I clinical trial showed no drug-related death or grade IV toxicity in 17 patients who participated in the treatment [211].
HDAC	Panobinostat + Erlotinib	Phase I	Among 42 patients, DCR was 54%, PR was 3, SD was 3, PFS was 4.7 months, OS was 41 months in *EGFR* mutation NSCLC. (NCT00738751)

Abbreviations: CI, confidence interval; DCR, disease control rate; DNMT, DNA methyltransferase; HDAC, histone deacetylase; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time-to-progression.

3.3 Non-Coding RNA

Non-coding RNAs are involved in the occurrence and development of lung cancer. They are closely related to targeted therapy resistance, among which microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) have been most widely studied [170,212,213]. Although most studies are preclinical, emerging positive results suggest non-coding RNAs as potential therapeutic targets for NSCLC (Table 3). MiRNAs typically consist of 18–25 nucleotides that target RNA to regulate gene expression. Their contribution to TKI resistance involves multiple signaling pathways (such as PI3K/AKT/mTOR pathway) and EMT process [214]. For example, miR-483-3p can induce EMT and produce resistance to gefitinib through methylation of its own promoter [215]. In both univariate and multivariate analyses, gefitinib was associated with a significant improvement in OS in NSCLC patients with reduced miR-21 expression, suggesting targeting specific miRNA may promote response to EGFR-TKI [216]. Moreover, miRNAs are also involved in chemotherapy or radiotherapy resistance. After radiotherapy, NRF2-induced up-regulation of miR-140 transcription plays an important role in obtaining radiation protection [217].

LncRNA is non-coding RNA with a length >200 bp, which is a major regulator of gene expression [212]. LncRNA can interact with miRNA and affect the proliferation, invasion and metastasis of NSCLC cells [218]. LncRNA XLOC_008466 is highly expressed in patients with NSCLC and binds to miR-874 to down-regulate its level and increase miR-874 downstream target expression to promote cancer cell proliferation and invasion [219]. A tumour suppressor lncRNA SNHG10 can significantly reduce the miRNA-21 level and is positively associated with better survival and prognosis [220]. LncRNA can also interact with various signaling pathways such as Wnt, STAT3, PTEN/PI3K/AKT pathways, as well as histone modifiers like EZH2 [212]. For example, lncRNA CBR3-AS1 promotes migration and invasion of lung adenocarcinoma cells by activating Wnt/β-catenin signaling pathway [221]. Another LncRNA, TSLNC8, significantly enhanced the anti-tumour effect of osimertinib by inhibiting the EGFR-

STAT3 signaling pathway [222]. LncRNA CASC9 repressed tumour suppressor DUSP1 by recruiting EZH2, thereby promoting gefitinib resistance *in vitro* and *in vivo* [100]. Moreover, the expression of LncRNA H19 is increased in gefitinib-resistant cells, and it can be transferred to non-resistant cells through exosomes to "spread" drug resistance [223]. Numerous preclinical studies (Table 3) suggested the potential of lncRNA in suppressing cancer progression and the occurrence of drug resistance, while current clinical trials of lncRNA-based therapies for NSCLC remain rare.

CircRNAs are a kind of non-coding RNAs with a stable covalent closed loop structure, with recently reported involvement in lung cancer development [224]. The production of some circRNAs is closely related to the oncogene fusion gene. F-circEA-2a, a novel circRNA produced by the *EML4-ALK* fusion gene, promotes the migration and invasion of cancer cells in EML4-ALK positive NSCLC [225]. An important function of circRNAs is to act as miRNA sponges to interact with miRNAs, forming a circRNA-miRNA-mRNA regulatory axis in lung cancer that regulates related gene expression [226,227]. CiR-7 interacts with miR-7 and down-regulates miR-7 level, thus promoting lung cancer cell proliferation, migration and invasion by upregulating genes such as NF-κB, EGRF, CCNE1, PIK3CD, etc. [228,229]. In addition, a recent study has shown that circRNA is associated with drug resistance. The up-regulation of hsa_circ_0004015 significantly increased cellular resistance to gefitinib, while its down-regulation decreased gefitinib IC50 in resistant cancer cells, mechanistically via a hsa_circ_0004015/miR-1183/PDPK1 axis [230]. More agents targeting circRNAs are summarized in Table 3.

Table 3: Non-coding RNAs as potential target or potential therapeutic agent for NSCLC treatment

Type	Name	Association with NSCLC	Preclinical data
MicroRNA	miR-200c	Potential therapeutic agent	Among 66 NSCLC patients with wild-type EGFR, high level of miR-200c expression was associated with higher DCR, longer PFS and longer OS compared with low miR-200c expression subgroup [231].
MicroRNA	miR-124	Potential therapeutic agent	Manipulation of miR-124 restored cellular sensitivity to acquired gefitinib resistance. MiR-124 depletion induced gefitinib resistance [232].
MicroRNA	miR-21 miR-10b	Potential target	In both univariate and multivariate analyses (n = 201), gefitinib was associated with a significant improvement in OS in patients with reduced miR-21 expression, miR-10b is highly expressed in progressive disease compared with CR or SD ($p < 0.001$) [216].
MicroRNA	miR-214	Potential target	Down-regulation of miR-214 may reverse acquired resistance to erlotinib in NSCLC through mediating its direct target gene LHX6 expression [233].
MicroRNA	miR-181a	Potential target	MiR-181a is significantly up-regulated in gefitinib-resistant cells compared with gefitinib-sensitive cells. Upregulation of miR-181a caused resistance of gefitinib, whereas downregulation of miR-181a sensitized NSCLC cells to gefitinib [234].
LncRNA	BRCAT54	Potential therapeutic agent	BRCAT54 was identified as a tumour suppressor in NSCLC. Overexpression of BRCAT54 inhibited proliferation, migration and activated apoptosis in NSCLC cells [235].

(Continued)

Table 3 (continued)

Type	Name	Association with NSCLC	Preclinical data
LncRNA	AC079630.4	Potential therapeutic agent	LncRNA of AC079630.4 was identified as a tumour suppressor in lung cancer by the methods of bioinformatics analysis and experimental validation. Samples with low AC079630.4 expression had a more advanced pathological stage and a worse prognosis than those with high expression [13].
LncRNA	WT1-AS	Potential therapeutic agent	WT1-AS was downregulated in NSCLC and was correlated with poor survival, overexpression of WT1-AS inhibit the cell proliferation and EMT to decrease cell migration and invasion of NSCLC cells by downregulating UCA1 [236].
LncRNA	LINC01089	Potential therapeutic agent	LINC01089 improved OS of LUAD patients and was low-expressed in LUAD. LINC01089 inhibited lung adenocarcinoma cell proliferation and promoted apoptosis via sponging miR-543 [237].
LncRNA	LINC00673	Potential target	LINC00673 could sponge miR-150-5p and modulate the expression of a key EMT regulator ZEB1 indirectly; inhibition of LINC00673 significantly attenuated the tumourigenesis ability of A549 cells *in vivo* [238].
LncRNA	LINC01123	Potential target	LINC01123 is upregulated in NSCLC, correlates with prognosis, and controls proliferation and aerobic glycolysis by a positive feedback loop with c-Myc, it is expected to be a potential biomarker and therapeutic target for NSCLC [239].
LncRNA	CASC9	Potential target	CASC9 inhibition restored gefitinib sensitivity both *in vitro* and *in vivo*, whereas CASC9 overexpression promoted gefitinib resistance. CASC9 repressed the tumour suppressor DUSP1 by recruiting histone methyltransferase EZH2, thereby increasing the resistance to gefitinib [100].
LncRNA	GAS5	Potential target	The decrease in LncRNA GAS5 expression and the over-express of Ki67/EGFR occur in NSCLC tissues, the expressions of LncRNA GAS5, Ki67 and EGFR are connected with the progression, metastasis and prognosis of tumour; and LncRNA GAS5 is related to the expression of Ki67 and EGFR. These three factors are involved in the tumourigenesis and growth of the NSCLC process [240].
CircRNA	CiR-ITCH	Potential therapeutic agent	CiR-ITCH act as sponge of miR-7 and miR-214 to enhance ITCH expression, suppress the activation of Wnt/β-catenin signaling and thus inhibit cancer cell proliferation [241].

(Continued)

Table 3 (continued)

Type	Name	Association with NSCLC	Preclinical data
CircRNA	F-circEA-2a	Potential target	F-circEA-4a, generated from the back-splicing of EML4-ALK variant 3b, mainly locates in the cytoplasm and promotes cell migration and invasion, but has little effect on cell proliferation [225].
CircRNA	CiR-7	Potential target	CiR-7 functioned as miR-7 sponges to up-regulate the key targets of miR-7 including EGFR, CCNE1 and PIK3CD. The results *in vivo* further confirmed that CiR-7 functioned as oncogene [229].
CircRNA	hsa_circ_0004015	Potential target	Hsa_circ_0004015 could enhance the resistance of HCC827 to gefitinib. In mechanism, hsa_circ_0004015 acted as a sponge for miR-1183, and exert oncogenic effects by regulating miR-1183/PDPK1 axis [230].
CircRNA	Hsa_circ_100876	Potential target	Hsa_circ_100876 level was positively correlated with lymph node metastasis ($p = 0.001$) and tumour staging ($p = 0.001$) in NSCLC; Overall survival time of NSCLC patients with high hsa_circ_100876 expression was significantly shorter than for those patients with low hsa_circ_100876 expression ($p = 0.000$) [242].

Abbreviations: CR, complete response; DCR, disease control rate; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; SD, stable disease.

4 Discussion

The emergence and rapid development of targeted therapy in NSCLC treatment reflect the progress of precision oncology. Compared with traditional chemotherapy, targeted drugs have higher selectivity and better safety and greatly prolong the median survival of lung cancer patients. However, limited patients with specific mutations can be benefited; some well-known mutants like *KRAS* G12V and *KRAS* G13D and various rare mutants still lack long-term effective inhibitors. Moreover, drug resistance is always inevitable. Identifying new targets, understanding drug resistance mechanisms and developing new drugs or combination therapy strategies are crucial to benefit broader patients.

Emerging targetable epigenetic alterations provides new ideas for managing lung cancer and overcoming drug resistance. Accumulating preclinical studies have revealed its important role in the occurrence and development of lung cancer and the mechanism of drug resistance, suggesting broad application prospects. However, epigenetic therapy for NSCLC is still in its infancy; the mechanism of complex epigenetic networks in lung cancer remains unclear. Drugs targeting epigenetic alterations have not achieved satisfactory results in NSCLC clinical trials so far. Current problems in epigenetic targeting strategies must be solved, including relatively low specificity and sometimes two-edged effects of inhibitors targeting epigenetic regulations, including histone modification and DNA methylation. Developing inhibitors and drug delivery strategy with higher specificity and efficiency is warranted. Combination therapy is also a way to enhance the tumour-suppressing impact of epigenetic inhibitors while reducing/avoiding the impact of reactivated oncogenes. In addition, studies on identifying cohorts with higher sensitivity and determining appropriate doses are necessary to facilitate the application of epigenetic target-based treatment in clinical practice [11,172].

As technology advances and understanding deepens, deadlocks in targeted therapy are broken through one by one. Previously unidentified numerous and miscellaneous rare mutations have been identified nowadays in various stages of treatment, such as *EGFR* rare point mutations S768I, L861Q, G719X, G709X and rare secondary point mutations C797X, L718Q/V, L792H, G796S, indicating new targets for NSCLC treatment. Some mutants that were considered untargetable in the past may become targetable as research progresses. The emergence of KRAS G12 mutant inhibitors is a good example. New technologies such as AlphaFold2 and PROTACs are making powerful contributions to developing inhibitors against emerging targets, as well as dual inhibitors for different targets [72,243,244]. In addition, the complex network of drug resistance mechanisms is being gradually elucidated, including abnormal activation of bypass pathways, compensatory activation of downstream pathways, multi-target synergistic effects, and epigenetic heterogeneity, allowing increasing combination therapy strategies to be developed [245–247]. In general, drugs targeting epigenetics and driver mutations, as novel anti-tumour drugs or combination therapies, will open up a new era for the treatment of patients with NSCLC.

Authors' Contributions: All authors contributed to the conception and the main idea of the work. JJS, YCC and CTP wrote the manuscript. JJS, YCC, CTP, LWK, ZTZ, YKL, and KH analyzed the data and edited the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Ethics Approval and Informed Consent Statement: Not applicable.

Funding Statement: This work is supported by the Natural Science Foundation of China (82273838, 31971066 & 81703552), the Natural Science Foundation of Hubei Province (2021CFA004), the China Postdoctoral Science Foundation (2021M700050), and the Postdoctoral Innovation Research Program of Hubei Province.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

References

1. Cao, W., Chen, H. D., Yu, Y. W., Li, N., Chen, W. Q. (2021). Changing profiles of cancer burden worldwide and in China: A secondary analysis of the global cancer statistics 2020. *Chinese Medical Journal, 134(7),* 783–791. DOI 10.1097/CM9.0000000000001474.
2. Siegel, R. L., Miller, K. D., Fuchs, H. E., Jemal, A. (2022). Cancer statistics. *CA: A Cancer Journal for Clinicians, 72(1),* 7–33.
3. World Health Organization (2020). Global health estimates 2020: Deaths by cause, age, sex, by country and by region, 2000-2019. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death.
4. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I. et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 71(3),* 209–249. DOI 10.3322/caac.21660.
5. Wang, M., Herbst, R. S., Boshoff, C. (2021). Toward personalized treatment approaches for non-small-cell lung cancer. *Nature Medicine, 27(8),* 1345–1356. DOI 10.1038/s41591-021-01450-2.
6. Howlader, N., Forjaz, G., Mooradian, M. J., Meza, R., Kong, C. Y. et al. (2020). The effect of advances in lung-cancer treatment on population mortality. *New England Journal of Medicine, 383(7),* 640–649. DOI 10.1056/NEJMoa1916623.
7. Bajbouj, K., Al-Ali, A., Ramakrishnan, R. K., Saber-Ayad, M., Hamid, Q. (2021). Histone modification in NSCLC: Molecular mechanisms and therapeutic targets. *International Journal of Medical Sciences, 22(21),* 11701.
8. Gridelli, C., de Marinis, F., di Maio, M., Cortinovis, D., Cappuzzo, F. et al. (2011). Gefitinib as first-line treatment for patients with advanced non-small-cell lung cancer with activating epidermal growth factor receptor mutation: Review of the evidence. *Lung Cancer, 71(3),* 249–257. DOI 10.1016/j.lungcan.2010.12.008.

9. Ramalingam, S. S., Vansteenkiste, J., Planchard, D., Cho, B. C., Gray, J. E. et al. (2020). Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *New England Journal of Medicine, 382(1),* 41–50. DOI 10.1056/NEJMoa1913662.
10. Park, J. W., Han, J. W. (2019). Targeting epigenetics for cancer therapy. *Archives of Pharmacal Research, 42(2),* 159–170. DOI 10.1007/s12272-019-01126-z.
11. Liang, R., Li, X., Li, W., Zhu, X., Li, C. (2021). DNA methylation in lung cancer patients: Opening a "window of life" under precision medicine. *Biomedicine & Pharmacotherapy, 144(3),* 112202. DOI 10.1016/j.biopha.2021.112202.
12. Mamdani, H., Jalal, S. I. (2020). Histone deacetylase inhibition in non-small cell lung cancer: Hype or hope? *Frontiers in Cell and Developmental Biology, 8,* 582370. DOI 10.3389/fcell.2020.582370.
13. Wang, L. F., Wu, L. P., Wen, J. D. (2021). LncRNA AC079630.4 expression associated with the progression and prognosis in lung cancer. *Aging, 13(14),* 18658–18668. DOI 10.18632/aging.203310.
14. Fois, S. S., Paliogiannis, P., Zinellu, A., Fois, A. G., Cossu, A. et al. (2021). Molecular epidemiology of the main druggable genetic alterations in non-small cell lung cancer. *International Journal of Medical Sciences, 22(2),* 612.
15. Chen, R., Manochakian, R., James, L., Azzouqa, A. G., Shi, H. et al. (2020). Emerging therapeutic agents for advanced non-small cell lung cancer. *Journal of Hematology & Oncology, 13(1),* 58. DOI 10.1186/s13045-020-00881-7.
16. Midha, A., Dearden, S., McCormack, R. (2015). EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: A systematic review and global map by ethnicity (mutMapII). *American Journal of Cancer Research, 5(9),* 2892–2911.
17. Harrison, P. T., Vyse, S., Huang, P. H. (2020). Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. *Seminars in Cancer Biology, 61(10),* 167–179. DOI 10.1016/j.semcancer.2019.09.015.
18. Friedlaender, A., Drilon, A., Weiss, G. J., Banna, G. L., Addeo, A. (2020). KRAS as a druggable target in NSCLC: Rising like a phoenix after decades of development failures. *Cancer Treatment Reviews, 85(1005–16),* 101978. DOI 10.1016/j.ctrv.2020.101978.
19. Adderley, H., Blackhall, F. H., Lindsay, C. R. (2019). KRAS-mutant non-small cell lung cancer: Converging small molecules and immune checkpoint inhibition. *EBioMedicine, 41(7689),* 711–716. DOI 10.1016/j.ebiom.2019.02.049.
20. Awad, M. M., Oxnard, G. R., Jackman, D. M., Savukoski, D. O., Hall, D. et al. (2016). MET Exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-met overexpression. *Journal of Clinical Oncology, 34(7),* 721–730. DOI 10.1200/JCO.2015.63.4600.
21. Pillai, R. N., Behera, M., Berry, L. D., Rossi, M. R., Kris, M. G. et al. (2017). HER2 mutations in lung adenocarcinomas: A report from the lung cancer mutation consortium. *Cancer, 123(21),* 4099–4105. DOI 10.1002/cncr.30869.
22. Gainor, J. F., Varghese, A. M., Ou, S. H., Kabraji, S., Awad, M. M. et al. (2013). ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: An analysis of 1,683 patients with non-small cell lung cancer. *Clininal Cancer Research, 19(15),* 4273–4281. DOI 10.1158/1078-0432.CCR-13-0318.
23. Lin, J. J., Shaw, A. T. (2017). Recent advances in targeting ROS1 in lung cancer. *Journal of Thoracic Oncology, 12(11),* 1611–1625. DOI 10.1016/j.jtho.2017.08.002.
24. Cardarella, S., Ogino, A., Nishino, M., Butaney, M., Shen, J. et al. (2013). Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. *Clininal Cancer Research, 19(16),* 4532–4540. DOI 10.1158/1078-0432.CCR-13-0657.
25. Le, X., Nilsson, M., Goldman, J., Reck, M., Nakagawa, K. et al. (2021). Dual EGFR-VEGF pathway inhibition: A promising strategy for patients with EGFR-mutant NSCLC. *Journal of Thoracic Oncology, 16(2),* 205–215. DOI 10.1016/j.jtho.2020.10.006.
26. Liu, Q., Yu, S., Zhao, W., Qin, S., Chu, Q. et al. (2018). EGFR-TKIs resistance via EGFR-independent signaling pathways. *Molecular Cancer, 17(1),* 53. DOI 10.1186/s12943-018-0793-1.

27. Kujtan, L., Subramanian, J. (2019). Epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of non-small cell lung cancer. *Expert Review of Anticancer Therapy, 19(7),* 547–559. DOI 10.1080/14737140.2019.1596030.
28. da Cunha Santos, G., Shepherd, F. A., Tsao, M. S. (2011). EGFR mutations and lung cancer. *Annual Review of Pathology, 6(1),* 49–69. DOI 10.1146/annurev-pathol-011110-130206.
29. Cataldo, V. D., Gibbons, D. L., Pérez-Soler, R., Quintás-Cardama, A. (2011). Treatment of non-small-cell lung cancer with Erlotinib or Gefitinib. *New England Journal of Medicine, 364(10),* 947–955. DOI 10.1056/NEJMct0807960.
30. Ayati, A., Moghimi, S., Salarinejad, S., Safavi, M., Pouramiri, B. et al. (2020). A review on progression of epidermal growth factor receptor (EGFR) inhibitors as an efficient approach in cancer targeted therapy. *Bioorganic Chemistry, 99(2007),* 103811. DOI 10.1016/j.bioorg.2020.103811.
31. Chong, C. R., Janne, P. A. (2013). The quest to overcome resistance to EGFR-targeted therapies in cancer. *Nature Medicine, 19(11),* 1389–1400. DOI 10.1038/nm.3388.
32. Ou, S. H. (2012). Second-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs): A better mousetrap? A review of the clinical evidence. *Critical Reviews in Oncology/Hematology, 83(3),* 407–421. DOI 10.1016/j.critrevonc.2011.11.010.
33. Scalvini, L., Castelli, R., La Monica, S., Tiseo, M., Alfieri, R. (2021). Fighting tertiary mutations in EGFR-driven lung-cancers: Current advances and future perspectives in medicinal chemistry. *Biochemical Pharmacology, 190(56),* 114643. DOI 10.1016/j.bcp.2021.114643.
34. Camidge, D. R., Pao, W., Sequist, L. V. (2014). Acquired resistance to TKIs in solid tumours: Learning from lung cancer. *Nature Reviews Clinical Oncology, 11(8),* 473–481. DOI 10.1038/nrclinonc.2014.104.
35. Nagasaka, M., Zhu, V. W., Lim, S. M., Greco, M., Wu, F. et al. (2021). Beyond Osimertinib: The development of third-generation EGFR tyrosine kinase inhibitors for advanced EGFR + NSCLC. *Journal of Thoracic Oncology, 16(5),* 740–763. DOI 10.1016/j.jtho.2020.11.028.
36. He, J., Huang, Z., Han, L., Gong, Y., Xie, C. (2021). Mechanisms and management of 3rd generation EGFRTKI resistance in advanced nonsmall cell lung cancer (review). *International Journal of Oncology, 59(5),* 90. DOI 10.3892/ijo.2021.5270.
37. Mok, T. S., Wu, Y. L., Ahn, M. J., Garassino, M. C., Kim, H. R. et al. (2017). Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *New England Journal of Medicine, 376(7),* 629–640. DOI 10.1056/NEJMoa1612674.
38. Soria, J. C., Ohe, Y., Vansteenkiste, J., Reungwetwattana, T., Chewaskulyong, B. et al. (2018). Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *New England Journal of Medicine, 378(2),* 113–125. DOI 10.1056/NEJMoa1713137.
39. Vaid, A. K., Gupta, A., Momi, G. (2021). Overall survival in stage IV EGFR mutationpositive NSCLC: Comparing first, second and third generation EGFRTKIs (review). *International Journal of Oncology, 58(2),* 171–184. DOI 10.3892/ijo.2021.5168.
40. Cho, B. C., Chewaskulyong, B., Lee, K. H., Dechaphunkul, A., Sriuranpong, V. et al. (2019). Osimertinib versus standard of care EGFR TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA Asian subset. *Journal of Thoracic Oncology, 14(1),* 99–106. DOI 10.1016/j.jtho.2018.09.004.
41. Shi, K., Wang, G., Pei, J., Zhang, J., Wang, J. et al. (2022). Emerging strategies to overcome resistance to third-generation EGFR inhibitors. *Journal of Hematology & Oncology, 15(1),* 94. DOI 10.1186/s13045-022-01311-6.
42. Passaro, A., Janne, P. A., Mok, T., Peters, S. (2021). Overcoming therapy resistance in EGFR-mutant lung cancer. *Nature Cancer, 2(4),* 377–391. DOI 10.1038/s43018-021-00195-8.
43. Tan, C. S., Kumarakulasinghe, N. B., Huang, Y. Q., Ang, Y. L. E., Choo, J. R. et al. (2018). Third generation EGFR TKIs: Current data and future directions. *Molecular Cancer, 17(1),* 29. DOI 10.1186/s12943-018-0778-0.
44. Piotrowska, Z., Nagy, R., Fairclough, S., Lanman, R., Marcoux, N. et al. (2017). OA 09.01 characterizing the genomic landscape of EGFR C797S in lung cancer using ctDNA next-generation sequencing. *Journal of Thoracic Oncology, (11),* 12. DOI 10.1016/j.jtho.2017.09.375.

45. Wang, S., Tsui, S. T., Liu, C., Song, Y., Liu, D. (2016). EGFR C797S mutation mediates resistance to third-generation inhibitors in T790M-positive non-small cell lung cancer. *Journal of Hematology & Oncology, 9(1),* 59. DOI 10.1186/s13045-016-0290-1.
46. Finlay, M. R. V., Barton, P., Bickerton, S., Bista, M., Colclough, N. et al. (2021). Potent and selective inhibitors of the epidermal growth factor receptor to overcome C797S-mediated resistance. *Journal of Medicinal Chemistry, 64(18),* 13704–13718. DOI 10.1021/acs.jmedchem.1c01055.
47. Jia, Y., Yun, C. H., Park, E., Ercan, D., Manuia, M. et al. (2016). Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors. *Nature, 534(7605),* 129–132. DOI 10.1038/nature17960.
48. To, C., Jang, J., Chen, T., Park, E., Mushajiang, M. et al. (2019). Single and dual targeting of mutant EGFR with an allosteric inhibitor. *Cancer Discovery, 9(7),* 926–943. DOI 10.1158/2159-8290.CD-18-0903.
49. Engelhardt, H., Böse, D., Petronczki, M., Scharn, D., Bader, G. et al. (2019). Start selective and rigidify: The discovery path toward a next generation of EGFR tyrosine kinase inhibitors. *Journal of Medicinal Chemistry, 62(22),* 10272–10293. DOI 10.1021/acs.jmedchem.9b01169.
50. Tumbrink, H. L., Heimsoeth, A., Sos, M. L. (2021). The next tier of EGFR resistance mutations in lung cancer. *Oncogene, 40(1),* 1–11. DOI 10.1038/s41388-020-01510-w.
51. Leonetti, A., Sharma, S., Minari, R., Perego, P., Giovannetti, E. et al. (2019). Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *British Journal of Cancer, 121(9),* 725–737. DOI 10.1038/s41416-019-0573-8.
52. Nakagawa, K., Garon, E. B., Seto, T., Nishio, M., Ponce Aix, S. et al. (2019). Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology, 20(12),* 1655–1669. DOI 10.1016/S1470-2045 (19)30634-5.
53. Soo, R. A., Han, J. Y., Dafni, U., Cho, B. C., Yeo, C. M. et al. (2022). A randomised phase II study of osimertinib and bevacizumab versus osimertinib alone as second-line targeted treatment in advanced NSCLC with confirmed EGFR and acquired T790M mutations: The European thoracic oncology platform (ETOP 10-16) BOOSTER trial. *Annals of Oncology, 33(2),* 181–192. DOI 10.1016/j.annonc.2021.11.010.
54. Matsuura, S., Morikawa, K., Ito, Y., Kagoo, N., Kubota, T. et al. (2020). Good response with durvalumab after chemoradiotherapy for epidermal growth factor receptor exon 20 insertion adenocarcinoma: A case report. *Respiratory Medicine Case Reports, 31,* 101236. DOI 10.1016/j.rmcr.2020.101236.
55. Remon, J., Hendriks, L. E. L., Cardona, A. F., Besse, B. (2020). EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins. *Cancer Treatment Reviews, 90(Suppl 4),* 102105. DOI 10.1016/j. ctrv.2020.102105.
56. Meador, C. B., Sequist, L. V., Piotrowska, Z. (2021). Targeting EGFR Exon 20 insertions in non-small cell lung cancer: Recent advances and clinical updates. *Cancer Discovery, 11(9),* 2145–2157. DOI 10.1158/2159-8290.CD-21-0226.
57. Dearden, S., Stevens, J., Wu, Y. L., Blowers, D. (2013). Mutation incidence and coincidence in non small-cell lung cancer: Meta-analyses by ethnicity and histology (mutMap). *Annals of Oncology, 24(9),* 2371–2376. DOI 10.1093/ annonc/mdt205.
58. Jacobs, F., Cani, M., Malapelle, U., Novello, S., Napoli, V. M. et al. (2021). Targeting KRAS in NSCLC: Old failures and new options for "Non-G12c" patients. *Cancers, 13(24),* 6332. DOI 10.3390/cancers13246332.
59. Veluswamy, R., Mack, P. C., Houldsworth, J., Elkhouly, E., Hirsch, F. R. (2021). KRAS G12C-mutant non-small cell lung cancer: Biology, developmental therapeutics, and molecular testing. *The Journal of Molecular Diagnostics, 23(5),* 507–520. DOI 10.1016/j.jmoldx.2021.02.002.
60. Corral de la Fuente, E., Olmedo Garcia, M. E., Gomez Rueda, A., Lage, Y., Garrido, P. (2021). Targeting KRAS in non-small cell lung cancer. *Frontiers in Oncology, 11,* 792635. DOI 10.3389/fonc.2021.792635.

61. Cox, A. D., Fesik, S. W., Kimmelman, A. C., Luo, J., Der, C. J. (2014). Drugging the undruggable RAS: Mission possible? *Nature Reviews Drug Discovery, 13(11),* 828–851. DOI 10.1038/nrd4389.
62. Ryan, M. B., Corcoran, R. B. (2018). Therapeutic strategies to target RAS-mutant cancers. *Nature Reviews Clinical Oncology, 15(11),* 709–720. DOI 10.1038/s41571-018-0105-0.
63. Huang, L., Guo, Z., Wang, F., Fu, L. (2021). KRAS mutation: From undruggable to druggable in cancer. *Signal Transduction and Targeted Therapy, 6(1),* 386. DOI 10.1038/s41392-021-00780-4.
64. Riely, G. J., Johnson, M. L., Medina, C., Rizvi, N. A., Miller, V. A. et al. (2011). A phase II trial of Salirasib in patients with lung adenocarcinomas with KRAS mutations. *Journal of Thoracic Oncology, 6(8),* 1435–1437. DOI 10.1097/JTO.0b013e318223c099.
65. Ostrem, J. M., Peters, U., Sos, M. L., Wells, J. A., Shokat, K. M. (2013). K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature, 503(7477),* 548–551. DOI 10.1038/nature12796.
66. Ostrem, J. M., Shokat, K. M. (2016). Direct small-molecule inhibitors of KRAS: From structural insights to mechanism-based design. *Nature Reviews Drug Discovery, 15(11),* 771–785. DOI 10.1038/nrd.2016.139.
67. Dunnett-Kane, V., Nicola, P., Blackhall, F., Lindsay, C. (2021). Mechanisms of resistance to KRAS(G12C) inhibitors. *Cancers, 13(1),* 151. DOI 10.3390/cancers13010151.
68. Skoulidis, F., Li, B. T., Dy, G. K., Price, T. J., Falchook, G. S. et al. (2021). Sotorasib for lung cancers with KRAS p.G12C mutation. *New England Journal of Medicine, 384(25),* 2371–2381. DOI 10.1056/NEJMoa2103695.
69. Desage, A. L., Leonce, C., Swalduz, A., Ortiz-Cuaran, S. (2022). Targeting KRAS mutant in non-small cell lung cancer: Novel insights into therapeutic strategies. *Frontiers in Oncology, 12,* 796832. DOI 10.3389/fonc.2022.796832.
70. Spira, A. I., Riely, G. J., Gadgeel, S. M., Heist, R. S., Ou, S. H. I. et al. (2022). KRYSTAL-1: Activity and safety of adagrasib (MRTX849) in patients with advanced/metastatic non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation. *Journal of Clinical Oncology, 40(16_suppl),* 9002. DOI 10.1200/JCO.2022.40.16_suppl.9002.
71. Riely, G. J., Ou, S. H. I., Rybkin, I., Spira, A., Papadopoulos, K. et al. (2021). 99O_PR KRYSTAL-1: Activity and preliminary pharmacodynamic (PD) analysis of adagrasib (MRTX849) in patients (Pts) with advanced non-small cell lung cancer (NSCLC) harboring KRASG12C mutation. *Journal of Thoracic Oncology, 16(4),* S751–S752. DOI 10.1016/S1556-0864(21)01941-9.
72. Burslem, G. M., Crews, C. M. (2020). Proteolysis-targeting chimeras as therapeutics and tools for biological discovery. *Cell, 181(1),* 102–114. DOI 10.1016/j.cell.2019.11.031.
73. Bond, M. J., Chu, L., Nalawansha, D. A., Li, K., Crews, C. M. (2020). Targeted degradation of oncogenic KRAS (G12C) by VHL-recruiting PROTACs. *ACS Central Science, 6(8),* 1367–1375. DOI 10.1021/acscentsci.0c00411.
74. Yang, F., Wen, Y., Wang, C., Zhou, Y., Zhou, Y. et al. (2022). Efficient targeted oncogenic KRAS(G12C) degradation via first reversible-covalent PROTAC. *European Journal of Medicinal Chemistry, 230,* 114088. DOI 10.1016/j.ejmech.2021.114088.
75. Wang, X., Allen, S., Blake, J. F., Bowcut, V., Briere, D. M. et al. (2022). Identification of MRTX1133, a noncovalent, potent, and selective KRAS(G12D) inhibitor. *Journal of Medicinal Chemistry, 65(4),* 3123–3133. DOI 10.1021/acs.jmedchem.1c01688.
76. Zhang, Z., Gao, R., Hu, Q., Peacock, H., Peacock, D. M. et al. (2020). GTP-state-selective cyclic peptide ligands of K-Ras(G12D) block its interaction with raf. *ACS Central Science, 6(10),* 1753–1761. DOI 10.1021/acscentsci.0c00514.
77. Addeo, A., Banna, G. L., Friedlaender, A. (2021). KRAS G12C mutations in NSCLC: From target to resistance. *Cancers, 13(11),* 2541. DOI 10.3390/cancers13112541.
78. Akhave, N. S., Biter, A. B., Hong, D. S. (2021). Mechanisms of resistance to KRAS(G12C)-targeted therapy. *Cancer Discovery, 11(6),* 1345–1352. DOI 10.1158/2159-8290.CD-20-1616.
79. Ryan, M. B., Fece de la Cruz, F., Phat, S., Myers, D. T., Wong, E. et al. (2020). Vertical pathway inhibition overcomes adaptive feedback resistance to KRAS(G12C) inhibition. *Clininal Cancer Research, 26(7),* 1633–1643. DOI 10.1158/1078-0432.CCR-19-3523.

80. Adachi, Y., Ito, K., Hayashi, Y., Kimura, R., Tan, T. Z. et al. (2020). Epithelial-to-mesenchymal transition is a cause of both intrinsic and acquired resistance to KRAS G12C inhibitor in KRAS G12C-mutant non-small cell lung cancer. *Clininal Cancer Research, 26(22),* 5962–5973. DOI 10.1158/1078-0432.CCR-20-2077.
81. Koga, T., Suda, K., Fujino, T., Ohara, S., Hamada, A. et al. (2021). KRAS secondary mutations that confer acquired resistance to KRAS G12C inhibitors, sotorasib and adagrasib, and overcoming strategies: Insights from *in vitro* experiments. *Journal of Thoracic Oncology, 16(8),* 1321–1332. DOI 10.1016/j.jtho.2021.04.015.
82. Tanaka, N., Lin, J. J., Li, C., Ryan, M. B., Zhang, J. et al. (2021). Clinical acquired resistance to KRAS(G12C) inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. *Cancer Discovery, 11(8),* 1913–1922. DOI 10.1158/2159-8290.CD-21-0365.
83. Zhao, Y., Murciano-Goroff, Y. R., Xue, J. Y., Ang, A., Lucas, J. et al. (2021). Diverse alterations associated with resistance to KRAS(G12C) inhibition. *Nature, 599(7886),* 679–683. DOI 10.1038/s41586-021-04065-2.
84. Awad, M. M., Liu, S., Rybkin, I. I., Arbour, K. C., Dilly, J. et al. (2021). Acquired resistance to KRAS(G12C) inhibition in cancer. *New England Journal of Medicine, 384(25),* 2382–2393. DOI 10.1056/NEJMoa2105281.
85. Hallin, J., Engstrom, L. D., Hargis, L., Calinisan, A., Aranda, R. et al. (2020). The KRAS(G12C) Inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. *Cancer Discovery, 10(1),* 54–71. DOI 10.1158/2159-8290.CD-19-1167.
86. Hillig, R. C., Sautier, B., Schroeder, J., Moosmayer, D., Hilpmann, A. et al. (2019). Discovery of potent SOS1 inhibitors that block RAS activation via disruption of the RAS-SOS1 interaction. *PNAS, 116(7),* 2551–2560. DOI 10.1073/pnas.1812963116.
87. Lee, M., Jain, P., Wang, F., Ma, P. C., Borczuk, A. et al. (2021). MET alterations and their impact on the future of non-small cell lung cancer (NSCLC) targeted therapies. *Expert Opinion on Therapeutic Targets, 25(4),* 249–268. DOI 10.1080/14728222.2021.1925648.
88. Dhillon, S. (2020). Capmatinib: First approval. *Drugs, 80(11),* 1125–1131. DOI 10.1007/s40265-020-01347-3.
89. Kato, T., Yang, J. C. -H., Ahn, M. -J., Sakai, H., Morise, M. et al. (2022). Tepotinib in Asian patients with advanced NSCLC with MET exon 14 (METex14) skipping. *Journal of Clinical Oncology, 40(16_suppl),* 9120. DOI 10.1200/JCO.2022.40.16_suppl.9120.
90. Mathieu, L. N., Larkins, E., Akinboro, O., Roy, P., Amatya, A. K. et al. (2022). FDA approval summary: Capmatinib and tepotinib for the treatment of metastatic NSCLC harboring MET Exon 14 skipping mutations or alterations. *Clininal Cancer Research, 28(2),* 249–254. DOI 10.1158/1078-0432.CCR-21-1566.
91. Markham, A. (2021). Savolitinib: First approval. *Drugs, 81(14),* 1665–1670. DOI 10.1007/s40265-021-01584-0.
92. Syed, Y. Y. (2021). Amivantamab: First approval. *Drugs, 81(11),* 1349–1353. DOI 10.1007/s40265-021-01561-7.
93. Del Re, M., Cucchiara, F., Petrini, I., Fogli, S., Passaro, A. et al. (2020). erbB in NSCLC as a molecular target: Current evidences and future directions. *ESMO Open, 5(4),* e000724. DOI 10.1136/esmoopen-2020-000724.
94. Wu, S. G., Shih, J. Y. (2018). Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer. *Molecular Cancer, 17(1),* 38. DOI 10.1186/s12943-018-0777-1.
95. Zhu, J., Yang, Q., Xu, W. (2021). Iterative upgrading of small molecular tyrosine kinase inhibitors for EGFR mutation in NSCLC: Necessity and perspective. *Pharmaceutics, 13(9),* 1500. DOI 10.3390/pharmaceutics13091500.
96. Li, B. T., Smit, E. F., Goto, Y., Nakagawa, K., Udagawa, H. et al. (2022). Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. *New England Journal of Medicine, 386(3),* 241–251. DOI 10.1056/NEJMoa2112431.
97. Wang, H., He, Y., Zhao, W., Tong, Z. (2022). Ado-trastuzumab emtansine in the treatment of lung adenocarcinoma with ERBB2 mutation: A case report and literature review. *Anticancer Drugs, 33(8),* 773–777. DOI 10.1097/CAD.0000000000001369.
98. Riudavets, M., Sullivan, I., Abdayem, P., Planchard, D. (2021). Targeting HER2 in non-small-cell lung cancer (NSCLC): A glimpse of hope? An updated review on therapeutic strategies in NSCLC harbouring HER2 alterations. *ESMO Open, 6(5),* 100260. DOI 10.1016/j.esmoop.2021.100260.
99. Shaw, A. T., Yeap, B. Y., Mino-Kenudson, M., Digumarthy, S. R., Costa, D. B. et al. (2009). Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *Journal of Clinical Oncology, 27(26),* 4247–4253. DOI 10.1200/JCO.2009.22.6993.

100. Chen, Z., Chen, Q., Cheng, Z., Gu, J., Feng, W. et al. (2020). Long non-coding RNA CASC9 promotes gefitinib resistance in NSCLC by epigenetic repression of DUSP1. *Cell Death & Disease, 11(10),* 858. DOI 10.1038/s41419-020-03047-y.
101. Yanagitani, N., Uchibori, K., Koike, S., Tsukahara, M., Kitazono, S. et al. (2020). Drug resistance mechanisms in Japanese anaplastic lymphoma kinase-positive non-small cell lung cancer and the clinical responses based on the resistant mechanisms. *Cancer Science, 111(3),* 932–939. DOI 10.1111/cas.14314.
102. Gainor, J. F., Dardaei, L., Yoda, S., Friboulet, L., Leshchiner, I. et al. (2016). Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discovery, 6(10),* 1118–1133. DOI 10.1158/2159-8290.CD-16-0596.
103. Costa, D. B., Shaw, A. T., Ou, S. H., Solomon, B. J., Riely, G. J. et al. (2015). Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. *Journal of Clinical Oncology, 33(17),* 1881–1888. DOI 10.1200/JCO.2014.59.0539.
104. Zou, H. Y., Friboulet, L., Kodack, D. P., Engstrom, L. D., Li, Q. et al. (2015). PF-06463922, an ALK/ROS1 inhibitor, overcomes resistance to first and second generation ALK inhibitors in preclinical models. *Cancer Cell, 28(1),* 70–81. DOI 10.1016/j.ccell.2015.05.010.
105. Katayama, R., Khan, T. M., Benes, C., Lifshits, E., Ebi, H. et al. (2011). Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. *PNAS, 108(18),* 7535–7540. DOI 10.1073/pnas.1019559108.
106. Solomon, B. J., Besse, B., Bauer, T. M., Felip, E., Soo, R. A. et al. (2018). Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. *The Lancet Oncology, 19(12),* 1654–1667. DOI 10.1016/S1470-2045(18)30649-1.
107. Arnaoutakis, K. (2015). Crizotinib in ROS1-rearranged non-small-cell lung cancer. *New England Journal of Medicine, 372(7),* 683–684. DOI 10.1056/NEJMc1415359.
108. Lim, S. M., Kim, H. R., Lee, J. S., Lee, K. H., Lee, Y. G. et al. (2017). Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. *Journal of Clinical Oncology, 35(23),* 2613–2618. DOI 10.1200/JCO.2016.71.3701.
109. Desai, A. V., Robinson, G. W., Gauvain, K., Basu, E. M., Macy, M. E. et al. (2022). Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG). *Neuro-Oncology, 24(10),* 1776–1789. DOI 10.1093/neuonc/noac087.
110. Frampton, J. E. (2021). Entrectinib: A review in NTRK + solid tumours and ROS1 + NSCLC. *Drugs, 81(6),* 697–708. DOI 10.1007/s40265-021-01503-3.
111. Facchinetti, F., Loriot, Y., Kuo, M. S., Mahjoubi, L., Lacroix, L. et al. (2016). Crizotinib-resistant ROS1 Mutations reveal a predictive kinase inhibitor sensitivity model for ROS1- and ALK-rearranged lung cancers. *Clininal Cancer Research, 22(24),* 5983–5991. DOI 10.1158/1078-0432.CCR-16-0917.
112. Drilon, A., Jenkins, C., Iyer, S., Schoenfeld, A., Keddy, C. et al. (2021). ROS1-dependent cancers-biology, diagnostics and therapeutics. *Nature Reviews Clinical Oncology, 18(1),* 35–55. DOI 10.1038/s41571-020-0408-9.
113. Lin, J. J., Choudhury, N. J., Yoda, S., Zhu, V. W., Johnson, T. W. et al. (2021). Spectrum of mechanisms of resistance to crizotinib and lorlatinib in ROS1 fusion-positive lung cancer. *Clininal Cancer Research, 27(10),* 2899–2909. DOI 10.1158/1078-0432.CCR-21-0032.
114. Katayama, R., Gong, B., Togashi, N., Miyamoto, M., Kiga, M. et al. (2019). The new-generation selective ROS1/NTRK inhibitor DS-6051b overcomes crizotinib resistant ROS1-G2032R mutation in preclinical models. *Nature Communications, 10(1),* 3604. DOI 10.1038/s41467-019-11496-z.
115. Takamori, S., Matsubara, T., Haratake, N., Toyokawa, G., Fujishita, T. et al. (2021). Targeted therapy for RET fusion lung cancer: Breakthrough and unresolved issue. *Frontiers in Oncology, 11,* 704084. DOI 10.3389/fonc.2021.704084.
116. Drusbosky, L. M., Rodriguez, E., Dawar, R., Ikpeazu, C. V. (2021). Therapeutic strategies in RET gene rearranged non-small cell lung cancer. *Journal of Hematology & Oncology, 14(1),* 50. DOI 10.1186/s13045-021-01063-9.

117. Cascetta, P., Sforza, V., Manzo, A., Carillio, G., Palumbo, G. et al. (2021). RET inhibitors in non-small-cell lung cancer. *Cancers, 13(17),* 4415. DOI 10.3390/cancers13174415.
118. Markham, A. (2020). Selpercatinib: First approval. *Drugs, 80(11),* 1119–1124. DOI 10.1007/s40265-020-01343-7.
119. Goto, K., Oxnard, G. R., Tan, D. S. -W., Loong, H. H. F., Bauer, T. M. et al. (2020). Selpercatinib (LOXO-292) in patients with RET-fusion + non-small cell lung cancer. *Journal of Clinical Oncology, 38(15_suppl),* 3584. DOI 10.1200/JCO.2020.38.15_suppl.3584.
120. Drilon, A., Oxnard, G. R., Tan, D. S. W., Loong, H. H. F., Johnson, M. et al. (2020). Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. *New England Journal of Medicine, 383(9),* 813–824. DOI 10.1056/NEJMoa2005653.
121. Piotrowska, Z., Isozaki, H., Lennerz, J. K., Gainor, J. F., Lennes, I. T. et al. (2018). Landscape of acquired resistance to osimertinib in EGFR-mutant NSCLC and clinical validation of combined EGFR and RET inhibition with osimertinib and BLU-667 for acquired RET fusion. *Cancer Discovery, 8(12),* 1529–1539. DOI 10.1158/2159-8290.CD-18-1022.
122. Taieb, J., Jung, A., Sartore-Bianchi, A., Peeters, M., Seligmann, J. et al. (2019). The evolving biomarker landscape for treatment selection in metastatic colorectal cancer. *Drugs, 79(13),* 1375–1394. DOI 10.1007/s40265-019-01165-2.
123. García-Alonso, S., Mesa, P., Ovejero, L. P., Aizpurua, G., Lechuga, C. G. et al. (2022). Structure of the RAF1-HSP90-CDC37 complex reveals the basis of RAF1 regulation. *Molecular Cell, 82(18),* 3438–3452.e3438. DOI 10.1016/j.molcel.2022.08.012.
124. Sforza, V., Palumbo, G., Cascetta, P., Carillio, G., Manzo, A. et al. (2022). BRAF inhibitors in non-small cell lung cancer. *Cancers, 14(19),* 4863. DOI 10.3390/cancers14194863.
125. Paik, P. K., Arcila, M. E., Fara, M., Sima, C. S., Miller, V. A. et al. (2011). Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. *Journal of Clinical Oncology, 29(15),* 2046–2051. DOI 10.1200/JCO.2010.33.1280.
126. Marchetti, A., Felicioni, L., Malatesta, S., Grazia Sciarrotta, M., Guetti, L. et al. (2011). Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. *Journal of Clinical Oncology, 29(26),* 3574–3579. DOI 10.1200/JCO.2011.35.9638.
127. Wu, C. P., S, V. A. (2014). The pharmacological impact of ATP-binding cassette drug transporters on vemurafenib-based therapy. *Acta pharmaceutica Sinica B, 4(2),* 105–111. DOI 10.1016/j.apsb.2013.12.001.
128. Chan, X. Y., Singh, A., Osman, N., Piva, T. J. (2017). Role played by signalling pathways in overcoming BRAF inhibitor resistance in melanoma. *International Journal of Medical Sciences, 18(7),* 1527.
129. Planchard, D., Smit, E. F., Groen, H. J. M., Mazieres, J., Besse, B. et al. (2017). Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: An open-label, phase 2 trial. *The Lancet Oncology, 18(10),* 1307–1316. DOI 10.1016/S1470-2045(17)30679-4.
130. Ho, C. C., Liao, W. Y., Lin, C. A., Shih, J. Y., Yu, C. J. et al. (2017). Acquired BRAF V600E mutation as resistant mechanism after treatment with osimertinib. *Journal of Thoracic Oncology, 12(3),* 567–572. DOI 10.1016/j.jtho.2016.11.2231.
131. Kazandjian, D., Blumenthal, G. M., Yuan, W., He, K., Keegan, P. et al. (2016). FDA approval of gefitinib for the treatment of patients with metastatic EGFR mutation-positive non-small cell lung cancer. *Clininal Cancer Research, 22(6),* 1307–1312. DOI 10.1158/1078-0432.CCR-15-2266.
132. Rosell, R., Carcereny, E., Gervais, R., Vergnenegre, A., Massuti, B. et al. (2012). Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *The Lancet Oncology, 13(3),* 239–246. DOI 10.1016/S1470-2045(11)70393-X.
133. Shi, Y. K., Wang, L., Han, B. H., Li, W., Yu, P. et al. (2017). First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): A phase 3, open-label, randomized study. *Annals of Oncology, 28(10),* 2443–2450. DOI 10.1093/annonc/mdx359.

134. Park, K., Tan, E. H., O'Byrne, K., Zhang, L., Boyer, M. et al. (2016). Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial. *The Lancet Oncology, 17(5),* 577–589. DOI 10.1016/S1470-2045(16)30033-X.

135. Wu, Y. L., Cheng, Y., Zhou, X., Lee, K. H., Nakagawa, K. et al. (2017). Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. *The Lancet Oncology, 18(11),* 1454–1466. DOI 10.1016/S1470-2045(17)30608-3.

136. Sequist, L. V., Besse, B., Lynch, T. J., Miller, V. A., Wong, K. K. et al. (2010). Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: Results of a phase II trial in patients with advanced non-small-cell lung cancer. *Journal of Clinical Oncology, 28(18),* 3076–3083. DOI 10.1200/JCO.2009.27.9414.

137. Sequist, L. V., Soria, J. C., Camidge, D. R. (2016). Update to rociletinib data with the RECIST confirmed response rate. *New England Journal of Medicine, 374(23),* 2296–2297. DOI 10.1056/NEJMc1602688.

138. Yang, J. C., Reckamp, K. L., Kim, Y. C., Novello, S., Smit, E. F. et al. (2021). Efficacy and safety of rociletinib versus chemotherapy in patients with EGFR-mutated NSCLC: The results of TIGER-3, a Phase 3 randomized study. *JTO Clinical and Research Reports, 2(2),* 100114. DOI 10.1016/j.jtocrr.2020.100114.

139. Ahn, M. J., Han, J. Y., Lee, K. H., Kim, S. W., Kim, D. W. et al. (2019). Lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: Results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1–2 study. *The Lancet Oncology, 20(12),* 1681–1690. DOI 10.1016/S1470-2045(19)30504-2.

140. Zhou, Q., Wu, L., Feng, L., An, T., Cheng, Y. et al. (2019). Safety and efficacy of abivertinib (AC0010), a third-generation EGFR tyrosine kinase inhibitor, in Chinese patients with EGFR-T790M positive non-small cell lung cancer (NCSLC). *Journal of Clinical Oncology, 37(15_suppl),* 9091. DOI 10.1200/JCO.2019.37.15_suppl.9091.

141. Shi, Y., Hu, X., Zhang, S., Lv, D., Zhang, Y. et al. (2020). Efficacy and safety of alflutinib (AST2818) in patients with T790M mutation-positive NSCLC: A phase IIb multicenter single-arm study. *Journal of Clinical Oncology, 38(15_suppl),* 9602. DOI 10.1200/JCO.2020.38.15_suppl.9602.

142. Ramalingam, S. S., Zhou, C., Kim, T. M., Kim, S. W., Yang, J. C. -H. et al. (2021). Mobocertinib (TAK-788) in EGFR exon 20 insertion (ex20ins) + metastatic NSCLC (mNSCLC): Additional results from platinum-pretreated patients (pts) and EXCLAIM cohort of phase 1/2 study. *Journal of Clinical Oncology, 39(15_suppl),* 9014. DOI 10.1200/JCO.2021.39.15_suppl.9014.

143. Le, X., Goldman, J. W., Clarke, J. M., Tchekmedyian, N., Piotrowska, Z. et al. (2020). Poziotinib shows activity and durability of responses in subgroups of previously treated EGFR exon 20 NSCLC patients. *Journal of Clinical Oncology, 38(15_suppl),* 9514. DOI 10.1200/JCO.2020.38.15_suppl.9514.

144. Li, J., Zhao, J., Cao, B., Fang, J., Li, X. et al. (2022). A phase I/II study of first-in-human trial of JAB-21822 (KRAS G12C inhibitor) in advanced solid tumors. *Journal of Clinical Oncology, 40(16_suppl),* 3089. DOI 10.1200/JCO.2022.40.16_suppl.3089.

145. Zhou, Q., Yang, N., Zhao, J., Dong, X., Wang, H. et al. (2022). Phase I dose-escalation study of IBI351 (GFH925) monotherapy in patients with advanced solid tumors. *Journal of Clinical Oncology, 40(16_suppl),* 3110. DOI 10.1200/JCO.2022.40.16_suppl.3110.

146. Socinski, M. A., Pennell, N. A., Davies, K. D. (2021). MET Exon 14 skipping mutations in non-small-cell lung cancer: An overview of biology, clinical outcomes, and testing considerations. *JCO Precision Oncology, (5),* 653–663. DOI 10.1200/PO.20.00516.

147. Krebs, M., Spira, A. I., Cho, B. C., Besse, B., Goldman, J. W. et al. (2022). Amivantamab in patients with NSCLC with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study. *Journal of Clinical Oncology, 40(16_suppl),* 9008. DOI 10.1200/JCO.2022.40.16_suppl.9008.

148. Camidge, D. R., Bar, J., Horinouchi, H., Goldman, J. W., Moiseenko, F. V. et al. (2022). Telisotuzumab vedotin (Teliso-V) monotherapy in patients (pts) with previously treated c-Met-overexpressing (OE) advanced non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology, 40(16_suppl),* 9016. DOI 10.1200/JCO.2022.40.16_suppl.9016.

149. Hamilton, E. P., Barve, M. A., Bardia, A., Beeram, M., Bendell, J. C. et al. (2018). Phase 1 dose escalation of XMT-1522, a novel HER2-targeting antibody-drug conjugate (ADC), in patients (pts) with HER2-expressing breast, lung and gastric tumors. *Journal of Clinical Oncology, 36(15_suppl),* 2546. DOI 10.1200/JCO.2018.36.15_suppl.2546.

150. Solomon, B. J., Mok, T., Kim, D. W., Wu, Y. L., Nakagawa, K. et al. (2014). First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *New England Journal of Medicine, 371(23),* 2167–2177. DOI 10.1056/NEJMoa1408440.

151. Shaw, A. T., Kim, T. M., Crinò, L., Gridelli, C., Kiura, K. et al. (2017). Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): A randomised, controlled, open-label, phase 3 trial. *The Lancet Oncology, 18(7),* 874–886. DOI 10.1016/S1470-2045(17)30339-X.

152. Mok, T., Camidge, D. R., Gadgeel, S. M., Rosell, R., Dziadziuszko, R. et al. (2020). Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Annals of Oncology, 31(8),* 1056–1064. DOI 10.1016/j.annonc.2020.04.478.

153. Camidge, D. R., Kim, H. R., Ahn, M. J., Yang, J. C. H., Han, J. Y. et al. (2020). Brigatinib versus crizotinib in advanced ALK inhibitor-naive ALK-positive non-small cell lung cancer: Second interim analysis of the phase III ALTA-1L trial. *Journal of Clinical Oncology, 38(31),* 3592–3603. DOI 10.1200/JCO.20.00505.

154. Remon, J., Pignataro, D., Novello, S., Passiglia, F. (2021). Current treatment and future challenges in ROS1- and ALK-rearranged advanced non-small cell lung cancer. *Cancer Treatment Reviews, 95,* 102178. DOI 10.1016/j.ctrv.2021.102178.

155. Wu, Y. L., Yang, J. C., Kim, D. W., Lu, S., Zhou, J. et al. (2018). Phase II study of crizotinib in east Asian patients with ROS1-positive advanced non-small-cell lung cancer. *Journal of Clinical Oncology, 36(14),* 1405–1411. DOI 10.1200/JCO.2017.75.5587.

156. Shaw, A. T., Solomon, B. J., Chiari, R., Riely, G. J., Besse, B. et al. (2019). Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: A multicentre, open-label, single-arm, phase 1–2 trial. *The Lancet Oncology, 20(12),* 1691–1701. DOI 10.1016/S1470-2045(19)30655-2.

157. Gainor, J. F., Lee, D. H., Curigliano, G., Doebele, R. C., Kim, D. W. et al. (2019). Clinical activity and tolerability of BLU-667, a highly potent and selective RET inhibitor, in patients (pts) with advanced RET-fusion + non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology, 37(15_suppl),* 9008. DOI 10.1200/JCO.2019.37.15_suppl.9008.

158. Planchard, D., Smit, E. F., Groen, H. J. M., Mazieres, J., Besse, B. et al. (2017). Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: An open-label, phase 2 trial. *The Lancet Oncology, 18(10),* 1307–1316. DOI 10.1016/S1470-2045(17)30679-4.

159. Hyman, D. M., Puzanov, I., Subbiah, V., Faris, J. E., Chau, I. et al. (2015). Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *New England Journal of Medicine, 373(8),* 726–736. DOI 10.1056/NEJMoa1502309.

160. Jin, N., George, T. L., Otterson, G. A., Verschraegen, C., Wen, H. et al. (2021). Advances in epigenetic therapeutics with focus on solid tumors. *Clinical Epigenetics, 13(1),* 83. DOI 10.1186/s13148-021-01069-7.

161. Wang, Q., Chen, Y., Xie, Y., Yang, D., Sun, Y. et al. (2022). Histone H1.2 promotes hepatocarcinogenesis by regulating signal transducer and activator of transcription 3 signaling. *Cancer Science, 113(5),* 1679–1692. DOI 10.1111/cas.15336.

162. Liu, S., Sun, Y., Jiang, M., Li, Y., Tian, Y. et al. (2017). Glyceraldehyde-3-phosphate dehydrogenase promotes liver tumorigenesis by modulating phosphoglycerate dehydrogenase. *Hepatology, 66(2),* 631–645. DOI 10.1002/hep.29202.

163. Shi, Y. X., Wang, Y., Li, X., Zhang, W., Zhou, H. H. et al. (2017). Genome-wide DNA methylation profiling reveals novel epigenetic signatures in squamous cell lung cancer. *BMC Genomics, 18(1),* 901. DOI 10.1186/s12864-017-4223-3.

164. Wang, W., Wang, Q., Wan, D., Sun, Y., Wang, L. et al. (2017). Histone HIST1H1C/H1.2 regulates autophagy in the development of diabetic retinopathy. *Autophagy, 13(5),* 941–954. DOI 10.1080/15548627.2017.1293768.

165. Chen, H., Liu, C., Wang, Q., Xiong, M., Zeng, X. et al. (2022). Renal UTX-PHGDH-serine axis regulates metabolic disorders in the kidney and liver. *Nature Communications, 13(1),* 3835. DOI 10.1038/s41467-022-31476-0.

166. Nebbioso, A., Tambaro, F. P., Dell'Aversana, C., Altucci, L. (2018). Cancer epigenetics: Moving forward. *PLoS Genetics, 14(6),* e1007362. DOI 10.1371/journal.pgen.1007362.

167. Ding, Y., Li, J., Liu, S., Zhang, L., Xiao, H. et al. (2014). DNA hypomethylation of inflammation-associated genes in adipose tissue of female mice after multigenerational high fat diet feeding. *International Journal of Obesity, 38(2),* 198–204. DOI 10.1038/ijo.2013.98.
168. Wajapeyee, N., Gupta, R. (2021). Epigenetic alterations and mechanisms that drive resistance to targeted cancer therapies. *Cancer Research, 81(22),* 5589–5595. DOI 10.1158/0008-5472.CAN-21-1606.
169. Jamal-Hanjani, M., Wilson, G. A., McGranahan, N., Birkbak, N. J., Watkins, T. B. K. et al. (2017). Tracking the evolution of non-small-cell lung cancer. *New England Journal of Medicine, 376(22),* 2109–2121. DOI 10.1056/NEJMoa1616288.
170. Liu, W. J., Du, Y., Wen, R., Yang, M., Xu, J. (2020). Drug resistance to targeted therapeutic strategies in non-small cell lung cancer. *Pharmacology & Therapeutics, 206(3),* 107438. DOI 10.1016/j.pharmthera.2019.107438.
171. Quan, C., Chen, Y., Wang, X., Yang, D., Wang, Q. et al. (2020). Loss of histone lysine methyltransferase EZH2 confers resistance to tyrosine kinase inhibitors in non-small cell lung cancer. *Cancer Letters, 495,* 41–52. DOI 10.1016/j.canlet.2020.09.003.
172. Chao, Y. L., Pecot, C. V. (2021). Targeting epigenetics in lung cancer. *Cold Spring Harbor Perspectives in Medicine, 11(6),* a038000. DOI 10.1101/cshperspect.a038000.
173. Ahuja, N., Sharma, A. R., Baylin, S. B. (2016). Epigenetic therapeutics: A new weapon in the war against cancer. *Annual Review of Medicine, 67(1),* 73–89. DOI 10.1146/annurev-med-111314-035900.
174. Wang, J., Xiong, M., Fan, Y., Liu, C., Wang, Q. et al. (2022). Mecp2 protects kidney from ischemia-reperfusion injury through transcriptional repressing IL-6/STAT3 signaling. *Theranostics, 12(8),* 3896–3910. DOI 10.7150/thno.72515.
175. Al-Yozbaki, M., Jabre, I., Syed, N. H., Wilson, C. M. (2022). Targeting DNA methyltransferases in non-small-cell lung cancer. *Seminars in Cancer Biology, 83(1),* 77–87. DOI 10.1016/j.semcancer.2021.01.005.
176. Husni, R. E., Shiba-Ishii, A., Iiyama, S., Shiozawa, T., Kim, Y. et al. (2016). DNMT3a expression pattern and its prognostic value in lung adenocarcinoma. *Lung Cancer, 97(Suppl 1),* 59–65. DOI 10.1016/j.lungcan.2016.04.018.
177. Li, X. Y., Wu, J. Z., Cao, H. X., Ma, R., Wu, J. Q. et al. (2013). Blockade of DNA methylation enhances the therapeutic effect of gefitinib in non-small cell lung cancer cells. *Oncology Reports, 29(5),* 1975–1982. DOI 10.3892/or.2013.2298.
178. Duruisseaux, M., Esteller, M. (2018). Lung cancer epigenetics: From knowledge to applications. *Seminars in Cancer Biology, 51(Suppl 4),* 116–128. DOI 10.1016/j.semcancer.2017.09.005.
179. Xu, Q., Wang, C., Zhou, J. X., Xu, Z. M., Gao, J. et al. (2022). Loss of TET reprograms Wnt signaling through impaired demethylation to promote lung cancer development. *PNAS, 119(6),* e2107599119. DOI 10.1073/pnas.2107599119.
180. Forloni, M., Gupta, R., Nagarajan, A., Sun, L. S., Dong, Y. et al. (2016). Oncogenic EGFR represses the TET1 DNA demethylase to induce silencing of tumor suppressors in cancer cells. *Cell Reports, 16(2),* 457–471. DOI 10.1016/j.celrep.2016.05.087.
181. Su, S. F., Liu, C. H., Cheng, C. L., Ho, C. C., Yang, T. Y. et al. (2021). Genome-wide epigenetic landscape of lung adenocarcinoma links HOXB9 DNA methylation to intrinsic EGFR-TKI resistance and heterogeneous responses. *JCO Precision Oncology, 5(5),* 418–431. DOI 10.1200/PO.20.00151.
182. Liu, Y. C., Kwon, J., Fabiani, E., Xiao, Z., Liu, Y. V. et al. (2022). Demethylation and up-regulation of an oncogene after hypomethylating therapy. *New England Journal of Medicine, 386(21),* 1998–2010. DOI 10.1056/NEJMoa2119771.
183. Yang, J., Gao, C., Liu, M., Liu, Y. C., Kwon, J. et al. (2021). Targeting an inducible SALL4-mediated cancer vulnerability with sequential therapy. *Cancer Research, 81(23),* 6018–6028. DOI 10.1158/0008-5472.CAN-21-0030.
184. Topper, M. J., Vaz, M., Chiappinelli, K. B., DeStefano Shields, C. E., Niknafs, N. et al. (2017). Epigenetic therapy ties MYC depletion to reversing immune evasion and treating lung cancer. *Cell, 171(6),* 1284–1300.e21.
185. Bowman, G. D., Poirier, M. G. (2015). Post-translational modifications of histones that influence nucleosome dynamics. *Chemical Reviews, 115(6),* 2274–2295. DOI 10.1021/cr500350x.

186. Chen, Y., Liu, X., Li, Y., Quan, C., Zheng, L. et al. (2018). Lung cancer therapy targeting histone methylation: Opportunities and challenges. *Computational and Structural Biotechnology Journal, 16(1),* 211–223. DOI 10.1016/j.csbj.2018.06.001.

187. Huang, L., Yang, X., Peng, A., Wang, H., Lei, X. et al. (2015). Inhibitory effect of leonurine on the formation of advanced glycation end products. *Food & Function, 6(2),* 584–589. DOI 10.1039/C4FO00960F.

188. Huang, J., Wan, D., Li, J., Chen, H., Huang, K. et al. (2015). Histone acetyltransferase PCAF regulates inflammatory molecules in the development of renal injury. *Epigenetics, 10(1),* 62–72. DOI 10.4161/15592294.2014.990780.

189. Coe, B. P., Thu, K. L., Aviel-Ronen, S., Vucic, E. A., Gazdar, A. F. et al. (2013). Genomic deregulation of the E2F/Rb pathway leads to activation of the oncogene EZH2 in small cell lung cancer. *PLoS One, 8(8),* e71670. DOI 10.1371/journal.pone.0071670.

190. Murai, F., Koinuma, D., Shinozaki-Ushiku, A., Fukayama, M., Miyaozono, K. et al. (2015). EZH2 promotes progression of small cell lung cancer by suppressing the TGF-β-Smad-ASCL1 pathway. *Cell Discovery, 1(1),* 15026. DOI 10.1038/celldisc.2015.26.

191. Chen, Y. T., Zhu, F., Lin, W. R., Ying, R. B., Yang, Y. P. et al. (2016). The novel EZH2 inhibitor, GSK126, suppresses cell migration and angiogenesis via down-regulating VEGF-A. *Cancer Chemotherapy and Pharmacology, 77(4),* 757–765. DOI 10.1007/s00280-016-2990-1.

192. Zhang, H., Qi, J., Reyes, J. M., Li, L., Rao, P. K. et al. (2016). Oncogenic deregulation of EZH2 as an opportunity for targeted therapy in lung cancer. *Cancer Discovery, 6(9),* 1006–1021. DOI 10.1158/2159-8290.CD-16-0164.

193. Walter, D. M., Venancio, O. S., Buza, E. L., Tobias, J. W., Deshpande, C. et al. (2017). Systematic *in vivo* inactivation of chromatin-regulating enzymes identifies Setd2 as a potent tumor suppressor in lung adenocarcinoma. *Cancer Research, 77(7),* 1719–1729. DOI 10.1158/0008-5472.CAN-16-2159.

194. Mazur, P. K., Reynoird, N., Khatri, P., Jansen, P. W., Wilkinson, A. W. et al. (2014). SMYD3 links lysine methylation of MAP3K2 to Ras-driven cancer. *Nature, 510(7504),* 283–287. DOI 10.1038/nature13320.

195. Tulchinsky, E., Demidov, O., Kriajevska, M., Barlev, N. A., Imyanitov, E. (2019). EMT: A mechanism for escape from EGFR-targeted therapy in lung cancer. *Biochimica et Biophysica Acta Reviews on Cancer, 1871(1),* 29–39. DOI 10.1016/j.bbcan.2018.10.003.

196. Bora-Singhal, N., Mohankumar, D., Saha, B., Colin, C. M., Lee, J. Y. et al. (2020). Novel HDAC11 inhibitors suppress lung adenocarcinoma stem cell self-renewal and overcome drug resistance by suppressing Sox2. *Scientific Reports, 10(1),* 4722. DOI 10.1038/s41598-020-61295-6.

197. Tanimoto, A., Takeuchi, S., Arai, S., Fukuda, K., Yamada, T. et al. (2017). Histone deacetylase 3 inhibition overcomes BIM deletion polymorphism-mediated osimertinib resistance in EGFR-mutant lung cancer. *Clininal Cancer Research, 23(12),* 3139–3149. DOI 10.1158/1078-0432.CCR-16-2271.

198. Lin, C. Y., Huang, K. Y., Lin, Y. C., Yang, S. C., Chung, W. C. et al. (2021). Vorinostat combined with brigatinib overcomes acquired resistance in EGFR-C797S-mutated lung cancer. *Cancer Letters, 508,* 76–91. DOI 10.1016/j.canlet.2021.03.022.

199. Witta, S. E., Jotte, R. M., Konduri, K., Neubauer, M. A., Spira, A. I. et al. (2012). Randomized phase II trial of erlotinib with and without entinostat in patients with advanced non-small-cell lung cancer who progressed on prior chemotherapy. *Journal of Clinical Oncology, 30(18),* 2248–2255. DOI 10.1200/JCO.2011.38.9411.

200. Dong, H., Yin, H., Zhao, C., Cao, J., Xu, W. et al. (2019). Design, synthesis and biological evaluation of novel osimertinib-based HDAC and EGFR dual inhibitors. *Molecules, 24(13),* 2407. DOI 10.3390/molecules24132407.

201. Lee, S. Y., Hong, E. H., Jeong, J. Y., Cho, J., Seo, J. H. et al. (2019). Esterase-sensitive cleavable histone deacetylase inhibitor-coupled hyaluronic acid nanoparticles for boosting anticancer activities against lung adenocarcinoma. *Biomaterials Science, 7(11),* 4624–4635. DOI 10.1039/C9BM00895K.

202. Bertrand, P., Blanquart, C., Héroguez, V. (2019). The ROMP: A powerful approach to synthesize novel pH-sensitive nanoparticles for tumor therapy. *Biomolecules, 9(2),* 60. DOI 10.3390/biom9020060.

203. Kassouf, E., Tehfe, M. A., Florescu, M., Soulieres, D., Lemieux, B. et al. (2015). Phase I and II studies of the decitabine-genistein drug combination in advanced solid tumors. *Journal of Clinical Oncology, 33(15_suppl),* e13556. DOI 10.1200/jco.2015.33.15_suppl.e13556.

204. Juergens, R. A., Vendetti, F., Coleman, B., Sebree, R. S., Rudek, M. A. et al. (2009). Interim analysis of a phase II trial of 5-azacitidine (5AC) and entinostat (SNDX-275) in relapsed advanced lung cancer (NSCLC). *Journal of Clinical Oncology, 27(15_suppl),* 8055. DOI 10.1200/jco.2009.27.15_suppl.8055.
205. Traynor, A. M., Dubey, S., Eickhoff, J., Kolesar, J. M., Marcotte, S. M. et al. (2007). A phase II study of vorinostat (NSC 701852) in patients (pts) with relapsed non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology, 25(18_suppl),* 18044. DOI 10.1200/jco.2007.25.18_suppl.18044.
206. Hoang, T., Campbell, T. C., Zhang, C., Kim, K., Kolesar, J. M. et al. (2014). Vorinostat and bortezomib as third-line therapy in patients with advanced non-small cell lung cancer: A wisconsin oncology network phase II study. *Investigational New Drugs, 32(1),* 195–199. DOI 10.1007/s10637-013-9980-5.
207. Takeuchi, S., Hase, T., Shimizu, S., Ando, M., Hata, A. et al. (2020). Phase I study of vorinostat with gefitinib in BIM deletion polymorphism/epidermal growth factor receptor mutation double-positive lung cancer. *Cancer Science, 111(2),* 561–570.
208. Gerber, D. E., Skelton, R., Dong, Y., Loudat, L., Dowell, J. et al. (2013). Phase I and pharmacodynamic study of the histone deacetylase (HDAC) inhibitor romidepsin plus erlotinib in previously treated advanced non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology, 31(15_suppl),* 8088.
209. Reid, T., Weeks, A., Vakil, M., Cosgriff, T., Harper, T. et al. (2004). Dose escalation study of pivanex (a histone deacetylase inhibitor) in combination with docetaxel for advanced non-small cell lung cancer. *Journal of Clinical Oncology, 22(14_suppl),* 7279.
210. Witta, S. E., Jotte, R. M., Konduri, K., Neubauer, M. A., Spira, A. I. et al. (2012). Randomized phase II trial of erlotinib with and without entinostat in patients with advanced non-small-cell lung cancer who progressed on prior chemotherapy. *Journal of Clinical Oncology, 30(18),* 2248–2255.
211. Dasari, A., Gore, L., Messersmith, W. A., Diab, S., Jimeno, A. et al. (2010). A phase I safety and tolerability study of vorinostat (V) in combination with sorafenib (S) in patients with advanced solid tumors, with exploration of two tumor-type specific expanded cohorts at the recommended phase II dose (renal and non-small cell lung carcinoma). *Journal of Clinical Oncology, 28(15_suppl),* 2562.
212. Entezari, M., Ghanbarirad, M., Taheriazam, A., Sadrkhanloo, M., Zabolian, A. et al. (2022). Long non-coding RNAs and exosomal lncRNAs: Potential functions in lung cancer progression, drug resistance and tumor microenvironment remodeling. *Biomedicine & Pharmacotherapy, 150(1),* 112963. DOI 10.1016/j.biopha.2022.112963.
213. Chen, Y., Zitello, E., Guo, R., Deng, Y. (2021). The function of LncRNAs and their role in the prediction, diagnosis, and prognosis of lung cancer. *Clinical and Translational Medicine, 11(4),* e367. DOI 10.1002/ctm2.367.
214. Leonetti, A., Assaraf, Y. G., Veltsista, P. D., El Hassouni, B., Tiseo, M. et al. (2019). MicroRNAs as a drug resistance mechanism to targeted therapies in EGFR-mutated NSCLC: Current implications and future directions. *Drug Resistance Updates, 42(9),* 1–11. DOI 10.1016/j.drup.2018.11.002.
215. Yue, J., Lv, D., Wang, C., Li, L., Zhao, Q. et al. (2018). Epigenetic silencing of miR-483-3p promotes acquired gefitinib resistance and EMT in EGFR-mutant NSCLC by targeting integrin β3. *Oncogene, 37(31),* 4300–4312. DOI 10.1038/s41388-018-0276-2.
216. Shen, Y., Tang, D., Yao, R., Wang, M., Wang, Y. et al. (2013). microRNA expression profiles associated with survival, disease progression, and response to gefitinib in completely resected non-small-cell lung cancer with EGFR mutation. *Medical Oncology, 30(4),* 750. DOI 10.1007/s12032-013-0750-1.
217. Duru, N., Gernapudi, R., Zhang, Y., Yao, Y., Lo, P. K. et al. (2015). NRF2/miR-140 signaling confers radioprotection to human lung fibroblasts. *Cancer Letters, 369(1),* 184–191. DOI 10.1016/j.canlet.2015.08.011.
218. Hu, Q., Ma, H., Chen, H., Zhang, Z., Xue, Q. (2022). LncRNA in tumorigenesis of non-small-cell lung cancer: From bench to bedside. *Cell Death Discovery, 8(1),* 359. DOI 10.1038/s41420-022-01157-4.
219. Yang, R., Li, P., Zhang, G., Lu, C., Wang, H. et al. (2017). Long non-coding RNA XLOC_008466 functions as an oncogene in human non-small cell lung cancer by targeting miR-874. *Cellular Physiology and Biochemistry, 42(1),* 126–136. DOI 10.1159/000477121.
220. Liang, M., Wang, L., Cao, C., Song, S., Wu, F. (2020). LncRNA SNHG10 is downregulated in non-small cell lung cancer and predicts poor survival. *BMC Pulmonary Medicine, 20(1),* 273. DOI 10.1186/s12890-020-01281-w.

221. Hou, M., Wu, N., Yao, L. (2021). LncRNA CBR3-AS1 potentiates Wnt/β-catenin signaling to regulate lung adenocarcinoma cells proliferation, migration and invasion. *Cancer Cell International, 21(1),* 36. DOI 10.1186/s12935-020-01685-y.

222. Zhou, S. Z., Li, H., Wang, Z. W., Wang, M. H., Li, N. et al. (2020). LncRNA TSLNC8 synergizes with EGFR inhibitor osimertinib to inhibit lung cancer tumorigenesis by blocking the EGFR-STAT3 pathway. *Cell Cycle, 19(21),* 2776–2792. DOI 10.1080/15384101.2020.1820697.

223. Lei, Y., Guo, W., Chen, B., Chen, L., Gong, J. et al. (2018). Tumor-released lncRNA H19 promotes gefitinib resistance via packaging into exosomes in non-small cell lung cancer. *Oncology Reports, 40(6),* 3438–3446. DOI 10.3892/or.2018.6762.

224. Lei, B., Tian, Z., Fan, W., Ni, B. (2019). Circular RNA: A novel biomarker and therapeutic target for human cancers. *International Journal of Medical Sciences, 16(2),* 292–301. DOI 10.7150/ijms.28047.

225. Tan, S., Sun, D., Pu, W., Gou, Q., Guo, C. et al. (2018). Circular RNA F-circEA-2a derived from EML4-ALK fusion gene promotes cell migration and invasion in non-small cell lung cancer. *Molecular Cancer, 17(1),* 138. DOI 10.1186/s12943-018-0887-9.

226. Wang, C., Tan, S., Li, J., Liu, W. R., Peng, Y. et al. (2020). CircRNAs in lung cancer-biogenesis, function and clinical implication. *Cancer Letters, 492,* 106–115. DOI 10.1016/j.canlet.2020.08.013.

227. Liang, Z. Z., Guo, C., Zou, M. M., Meng, P., Zhang, T. T. (2020). circRNA-miRNA-mRNA regulatory network in human lung cancer: An update. *Cancer Cell International, 20(1),* 173. DOI 10.1186/s12935-020-01245-4.

228. Su, C., Han, Y., Zhang, H., Li, Y., Yi, L. et al. (2018). CiRS-7 targeting miR-7 modulates the progression of non-small cell lung cancer in a manner dependent on NF-κB signalling. *Journal of Cellular and Molecular Medicine, 22(6),* 3097–3107. DOI 10.1111/jcmm.13587.

229. Zhang, X., Yang, D., Wei, Y. (2018). Overexpressed CDR1as functions as an oncogene to promote the tumor progression via miR-7 in non-small-cell lung cancer. *OncoTargets and Therapy, 11,* 3979–3987. DOI 10.2147/OTT.

230. Zhou, Y., Zheng, X., Xu, B., Chen, L., Wang, Q. et al. (2019). Circular RNA hsa_circ_0004015 regulates the proliferation, invasion, and TKI drug resistance of non-small cell lung cancer by miR-1183/PDPK1 signaling pathway. *Biochemical and Biophysical Research Communications, 508(2),* 527–535. DOI 10.1016/j.bbrc.2018.11.157.

231. Li, J., Li, X., Ren, S., Chen, X., Zhang, Y. et al. (2014). miR-200c overexpression is associated with better efficacy of EGFR-TKIs in non-small cell lung cancer patients with EGFR wild-type. *Oncotarget, 5(17),* 7902–7916. DOI 10.18632/oncotarget.2302.

232. Hu, F. Y., Cao, X. N., Xu, Q. Z., Deng, Y., Lai, S. Y. et al. (2016). miR-124 modulates gefitinib resistance through SNAI2 and STAT3 in non-small cell lung cancer. *Journal of Huazhong University of Science and Technology, 36(6),* 839–845. DOI 10.1007/s11596-016-1672-x.

233. Liao, J., Lin, J., Lin, D., Zou, C., Kurata, J. et al. (2017). Down-regulation of miR-214 reverses erlotinib resistance in non-small-cell lung cancer through up-regulating LHX6 expression. *Scientific Reports, 7(1),* 781. DOI 10.1038/s41598-017-00901-6.

234. Ping, W., Gao, Y., Fan, X., Li, W., Deng, Y. et al. (2018). MiR-181a contributes gefitinib resistance in non-small cell lung cancer cells by targeting GAS7. *Biochemical and Biophysical Research Communications, 495(4),* 2482–2489. DOI 10.1016/j.bbrc.2017.12.096.

235. Yang, W., Qian, Y., Gao, K., Zheng, W., Wu, G. et al. (2021). LncRNA BRCAT54 inhibits the tumorigenesis of non-small cell lung cancer by binding to RPS9 to transcriptionally regulate JAK-STAT and calcium pathway genes. *Carcinogenesis, 42(1),* 80–92. DOI 10.1093/carcin/bgaa051.

236. Wan, Y., Yao, D., Fang, F., Wang, Y., Wu, G. et al. (2021). LncRNA WT1-AS downregulates lncRNA UCA1 to suppress non-small cell lung cancer and predicts poor survival. *BMC Cancer, 21(1),* 104. DOI 10.1186/s12885-020-07767-4.

237. Xu, Y., Lin, L., Lv, D., Yan, S., He, S. et al. (2021). LncRNA-LINC01089 inhibits lung adenocarcinoma cell proliferation and promotes apoptosis via sponging miR-543. *Tissue & Cell, 72(Suppl 1),* 101535. DOI 10.1016/j.tice.2021.101535.

238. Lu, W., Zhang, H., Niu, Y., Wu, Y., Sun, W. et al. (2017). Long non-coding RNA linc00673 regulated non-small cell lung cancer proliferation, migration, invasion and epithelial mesenchymal transition by sponging miR-150-5p. *Molecular Cancer, 16(1),* 118. DOI 10.1186/s12943-017-0685-9.

239. Hua, Q., Jin, M., Mi, B., Xu, F., Li, T. et al. (2019). LINC01123, a c-Myc-activated long non-coding RNA, promotes proliferation and aerobic glycolysis of non-small cell lung cancer through miR-199a-5p/c-Myc axis. *Journal of Hematology & Oncology, 12(1),* 91. DOI 10.1186/s13045-019-0773-y.

240. Fu, Y., Liu, L., Zhan, J., Zhan, H., Qiu, C. (2021). LncRNA GAS5 expression in non-small cell lung cancer tissues and its correlation with Ki67 and EGFR. *American Journal of Translational Research, 13(5),* 4900–4907.

241. Wan, L., Zhang, L., Fan, K., Cheng, Z. X., Sun, Q. C. et al. (2016). Circular RNA-ITCH suppresses lung cancer proliferation via inhibiting the Wnt/β-catenin pathway. *BioMed Research International, 2016(1),* 1579490. DOI 10.1155/2016/1579490.

242. Yao, J. T., Zhao, S. H., Liu, Q. P., Lv, M. Q., Zhou, D. X. et al. (2017). Over-expression of CircRNA_100876 in non-small cell lung cancer and its prognostic value. *Pathology, Research and Practice, 213(5),* 453–456. DOI 10.1016/j.prp.2017.02.011.

243. Humphreys, I. R., Pei, J., Baek, M., Krishnakumar, A., Anishchenko, I. et al. (2021). Computed structures of core eukaryotic protein complexes. *Science, 374(6573),* eabm4805. DOI 10.1126/science.abm4805.

244. Wang, C., Yang, C., Chen, Y. C., Ma, L., Huang, K. (2019). Rational design of hybrid peptides: A novel drug design approach. *Current Medical Science, 39(3),* 349–355. DOI 10.1007/s11596-019-2042-2.

245. Liu, X., Chen, Y., Li, Y., Petersen, R. B., Huang, K. (2019). Targeting mitosis exit: A brake for cancer cell proliferation. *Biochimica et Biophysica Acta Reviews on Cancer, 1871(1),* 179–191. DOI 10.1016/j.bbcan.2018.12.007.

246. Sun, L., Marmarelis, M. E., Langer, C. J. (2021). Systemic therapy for mutation-driven NSCLC. *Seminars in Radiation Oncology, 31(2),* 140–148. DOI 10.1016/j.semradonc.2020.11.011.

247. Tan, A. C., Tan, D. S. W. (2022). Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. *Journal of Clinical Oncology, 40(6),* 611–625. DOI 10.1200/JCO.21.01626.