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REVIEW

Recent Progress in Rare Oncogenic Drivers and Targeted Therapy For Non-Small Cell Lung Cancer

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Abstract: Non-small cell lung cancer (NSCLC) is frequently associated with oncogenic driver mutations, which play an important role in carcinogenesis and cancer progression. Targeting epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase rearrangements has become standard therapy for patients with these aberrations because of the greater improvement of survival, tolerance, and quality-of-life compared to chemotherapy. Clinical trials for emerging therapies that target other less common driver genes are generating mixed results. Here, we review the literature on rare drivers in NSCLC with frequencies lower than 5% (e.g., ROS1, RET, MET, BRAF, NTRK, HER2, NRG1, FGFR1, PIK3CA, DDR2, and EGFR exon 20 insertions). In summary, targeting rare oncogenic drivers in NSCLC has achieved some success. With the development of new inhibitors that target these rare drivers, the spectrum of targeted therapy has been expanded, although acquired resistance is still an unavoidable problem.

Keywords: non-small cell lung cancer, oncogenic driver, targeted therapy

Introduction

Lung cancer is the most common malignant disease with poor survival; the vast majority of cases are non-small cell lung cancer (NSCLC). The treatment strategy for NSCLC has been revolutionized by the discovery of molecular alterations that drive tumor initiation and progression. Epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and KRAS are the most frequent oncogenic drivers of NSCLC, and the targeting of EGFR mutations and *ALK* rearrangements has achieved great success. To date, the US Food and Drug Administration (FDA) has approved five EGFR tyrosine kinase inhibitors (TKIs) as the standard treatment for patients with activating EGFR mutations in NSCLC, including first-generation gefitinib and erlotinib, second-generation afatinib and dacomitinib, and third-generation osimertinib. There are also currently five FDA-approved inhibitors of *ALK* rearrangements, including first-generation crizotinib, second-generation ceritinib, alectinib, and brigatinib, and third-generation lorlatinib. The second- and third-generation inhibitors have exhibited enhanced activity against central nervous system (CNS) lesions and acquired resistance to crizotinib resulting from secondary ALK mutations. These achievements have led to clinical trials targeting less common driver genes, such as ROS1, RET, MET, BRAF, NTRK, HER2, NRG1, FGFR1, PIK3CA, DDR2, and EGFR exon 20 insertions (ins). In this review, we focus on these rare drivers and summarize their molecular biology, clinical features, targeted therapy, and acquired resistance.

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ROS1 Rearrangements

Human proto-oncogene ROS1, which is located on chromosome band 6q22.1, is also known as MCF3 or c-ros-1.[1,2] It encodes a receptor tyrosine kinase (RTK) that contains an extracellular or ectodomain, a single-pass transmembrane region with a hydrophobic stretch, and an intracellular carboxyl-terminal tyrosine kinase domain.[3] Although the exact mechanisms by which *ROS1* rearrangements promote carcinogenesis remain unclear, because most fusion partners of ROS1 lack dimerization domains,[4] *ROS1* rearrangements are believed to promote signal transduction programs, proliferation, and cell survival through the upregulation of SHP-1 and SHP-2 and activation of the PI3K/AKT/mTOR, JAK/STAT, and MAPK/ERK pathways[5–7] (Figure 1).

ROS1 fusion detection methods include fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), reverse transcription-polymerase chain reaction (RT-PCR), and next-generation sequencing (NGS). FISH is the most common method, but formal screening recommendations for ROS1 fusions have not been established.[4] *ROS1* rearrangements are found in 1 to 2% of NSCLC. Over 14 types of ROS1 fusion partner genes have been reported, including CD74, SLC34A2, SDC4, EZR, FIG, TPM3, LRIG3, KDELR2, CCDC6, MSN, TMEM106B, TPD52L, CLTC, and LIMA1, with the most frequent fusion partner being CD74 (40 to 45%).[4,8] Recent research found that patients with the CD74-ROS1 fusion were more susceptible to brain metastases and had lower objective response rates (ORR) to crizotinib than non-CD74-ROS1 patients, suggesting that the efficacy and prognosis of patients with advanced *ROS1*-rearranged NSCLC may be influenced by the type of ROS1 fusion partner.[9] ROS1 fusions rarely overlap with other driver mutations, such as EGFR, ALK, or KRAS.[10] ROS1 and ALK share a 49% amino acid sequence identity in the kinase domain and 77% identity in the adenosine triphosphate (ATP)-binding site,[11] suggesting that ALK-TKIs may also inhibit ROS1. Similar to ALK, patients with *ROS1*-rearranged NSCLC are often younger, Asian ethnicity, have a non-smoking or light-smoking history, and advanced-stage disease with adenocarcinoma histology.[12]

Crizotinib

Crizotinib is a drug that targets ALK, ROS1, and MET, which has been used successfully to treat patients with advanced ALK-rearranged NSCLC.[13,14] In a phase I study (PROFILE 1001) consisting of 50 patients with *ROS1*-rearranged advanced NSCLC, the ORR for crizotinib was
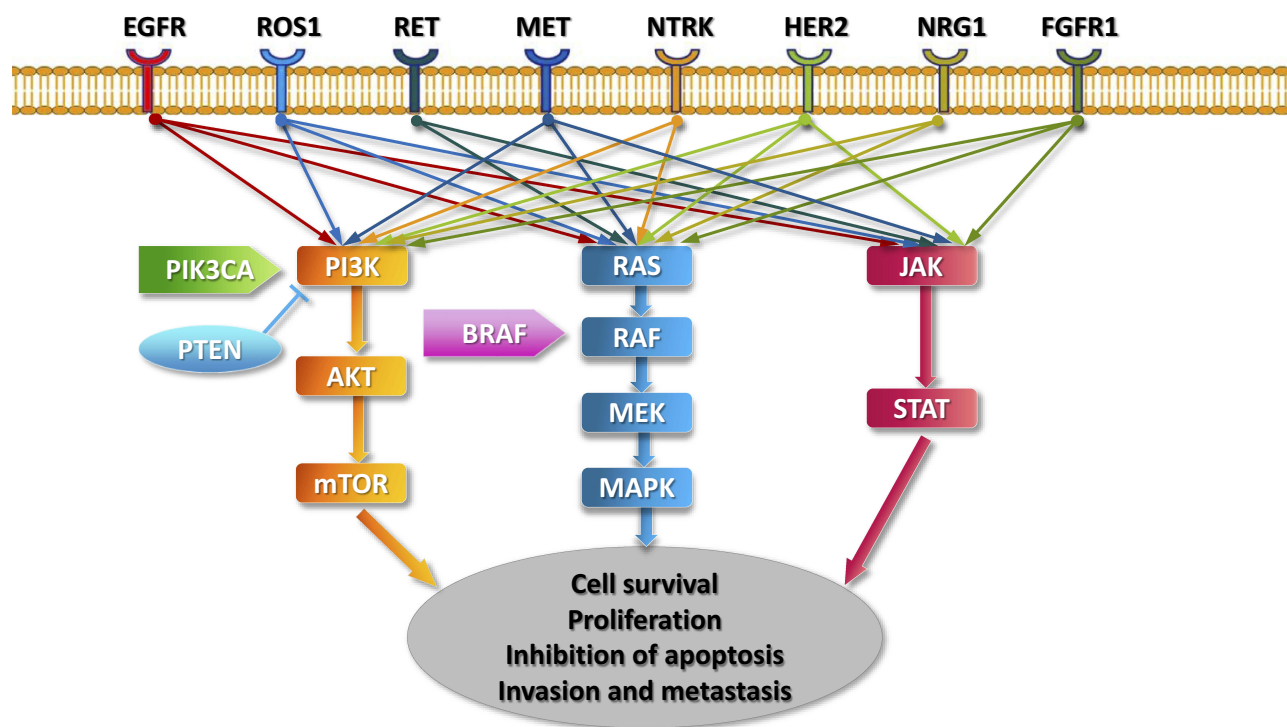

Figure 1 Key signaling pathways of oncogenic drivers in NSCLC.

72% with three complete responses and 33 partial responses, the median progression-free survival (PFS) was 19.2 months, and the safety profile of crizotinib was similar to that of patients with *ALK*-rearranged NSCLC[11] (Table 1). Based on the study, crizotinib became the first targeted agent approved by the FDA for the treatment of advanced *ROS1*-rearranged NSCLC in March 2016. Crizotinib also demonstrated high response rates (71% to 80%; median PFS 9 to 10 months) in *ROS1*-rearranged NSCLC in two additional studies.[15,16] Since 2017, National Comprehensive Cancer Network (NCCN) guidelines recommend that crizotinib be used for patients with known *ROS1* rearrangements (grade 2A recommendation).[17]

Similar to ALK or EGFR inhibition, acquired resistance is an important issue for the inhibition of ROS1. Mechanisms of acquired crizotinib resistance include acquired secondary mutations in the ROS1 kinase domain, bypassing signaling activation, and phenotypic changes. Mutations within the ROS1 kinase domain occur in 50 to 60% of crizotinib-resistant tumors.[18] The ROS1 G2032R mutation, which is analogous to ALK G1202R, has been the most frequent mutation identified.[18–20] Additional mutations reported in clinical samples include D2033N (analogous to ALK D1203N), S1986Y/F (analogous to ALK C1156Y),[18,21] L2026M (analogous to ALK L1196M), and L1951R (no known analogous mutation in ALK).[22]

Ceritinib

Ceritinib is a potent and selective ALK inhibitor that also inhibits ROS1. In a phase II study (NCT01964157), 32 patients with *ROS1*-rearranged advanced NSCLC were treated with ceritinib, the ORR was 62% and disease control rate (DCR) was 81%. The median PFS in this study was 9.3 months for all patients and 19.3 months for crizotinib-naïve patients with a median OS of 24 months. In eight patients with brain metastases, the intracranial ORR was 25% with an intracranial DCR of 63%.[23] Based on the efficacy and safety demonstrated in this study, ceritinib became the second targeted agent recommended by the NCCN Guidelines for the treatment of advanced *ROS1*-rearranged NSCLC since November 2017. However, the toxicities of ceritinib should be taken into consideration due to the higher frequency of adverse events, such as diarrhea, nausea, anorexia, and vomiting compared to crizotinib.[10]

Entrectinib (RXDX-101)

Entrectinib is a multikinase inhibitor that targets ROS1, ALK, and tropomyosin receptor kinase (TRK) rearrangements and can effectively penetrate the blood-brain barrier.[24,25] An integrated analysis of three studies (the phase II STARTRK-2 trial, phase I STARTRK-1 study, and the phase I ALKA-372-001 trial) for entrectinib in *ROS1*-positive NSCLC was presented at the 2018 World Conference on Lung Cancer (WCLC). For this analysis, 53 *ROS1*-rearranged and ROS1-inhibitor-naive NSCLC patients were evaluated, and the ORR was 77.4%, the intracranial ORR was 73.9%, the median duration of response (DOR) was 24.6 months, and the median PFS was 19.0 months (without CNS metastases: 26.3 months; with CNS metastases: 13.6 months).[26] Early research found that entrectinib did not show activity against the ROS1 resistance mutations L2026M, G2032R, and D2033N.[24,25] Based on these results, entrectinib has recently been recommended by the NCCN Guidelines for the first-line treatment of advanced *ROS1*-rearranged NSCLC.[27] The global phase II STARTRK-2 trial (NCT02568267) is still ongoing.

Lorlatinib

Second-line TKIs are being developed, such as lorlatinib, which was developed to target crizotinib-resistant *ALK*-rearranged NSCLC. It has in vitro activity against several crizotinib-resistant mutations, including L2026M,[28,29] S1986Y/F,[28] and D2033N.[21] In a phase I trial for *ALK*- and *ROS1*-rearranged NSCLC, the 12 patients with *ROS1*-rearranged lung adenocarcinomas had an ORR of 50% with a median PFS of seven months.[30] In a phase II trial of *ROS1*-positive patients, 70% of which were crizotinib-resistant, lorlatinib produced an overall ORR of 36.2%, intracranial ORR of 56%, and a median PFS of 9.6 months.[31] Thus, lorlatinib has been recommended by the NCCN Guidelines for the treatment of advanced *ROS1*-rearranged NSCLC that progressed after crizotinib, entrectinib or ceritinib.[27]

DS-6051b

DS-6051b is an oral, small molecule TKI with high affinity for ROS1 and NTRK kinases. In a phase I study (NCT02675491) evaluating DS-6051b in 15 Japanese patients with *ROS1*-rearranged NSCLCs, the ORR was 58.3% in patients with assessable target lesions and 66.7% in crizotinib-naïve patients, and the DCR was 100%.[32] Another phase I/Ib study (NCT02279433) of DS-6051b in advanced solid tumors is ongoing.

Repotrectinib (TPX-0005)

Repotrectinib (TPX-0005) is a potent ALK/ROS1/TRK inhibitor that demonstrated encouraging clinical activity

Table 1 Clinical Trials for the Treatment of Advanced NSCLC with Targetable Oncogenic Drivers and Targeted Therapies Recommended by NCCN, or Approved by FDA or EMA

Targetable Driver genes	Incidence	Targeted Agent	Clinical Trials	Phase	Patients Included	Results	Approved or Recommended by
ROS1 rearrangements	1–2%	Crizotinib[11]	PROFILE 1001 (NCT00585195)	I	ROS1-rearranged NSCLC	n=50, ORR 72%, mPFS 19.2 mo	NCCN, FDA, EMA
		Ceritinib[23]	NCT01964157	II	ROS1-rearranged NSCLC	n=32, ORR 62%, DCR 81%, mPFS 9.3 mo for all pts, 19.3 mo for crizotinib-naïve pts	NCCN
		Entrectinib (RXDX-101)[26]	ALKA-372-001 (EudraCT 2012–0001), STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267)	I/II	ROS1-rearranged NSCLC	n=53, ORR 77.4% (intracranial ORR, 73.9%), mDOR 24.6 mo, mPFS 19.0 mo (without CNS metastases: 26.3 mo; with CNS metastases: 13.6 mo)	NCCN, FDA
		Lorlatinib[31]	NCT01970865	II	ROS1-rearranged NSCLC	n=47, ORR 36.2%, mPFS 9.6 mo	NCCN
		DS-6051b[32]	NCT02675491	I	Advanced solid malignant tumors harboring either ROS1 or NTRK fusion.	n=15, ORR 58.3% in pts with target lesions, 66.7% in crizotinib-naïve pts, DCR 100%.	
		DS-6051b	NCT02279433	I/Ib	Solid tumors harboring ROS1 or NTRK1, NTRK2, or NTRK3 rearrangements	Ongoing	
		Repotrectinib (TPX-0005)[33]	TRIDENT-1 (NCT03093116)	I/II	Solid malignancies harboring ALK, ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangements	n=11, ORR 82% for TKI-naive pts, n=18, ORR 39% for pts pretreated with one TKI.	
RET rearrangements	1–2%	Vandetanib[48]	NCT01823068	II	RET-rearranged NSCLC	n=18, ORR 18%, mPFS 4.5 mo, mOS 11.6 mo	NCCN*
		Vandetanib[46]	UMIN000010095	II	RET-rearranged NSCLC	n=19, ORR 53%, mPFS 4.7 mo, mOS 11.1 mo	NCCN*
		Cabozantinib[45]	NCT01639508	II	RET-rearranged NSCLC	n=26, ORR 28%, mPFS 5.5 mo, mOS 9.9 mo	NCCN*
		Lenvatinib[47]	NCT01877083	II	RET-rearranged NSCLC	n=25, ORR 16%, mPFS 7.3 mo	
		Alectinib	NCT03131206	I/II	RET-rearranged NSCLC	Ongoing	
		Selpercatinib (LOXO-292)[51]	LIBRETTO-001 (NCT03157128)	I/II	RET-rearranged NSCLC	n=30, ORR 77%	FDA

	Drug	Trial	Phase	Indication	Results	Approval
	Selpercatinib (LOXO-292)[52]	LIBRETTO-001 (NCT03157128)	I/II	RET-rearranged NSCLC	n=105, ORR 68%, CNS ORR 91%, mDOR 20.3 mo, mPFS 18.4 mo for pre-treated pts. n=34, ORR 85%, mDOR, mPFS were not reached for treatment-naïve pts.	FDA
	BLU-667[54]	NCT03037385	I	RET-rearranged NSCLC	n=11, ORR 45%	
MET exon 14 skipping mutation / 3%	Crizotinib[62]	PROFILE 1001	I	MET exon 14 skipping mutant NSCLC	n=65, ORR 32%, mPFS 7.3 mo, mOS 20.5 mo	NCCN*, FDA
	Capmatinib (INC280)[67]	GEOMETRY mono-1 (NCT02414139)	II	MET exon 14 mutant or MET amplified NSCLC	n=69, ORR 40.6%, mPFS 5.4 mo for pretreated pts. n=28, ORR 67.9%, mPFS 9.7 mo for treatment-naïve pts	FDA
	Tepotinib[68]	NCT02864992	II	MET exon 14 skipping mutant NSCLC	n=41, ORR 35%	FDA
	Savolitinib[69]	NCT02897479	II	MET exon 14 skipping mutant PSC or other types of NSCLC	n=31, ORR 51.6%, mPFS was not reached.	
MET amplification / 1–5%	Tepotinib + gefitinib[70]	NCT01982955	Ib/II	MET amplified NSCLC	n=12, ORR 66.7%, mPFS 21.2 mo	
	Tepotinib + gefitinib[70]	NCT01982955	Ib/II	High MET-expressing NSCLC	n=19, ORR 33.3%, mPFS 8.3 mo	
	Savolitinib + osimertinib[71]	TATTON (NCT02143466)	Ib	EGFR-mutant NSCLC that had developed resistance to first- or second-generation EGFR-TKI through MET gene amplification	n=46, ORR 52%, mDOR 7.1 mo	
	Savolitinib + osimertinib[71]	TATTON (NCT02143466)	Ib	EGFR-mutant NSCLC that had developed resistance to third-generation EGFR-TKI through MET gene amplification	n=48, ORR 28%, mDOR 9.7 mo	
	Savolitinib + osimertinib	SAVANNAH (NCT03778229)	II	EGFRm+ MET+, NSCLC progressed following osimertinib treatment	Ongoing	
BRAF mutation / 2–4%	Dabrafenib[77]	NCT01336634	II	Treated and untreated BRAFV600E + NSCLC	n=78, ORR 33%, mPFS 5.5 mo, mOS of 12.7 mo	

(Continued)

Table I (Continued).

Targetable Driver genes	Incidence	Targeted Agent	Clinical Trials	Phase	Patients Included	Results	Approved or Recommended by
		Dabrafenib + trametinib[78]	NCT01336634	II	Untreated BRAFV600E+ NSCLC	n=36, ORR 64%, mPFS 10.9 mo, mOS 24.6 mo	NCCN, FDA, EMA
		Dabrafenib + trametinib[79]	NCT01336634	II	Chemotherapy-pretreated BRAFV600E+ NSCLC	n=57, ORR 63%, mPFS 10.2 mo, mOS 18.2 mo	NCCN, FDA, EMA
NTRK rearrangements	3–4%	Larotrectinib (LOXO-101)[92]	NCT02576431	II	NTRK fusion-positive solid tumors	n=55, ORR 75% regardless of tumor type, mDOR and mPFS were not reached.	NCCN, FDA, EMA
		LOXO-195	NCT03215511	I/II	NTRK fusion cancers treated with a prior TRK inhibitor	Ongoing	
		Entrectinib (RXDX-101)[96]	ALKA-372-001 (EudraCT 2012–0001), STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267)	I/II	NTRK fusion-positive solid tumors	n=54, ORR 57.4%, mPFS 11.2 mo, mOS 20.9 mo	NCCN, FDA, EMA
HER2 mutation	2–4%	Afatinib[102]	A retrospective international multicentre study		HER2-mutant lung adenocarcinomas	n=27, mTTF 3 mo, mDOR 6 mo, OS 23 mo	
		Afatinib[103]	Supported by Boehringer Ingelheim. No grant number is applicable.		Heavily pretreated exon 20 ins NSCLC	n=10, mTTF 9.6 mo, ORR 33%, DCR 100%	
		Trastuzumab in combination with chemotherapy or ado-trastuzumab emtansine (T-DM1)[101]	A retrospective study		HER2-mutant NSCLC	n=58, ORR 50.9%, mPFS 4.8 mo, mOS 13.3 mo.	
		Neratinib, lapatinib or afatinib[101]	A retrospective study		HER2-mutant NSCLC	n=29, ORR 7.4%, mPFS 3.4 mo, mOS 6.5 mo.	
		Ado-trastuzumab emtansine (T-DM1)[104]	NCT02675829	II	HER2-mutant NSCLC	n=18, ORR 44%, mPFS 5 mo	NCCN*
		Poziotinib[106]	NCT03066206	II	HER2 exon 20 ins NSCLC	n=12, mPFS 5.1 mo	
		Trastuzumab deruxtecan (DS-8201a)[107]	NCT03505710	II	HER2-overexpressing or mutated, unresectable, and/or metastatic NSCLC	Ongoing	

EGFR exon 20 ins	1.80%	Poziotinib[106]	NCT03066206	II	EGFR or HER2 exon 20 ins NSCLC	n=44, ORR 55%, mPFS 5.5 mo
		Poziotinib[114]	NCT03318939	II	EGFR or HER2 exon 20 ins NSCLC	n=30, ORR 40%, mDOR 6.6 mo
		TAK-788[115]	NCT02716116	I/II	EGFR exon 20 insertion NSCLC	n=28, ORR 43%, mPFS 7.3 mo
FGFR1 amplification	20% squamous-NSCLC	Nintedanib[133]	NCT01948141	II	FGFR1-amplified pretreated squamous-NSCLC	n=6, 6-month PFS was observed within the entire 6 pts
		Dovitinib	NCT01861197	II	FGFR1-amplified pretreated squamous-NSCLC	Ongoing
		BGJ398[134]	NCT01004224	I	FGFR1-amplified squamous-NSCLC	n=36, ORR 11.1%, DCR 50%
		Erdafitinib (JNJ-42756493)	NCT02699606	IIa	Asian participants with various malignant tumors, including NSCLC	Ongoing
PIK3CA mutation or amplification	2–5%	Pictilisib (GDC-0941) + cytotoxic chemotherapy	NCT00974584	Ib	Advanced NSCLC	Completed, results have not yet been released
		Pictilisib (GDC-0941) + cytotoxic chemotherapy	NCT01493843	II	Previously untreated NSCLC	Completed, results have not yet been released
		Pilaralisib (SAR245408, XL147) + carboplatin/paclitaxel	NCT00756847	I	Adults with solid tumors	Completed, results have not yet been released
DDR2 mutation	4%	Dasatinib[152]	NCT01514864	II	Advanced cancers harboring DDR2 mutation or inactivating BRAF mutation	Terminated due to lack of efficacy
		Dasatinib + crizotinib	NCT01744652	II	Advanced cancer	Ongoing

Note: *Available targeted agents with activity against corresponding driver event in lung cancer.
Abbreviations: NSCLC, non-small cell lung cancer; mPFS, median progression-free survival; ORR, objective response rates; mo, months; pts, patients; mDOR, median duration of response; mTTF, median time-to-treatment failure; CNS, central nervous system; NCCN, National Comprehensive Cancer Network; FDA, the US Food and Drug Administration; EMA, European Medicines Agency; ins, insertion.

in patients with ROS1 fusion-positive NSCLC and in patients with secondary mutations resistant to prior TKI. In an ongoing phase I/II trial (TRIDENT-1, NCT03093116), repotrectinib showed an ORR of 82% in 11 TKI-naive *ROS1*-positive NSCLC patients, and an ORR of 39% in 18 patients pretreated with only one prior TKI. Tumor regression occurred in all five patients with G2032R mutation resistant to prior crizotinib treatment.[33]

RET Rearrangements

The RET (rearranged during transfection) proto-oncogene is located on chromosome 10q11.2, where it encodes a RTK.[34] RET consists of an extracellular domain, a transmembrane domain, and an intracellular tyrosine kinase.[35] In NSCLC, at least 12 different gene partners have been described for RET, including KIF5B, CCDC6, NCOA4, MYO5C, EPHA5, TRIM33, CLIP1, ERC1, PICALM, FRMD4A, RUFY2, TRIM24[36] with the most frequent fusion partner being KIF5B (72%).[37] All RET fusions preserve the tyrosine kinase activity, and each RET partner protein contains a coiled-coil domain, which can promote ligand-independent dimerization and constitutive activation of RET.[38] Thus, activation of downstream pathways (e.g., JAK/STAT3 and RAS/RAF/MEK/ERK) leads to cellular proliferation, migration, and differentiation.[39]

RET rearrangements can be detected by FISH, NGS, and RT-PCR, but cannot be adequately detected by IHC.[40] At present, there is no gold-standard method for the identification of *RET* rearrangements. *RET* rearrangements have been observed in approximately 1 to 2% of NSCLC.[41] Similar to *ROS-1* rearrangements, *RET* rearrangements in NSCLC are more commonly found among non-smokers or former light smokers less than 60 years of age with adenocarcinoma histology, early lymph node metastases, and advanced disease.[41] The majority of patients with *RET* rearrangements have stage IV disease at the time of diagnosis, suggesting that *RET*-rearranged NSCLC may have a high metastatic potential.[37] In NSCLC, *RET* rearrangements are mutually exclusive with other driver mutations, such as ALK or ROS1 rearrangements or EGFR mutations,[39,42,43] suggesting that *RET* rearrangements are independent oncogenic drivers in this disease.

Multikinase RET Inhibitors

Several multikinase inhibitors with nonselective RET inhibitory activity are available for patients with *RET*-altered cancers (e.g., vandetanib, cabozantinib, lenvatinib, alectinib, and sunitinib) with response rates ranging from 16% to 53%, and median PFS from 4.5 to 7.3 months.[44–48] The use of multikinase RET inhibitors has often been associated with a high rate of toxicity due to their activity against VEGFR kinases or EGFR, and their efficacy has been limited.[44] Although cabozantinib and vandetanib have been recommended for use against *RET*-rearranged NSCLC by the NCCN guideline outside the context of a clinical trial, no approved standard therapies have been designed to target RET. Novel and potent inhibitors are being developed to selectively target the RET kinase.

Some resistance mechanisms of *RET* rearrangements are being discovered. Different fusion partners seem to have different therapeutic responses, and KIF5B-RET is associated with lower ORR. Other potential resistance mechanisms include missense mutations in RET, activation of downstream pathway molecules (e.g., ERK, AKT), and the amplification of MDM2.[49]

Selpercatinib (LOXO-292)

Selpercatinib is a novel, highly selective, ATP-competitive small molecule RET inhibitor that has significant CNS penetration, and a low potential for drug interactions.[50] It was approved by the FDA for the treatment of advanced *RET*-rearranged NSCLC and medullary thyroid cancers with a breakthrough therapy designation in September 2018. This approval was based on the data from a phase I/II trial (LIBRETTO-001, NCT03157128) reported at the 2018 ASCO meeting, in 30 response-evaluable patients with RET fusion-positive NSCLC, tumor regression occurred regardless of the RET fusion partner, with an ORR of 77% and another 13% of the patients experiencing stable disease.[51] The updated results of this study have been presented at the 2019 WCLC. In 105 previously treated patients, selpercatinib demonstrated an overall ORR of 68% and a CNS ORR of 91%. The median PFS and DOR was 18.4 months and 20.3 months, respectively. In 34 treatment-naive patients, the ORR was 85%, and the median DOR and PFS were not reached.[52]

BLU-667

BLU-667 (NCT03037385) is another highly potent and selective small-molecule RET inhibitor that has increased potency and decreased toxicity against RET alterations compared to multikinase inhibitors.[53] The preliminary analysis of a phase 1 BLU-667 clinical trial for *RET*-altered NSCLC, medullary thyroid cancers, and other advanced solid tumors was presented at the 2018 American

Association for Cancer Research (AACR) annual meeting. An ORR of 45% was observed among the 11 evaluable NSCLC patients, including heavily pretreated patients, who had received prior RET-targeting agents.[54]

MET Activation

MET (the mesenchymal-to-epithelial transition) is a receptor kinase that activates tyrosine kinases by binding the ligand hepatocyte growth factor (HGF) and inducing MET dimerization and autophosphorylation.[55] These effects activate downstream signaling pathways, including RAS/RAF/MAPK, PI3K/AKT/mTOR, WNT/β-catenin, and STAT, that play important roles in cell growth, apoptosis, motility, and invasiveness.[56,57] In NSCLC, several mechanisms of MET activation have been identified, including mutation, rearrangement or amplification of the MET gene, overexpression of MET or HGF protein.[55,58]

MET Exon 14 Skipping Mutation

MET exon 14 skipping mutations comprise approximately 3% of NSCLC cases and are more commonly found in females, elderly patients, non-smokers, pulmonary sarcomatoid carcinoma (PSC), and are associated with poor prognosis.[59,60] *MET* exon 14 skipping mutations are mutually exclusive with other known driver genes (e.g., EGFR, KRAS, and HER2 mutations or ALK, ROS1, and RET rearrangements), suggesting that they are independent carcinogenic drivers.[61] Clinical trials using MET-targeted TKIs (e.g., cabozantinib, capmatinib, crizotinib, merestinib, savolitinib, and tepotinib) for NSCLC patients with *MET* exon 14 altered-NSCLC are currently ongoing.

Crizotinib

Crizotinib has been approved for the treatment of *ALK*-positive or *ROS1*-positive lung cancers and has significant antineoplastic activity in patients with MET alteration.[61] In the PROFILE 1001 clinical trial, a cohort of 65 patients with *MET* exon 14-altered NSCLC were treated with crizotinib and achieved an ORR of 32%, a median PFS of 7.3 months, and a median OS of 20.5 months.[62] Secondary MET tyrosine kinase domain mutations (e.g., MET D1228 and Y1230) acquired after progression during crizotinib therapy are considered as the emerging mechanisms of resistance to MET inhibition.[63–65] Subsequent studies found that these mutations confer resistance to type I MET inhibitors which preferentially bind the active conformation of MET (e.g., crizotinib, savolitinib, and capmatinib) through impaired drug binding, while sensitivity to

type II inhibitors, which bind the inactive conformation (e.g., glesatinib and cabozantinib), is maintained.[66]

Capmatinib (INC280)

Another MET-selective agent, capmatinib, has demonstrated a clinically meaningful response rate and a manageable toxicity profile in patients with advanced-stage NSCLC that contain *MET* exon 14 mutations in an ongoing study (GEOMETRY mono-1, NCT02414139). Results demonstrated an ORR and median PFS of 40.6% and 5.4 months, respectively, among 69 pretreated patients and 67.9% and 9.7 months, respectively, for 28 treatment-naïve patients. Preliminary activity in patients with brain metastases was also observed with an intracranial ORR of 54% in 13 evaluable patients.[67] Based on these results, the FDA granted breakthrough therapy designation to capmatinib (INC280) as a first-line treatment for patients with metastatic *MET* exon14 skipping-mutated NSCLC in September 2019.

Tepotinib

Tepotinib, a MET-selective oral inhibitor, has demonstrated promising antitumor activity in patients with advanced NSCLC that harbor a *MET* exon 14 skipping mutation and a favorable safety profile with an ORR of 35% in 41 patients in an ongoing phase II study (VISION, NCT02864992).[68] Tepotinib was approved by the FDA with a breakthrough therapy designation in September 2019, for the treatment of patients with metastatic NSCLC harboring *MET* exon 14 skipping alterations who progressed following platinum-based chemotherapy.

Savolitinib

Savolitinib (AZD6094, HMPL-504, volitinib) is a potent and highly selective inhibitor of MET tyrosine kinase. The preliminary data from a phase II study of savolitinib in *MET* exon 14 skipping mutant PSC or other types of NSCLC (NCT02897479) were reported at the 2019 AACR Annual Meeting. Savolitinib showed encouraging antitumor activity and an acceptable safety profile. In 31 evaluable patients, the ORR was 51.6%, and the median PFS was not reached.[69]

MET Amplification

MET gene amplification occurs in 1 to 5% of treatment-naïve NSCLC,[56] but more often mediates bypass pathway activation in patients with acquired resistance to EGFR-TKIs. The combinations of EGFR- and MET-targeted therapeutics may be effective against these conditions.

Tepotinib + Gefitinib

A phase II trial showed that the combination of tepotinib and gefitinib improved the PFS and OS versus chemotherapy in patients with *MET*-amplified *EGFR*-mutant NSCLC that was resistant to prior EGFR-TKI therapy. The combination of tepotinib and gefitinib in *MET* amplification subgroups had an ORR of 66.7% and a median PFS of 21.2 months whereas chemotherapy had an ORR of 42.9% and a median PFS of 4.2 months. This combination also had an ORR of 68.4% and a median PFS of 8.3 months for patients with high MET-expressing tumors compared to 33.3% and 4.4 months with chemotherapy, respectively.[70]

Savolitinib + Osimertinib

The TATTON trial is a phase Ib clinical trial that is investigating the clinical response of adding MET inhibitor savolitinib to osimertinib in patients with *EGFR*-mutant NSCLC that developed resistance to prior EGFR-targeted therapies through *MET* gene amplification. The data were presented at the 2019 AACR Annual Meeting. This treatment regimen caused an ORR of 52% and a median DOR of 7.1 months in 46 patients, who were previously treated with a first- or second-generation EGFR-TKI. The ORR was 28%, and the median DOR was 9.7 months in 48 patients who received a prior third-generation EGFR-TKI.[71] A phase II SAVANNAH trial will further explore the combination in patients with *MET*-positive disease that has progressed on osimertinib.

BRAF Mutation

The B-Raf proto-oncoprotein (BRAF) is a serine/threonine kinase that regulates cell proliferation, differentiation, angiogenesis, and cell death. It functions downstream of RAS and signals through the MAPK/ERK pathway.[72] *BRAF* mutations appear in approximately 2 to 4% of NSCLC and are more commonly found in current or former smokers and female patients. V600E is the most common mutation and accounts for 1 to 2% of lung adenocarcinomas and roughly 50% of *BRAF*-mutant NSCLC. Compared with non-V600E genotypes, V600E is associated with more aggressive tumor histology and a poorer prognosis.[73,74] BRAF mutations are also commonly found in melanoma with a prevalence of 50%, and V600E is the most common mutation. Targeting BRAF has made some progress in the treatment of melanoma. Single-agent BRAF inhibitors (vemurafenib, dabrafenib) and the combination of dabrafenib and the mitogen-activated protein kinase (MEK) inhibitor, trametinib, have already been approved by the FDA for metastatic *BRAF* V600E-mutant melanoma and are being explored for BRAF-mutated NSCLC.[75]

A retrospective study EURAF evaluated the efficacy of different BRAF inhibitors, including vemurafenib, dabrafenib, and sorafenib, against advanced NSCLC harboring *BRAF* mutations. The PFS and median OS for BRAF inhibition therapy were five months and 10.2 months, respectively.[76] In chemotherapy-pretreated patients with NSCLC harboring *BRAF* V600E, the combination of dabrafenib and trametinib had an ORR of 63%, median PFS of 9.7 months, and median OS of 18.2 months. In treatment-naïve *BRAF* V600E-mutant metastatic NSCLC, this combination showed an ORR of 64%, median PFS of 10.9 months, and median OS of 24.6 months compared to an ORR of 33%, median PFS of 5.5 months, and median OS of 12.7 months for dabrafenib monotherapy.[77–79] Based on these results, the combination of dabrafenib and trametinib was approved in June 2017 by the regulatory authorities of both the US and European Union for treatment of advanced NSCLC harboring the *BRAF* V600E mutation regardless of the previous therapy.[80] Belvarafenib, a pan-RAF kinase inhibitor, was well-tolerated and exhibited antitumor activity in patients with advanced solid tumors harboring RAS or RAF mutations, and further investigation of its combination with the MEK inhibitor cobimetinib is ongoing (NCT02405065, NCT03118817).[81]

Several possible secondary resistance mechanisms to BRAF inhibitors have been proposed, including reactivation of ERK signaling through the MAPK pathway, bypassing of the MAPK pathway via the activation of alternative signaling pathways and other uncharacterized mechanisms.[82] The secondary resistance mechanism to the dual inhibition is more complex and requires further investigation.

NTRK Rearrangements

The neurotrophic tropomyosin receptor kinase (*NTRK*) genes (*NTRK1*, *NTRK2*, and *NTRK3*) encode three TRK proteins (TRKA, TRKB, and TRKC), which play an important role in the cell growth, differentiation, and apoptosis of peripheral and central nervous system neurons.[83] They activate downstream PI3K/AKT/mTOR, RAS/RAF/MAPK, PLC-γ, and protein kinase C pathways to control cell cycle progression, proliferation, apoptosis, and survival.[84–87] *NTRK1* and *NTRK2* rearrangements occur in 3 to 4% NSCLC,[88,89] and CD74, MPRIP, SQSTM1, TRIM24 are their known fusion partners.[90]

The clinical and pathologic features of patients with *NTRK1* and *NTRK2* rearrangements are not well characterized.

Larotrectinib (LOXO-101)

Larotrectinib (LOXO-101) is a highly selective pan-TRK inhibitor.[91] In an ongoing study of 55 patients with a variety of *NTRK* fusion-positive cancers, the ORR is 75% regardless of tumor type.[92] The results for four NSCLC patients enrolled in this study were reported at the 2018 WCLC. At the time of analysis, three of the four patients had ongoing responses to the drug (ranging from 5.7 to 12 months) whereas one patient had stable disease that finally progressed after 300 days of treatment.[93] The success of this trial led to FDA approval of larotrectinib for adult and pediatric patients with solid tumors harboring *NTRK* gene fusions in May 2018[94] Three different categories of mutations were observed after larotrectinib progression and may represent resistance mechanisms, including substitutions in the solvent front (NTRK1 p. G595R, NTRK3 p.G623R), the gatekeeper position (NTRK1 p.F589L), and the xDFG position (NTRK1 p. G667S, NTRK3 p.G696A).[92]

LOXO-195

LOXO-195 is a second-generation TRK-selective inhibitor that was developed to overcome *NTRK1* p.G595R-mediated resistance.[95] It has been used in two patients with *NTRK* fusion-positive cancer (colon and infantile fibrosarcoma) that progressed after larotrectinib treatment. Both patients achieved objective responses from LOXO-195 therapy.[95] Furthermore, a multicenter phase 1/2 clinical trial of LOXO-195 in patients with solid tumors harboring *NTRK* fusion is now underway (NCT03215511).

Entrectinib (RXDX-101)

The multi-kinase inhibitor entrectinib also showed anti-NTRK activity. The integrated analysis of STARTRK-1, STARTRK-2, and ALKA-372-001 trials we mentioned in ROS1 rearrangements also reported the efficacy of entrectinib in *NTRK* fusion-positive solid tumors. In 54 patients, it showed an ORR of 57.4%, a median PFS of 11.2 months, and a median OS of 20.9 months.[96] It was recommended by the NCCN Guidelines for the treatment of advanced *NTRK* fusion-positive NSCLC, and approved by FDA with breakthrough therapy designation.[27]

HER2 Mutation

As a membrane-bound tyrosine kinase in the ERBB family, human epidermal growth factor receptor 2 (HER2 or ERBB2) differs from EGFR (ERBB1) due to its lack of endogenous ligand. HER2 activates signal transduction pathways, including PI3K, MAPK, and JAK/STAT, through heterodimerization with other members of the ERBB family, which promotes cell proliferation and survival.[97] In NSCLC, *HER2* amplification is not considered to be oncogenic driver mutation, but one of the secondary mechanisms of resistance to EGFR-TKIs.[98] *HER2* mutation is regarded as potential drivers of oncogenesis which have been identified in approximately 2 to 4% of NSCLC and are associated with adenocarcinoma histology, female gender, Asian ethnicity, and never-smoked status, and the YVMA 776–779 ins in exon 20 is the most frequent *HER2* mutation.[99]

HER2-targeted therapies have had great success against breast cancer, including trastuzumab, pertuzumab, ado-trastuzumab emtansine (T-DM1), and lapatinib, which have been approved by the FDA for *HER2*-positive breast cancer.[100] However, currently available targeted drugs have limited activity in *HER2*-mutant NSCLC, and there are no HER2-targeted drugs approved for NSCLC.[101] A retrospective international multicenter study analyzed 27 patients with stage IV or recurrent *HER2*-mutant lung adenocarcinoma treated with afatinib and found a median time-to-treatment failure (TTF) of three months, and a median DOR of six months.[102] The responses appeared to be better in the exon 20 ins subgroups. A recent study of afatinib in heavily pretreated NSCLC patients showed a median TTF of 9.6 months, an ORR of 33%, and a DCR of 100% among ten patients with *HER2* exon 20 ins.[103] In a retrospective study of 101 NSCLC patients with *HER2* mutations, for 29 patients who received neratinib, lapatinib or afatinib, the ORR was 7.4%, and median PFS was 3.4 months; for 58 patients who received T-DM1 alone or trastuzumab in combination with chemotherapy, the ORR was 50.9%, and median PFS was 4.8 months.[101] A phase II basket trial assessed the activity of T-DM1 in 18 *HER2*-mutant NSCLC patients and showed an ORR of 44% with a median PFS of 5 months.[104] Poziotinib showed promising preclinical and early clinical activity in NSCLC patients with *HER2* or *EGFR* exon 20 ins,[105] in an ongoing phase II study (NCT03066206), initial responses of 50% and a median PFS of 5.1 months were observed in 12 evaluable

advanced *HER2* exon 20 ins NSCLC patients.[106] An ongoing phase I study of another novel HER2-targeted drug, trastuzumab deruxtecan (DS-8201a), demonstrated an ORR of 62.5% and DCR of 75% in 12 patients with HER2-expressing or -mutated NSCLC.[107] A phase II study for this drug against the same condition recently began accrual (NCT03505710).

The resistance mechanisms upon progression on HER2 targeted therapies are not fully understood. A recent study of trastuzumab in combination with chemotherapy or afatinib in 9 patients with *HER2*-mutant metastatic lung adenocarcinoma suggested that PIK3CA mutation and increased HER2 copy number may be potential resistance mechanisms.[108]

EGFR Exon 20 Ins

EGFR exon 20 ins mutations occur in about 1.8% of all NSCLC and 12% of cases with *EGFR* mutants.[109] Similar to classical activating *EGFR* mutations, *EGFR* exon 20 ins mutations are enriched in women, non-smokers, Asian populations, and tumors with adenocarcinoma histology.[110] *EGFR* exon 20 ins patients respond poorly to targeted EGFR inhibitors, including the third-generation inhibitor, osimertinib.[111–113]

Poziotinib

Poziotinib is a potent and clinically active inhibitor of *EGFR* and *HER2* exon 20 ins.[105] In a phase II trial for cancers containing these mutations, poziotinib treatment resulted in an ORR of 55% and a median PFS of 5.5 months for 44 advanced NSCLC patients with *EGFR* exon 20 ins. Responses were also observed in 62% of TKI-refractory patients (NCT03066206).[106] Although the FDA refused to grant breakthrough therapy designation to poziotinib for the treatment of patients with metastatic NSCLC containing *EGFR* exon 20 mutations, the preliminary results of poziotinib from an ongoing phase II clinical trial (NCT03318939) demonstrated an ORR of 40% and a median DOR of 6.6 months.[114]

TAK-788

TAK-788 is an oral inhibitor with potent, selective preclinical activity against EGFR/HER2, including exon 20 ins. Results from a Phase 1/2 (NCT02716116) showed TAK-788 yielded a median PFS of 7.3 months and an ORR of 43% in 28 patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 ins. In a patient subgroup

without brain metastases at baseline, the ORR was 56% (n = 9/16), and the median PFS was 8.1 months.[115]

NRG1 Fusion

The neuregulin 1 gene (*NRG1*) is located on chromosome 10q23.1.[116] *NRG1* fusion is a novel driver gene identified in many cancer types.[117] It can induce the expression of the extracellular EGF-like domain of NRG1, which binds to HER3 (ERBB3), thereby stimulating heterodimerization of HER3 with HER2, and subsequently actives the AKT and MAPK pathways.[118]

NRG1 fusion occurs in 1–2% of NSCLC,[119] and is mutually exclusive with other oncogenic alterations.[120] It is mainly identified using RNA-based assays. CD74 and SCLA3A2 are the most common upstream partners, and other partners include SDC4, SLC3A2, TNC, MDK, ATP1B1, DIP2B, RBPMS, MRPL13, ROCK1, DPYSL2, and PARP8.[117] NRG1 fusion is more common in women, never smokers and adenocarcinoma histology, especially mucinous subtypes.[117,121]

Based on the activation mechanism, targeting the HER2/HER3 signaling pathway is a possible therapeutic strategy for NRG1 fusion. The pan-ERBB inhibitor afatinib has been reported to have anti-tumor activity in several patients with NSCLC harboring *NRG1* fusion. In 2017, two patients with NRG1 fusion-positive stage IV NSCLC were reported to have a durable clinical response to afatinib of 10 and 12 months, respectively.[122] Another report presented at the 2019 WCLC showed four NSCLC patients with *NRG1* gene fusion achieved a certain degree of response or tumor stabilization when treated with afatinib.[123] Response to anti-ERBB3 monoclonal antibody GSK2849330 has also been reported.[120] Further studies are needed to explore targeted therapies for *NRG1* fusion.

FGFR1 Amplification

FGFR1 (fibroblast growth factor receptor 1) belongs to a family of four transmembrane tyrosine kinase receptors (FGFR1-4) that regulates angiogenesis, embryogenesis, inflammation, and malignant tumor cell proliferation through the downstream activation of the RAS/RAF/MAPK, PI3K/AKT/mTOR, STAT, and PLCγ pathways.[124,125] The *FGFR1* gene, located on chromosome 10q, is amplified in about 20% of squamous NSCLC, more common in males and active smokers, and may be a negative prognostic marker in early-stage NSCLC patients treated with surgery.[126] A 3.5-fold amplification of this gene was recognized as the distribution cut-off for patient survival and may represent a stratification

factor for clinical trials.[127–129] In addition, a recent study demonstrated that *FGFR* mutations might increase the risk of lymph node metastasis in squamous NSCLC and be an independent predictive factor for inferior survival.[130] There are currently two types of FGFR inhibitors: 1) molecules directed against the FGFR domain, which are selective FGFR TKIs; 2) multitarget inhibitors that are nonselective FGFR TKIs.

Nonselective FGFR TKIs

Clinical trials using nonselective FGFR TKIs (e.g., lucitanib, lenvatinib, dovitinib, nintedanib, ponatinib, cediranib, pazopanib, regorafenib, and brivanib) have demonstrated limited activity and undesired side toxicities, such as hypertension, proteinuria, cardiovascular events, and hypothyroidism due to VEGF inhibition.[131,132] Nintedanib is the only FGFR inhibitor approved by the European Medical Agency (EMA) for second-line treatment in combination with docetaxel for NSCLC patients with locally advanced, recurrent, or metastatic disease and adenocarcinoma histology.[132] In a phase II trial of nintedanib in patients with *FGFR1*-amplified pretreated squamous NSCLC, a 6-month PFS was observed for the six *FGFR1*-amplified patients (NCT01948141).[133] A phase II trial for another nonselective FGFR TKI, dovitinib, is ongoing in pretreated squamous NSCLC patients with *FGFR1* amplification (NCT01861197).

Selective FGFR TKIs

Clinical trials with selective FGFR TKIs, including BGJ398, AZD4547, debio-1347, LY2874455, ARQ-087, erdafitinib, and TAS-120, have had a range of activity.[131,132] An ORR of 11.1% and DCR of 50% were reported for 36 *FGFR1*-amplified squamous NSCLC patients treated with BGJ398.[134] Erdafitinib (JNJ-42756493) has demonstrated antitumor activity against urothelial carcinoma. In April 2019, it received accelerated approval from the FDA for the treatment of adults with locally advanced or metastatic urothelial carcinoma with *FGFR3* or *FGFR2* genetic alterations, who have progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.[135] A phase IIa study of erdafitinib in Asian participants with various malignant tumors, including NSCLC, is ongoing (NCT02699606).

PI3KCA Mutation or Amplification

Phosphatidylinositol-3 kinases (PI3K) belong to a family of heterodimeric kinases, which play an important role in the regulation of cell growth, survival, and motility. There are three classes of PI3K (I, II, and III), which impact cellular signal transduction in different roles. Phosphatidylinositol 3-kinase, catalytic (PI3KCA) is a catalytic subunit of the class IA PI3K. Aberrant activation of PI3KCA through gene mutation or amplification is associated with human carcinogenesis.[136] *PI3KCA* can also be activated by upstream growth factor receptors followed by subsequent activation of its downstream pathways, including AKT/mTORC1/p70S6K. Tumor suppressor PTEN is a key negative regulator of PI3K/AKT/mTOR activation through PIK3CA.[137,138]

PI3KCA amplification is more common in squamous NSCLC (33 to 37%) than adenocarcinoma (5 to 6%).[139,140] *PI3KCA* mutations occur in about 2 to 5% NSCLC and are also more prevalent in squamous NSCLC.[139–141] In adenocarcinoma, these mutations are associated with a poorer prognosis,[142] have been reported to be concurrent with other oncogenic drivers and may be related to resistance mechanisms against TKIs because they have also been found in *EGFR*-mutant NSCLC that has developed acquired resistance to EGFR-TKIs.[143,144]

The pan PI3K inhibitor Buparlisib (BKM120) did not demonstrate sufficient clinical activity in patients with relapsed NSCLC with *PI3KCA* mutation in a phase II study but had activity when combined with the mTOR inhibitor everolimus in NSCLC preclinical models. It also had activity in pretreated head and neck squamous cell carcinoma patients when combined with paclitaxel in a phase II study.[144–146] These trials suggest that the antitumor activity of a single PI3KCA-targeted agent may be limited, but combined therapy may provide better results. Additional clinical trials with other PI3K inhibitors combined with targeted agents and/or cytotoxic chemotherapy, such as pictilisib (GDC-0941) in combination with cytotoxic chemotherapy (e.g., paclitaxel, carboplatin, pemetrexed, and cisplatin) (NCT00974584, NCT01493843); pilaralisib (SAR245408, XL147) combined with carboplatin/paclitaxel (NCT00756847) have been completed, but the results have not yet been released.

DDR2 Mutation

Activating discoidin domain receptor 2 gene (*DDR2*) mutations have mainly been identified in approximately 4% of

squamous NSCLC. These mutations can promote carcinogenesis through cell migration and proliferation.[147,148] Dasatinib and its combination with erlotinib have demonstrated activity in NSCLC patients with *DDR2* mutations.[148–150] However, several dasatinib clinical trials were terminated prematurely due to intolerable toxicities, lack of efficacy, and slow accrual.[151,152] Because excessive toxicity could hinder the potential benefit of this drug, an ongoing phase II trial (NCT01744652) is currently trying to identify the highest tolerable drug doses for the combination of dasatinib and crizotinib that can be given to patients with advanced cancer.

Conclusion

With the rapid development of precision medicine over the past decade, many oncogenic drivers have been discovered, and a paradigmatic change has occurred in the diagnosis and treatment of patients with advanced NSCLC. EGFR- and ALK-targeted therapy has become standard therapy for patients with these mutations. In this review, we discussed the rare driver genes in NSCLC, focusing on the clinical characteristics, currently approved therapies, and resistance mechanisms. Although targeted therapies have been greatly successful in recent years, the benefits obtained are limited due to the inevitable development of drug resistance. To improve efficacy, overcome resistance, and minimize toxicity, further studies are needed to explore the resistance mechanisms and discover more effective targeted therapies.

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Disclosure

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