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Advances in the Treatment of Rare Mutations in Non-Small Cell Lung Cancer

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Abstract: Lung cancer is a malignant tumor with the highest morbidity and mortality rate worldwide, with nearly 2.5 million new cases and more than 1.8 million deaths reported globally in 2022. Lung cancer is broadly categorized into two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for about 85% of all cases. Early-stage lung cancers often present without obvious symptoms, resulting in most patients being diagnosed at an advanced stage where traditional chemotherapy has limited efficacy. Recent advances in molecular biology have elucidated the pivotal role of gene mutations in tumor development, paving the way for targeted therapies that have markedly benefited patients. Beyond the well-known epidermal growth factor receptor (EGFR) mutation, an increasing number of new molecular targets have been identified, including ROS1 rearrangement, BRAF mutation, NTRK fusion, RET fusion, MET mutation, KRAS G12C mutation, HER2 mutation, ALK rearrangement, and NRG1 fusion. Some of these targeted therapies have already been approved by the Food and Drug Administration (FDA), and many others are currently undergoing clinical trials. This review summarizes recent advances in NSCLC treatment with molecular targets, highlighting progress, challenges, and their impact on patient prognosis.

Keywords: non-small cell lung cancer, rare mutations, targeted therapy, immunotherapy

Introduction

Lung cancer is the malignant tumor with the highest morbidity and mortality rates worldwide, with 2.48 million new cases and 1.82 million deaths reported globally in 2022. The overall five-year survival rate for patients with advanced lung cancer is often less than 20%.[1] Lung cancer can be classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) according to the histological type, accounting for approximately 85% and 15%, respectively. NSCLC is further subdivided into adenocarcinoma (40%), squamous cell carcinoma (25–30%), and large cell carcinoma (5–10%).[2]

Traditionally, lung cancer has been treated with surgery and chemotherapy, and approximately 30% of patients with NSCLC are eligible for surgery. However, the incidence of postoperative recurrence or metastasis is as high as 21.7%, even in patients with completely resected stage I.[3] Similarly, chemotherapy has limited effectiveness, with a median survival of less than 9 months, a response rate of 25–35%, and a 2-year survival rate of only 10%.[4] In 2003, the FDA approved gefitinib as a first-line treatment for metastatic NSCLC with epidermal growth factor receptor (EGFR) mutations. A Phase III trial comparing the efficacy of gefitinib and platinum-based combinations showed that the 12-month progression-free survival (PFS) rate was 24.9% in the gefitinib group, compared to 6.7% in the carboplatin-paclitaxel group. This demonstrated that targeted therapy is superior to carboplatin combined with paclitaxel as an initial treatment for patients with EGFR-positive NSCLC, while gefitinib also exhibited lower toxicity in these patients.[5] As a result, the National Comprehensive Cancer Network (NCCN) guidelines recommend targeted therapy as a first-line treatment option for driver-positive patients receiving palliative care, marking the beginning of the targeted therapy era for advanced NSCLC.[6] Defining molecular subtypes is essential for targeted therapy in NSCLC, and the application of next-generation sequencing (NGS) has created opportunities to identify rare gene mutations. In recent years, in-depth

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research into the molecular biology of lung cancer and the development of targeted drugs have comprehensively transformed the treatment of advanced lung cancer. About 30%–50% of NSCLC patients have oncogenic driver alterations, and approximately 50%–75% of these patients can receive targeted therapy.[4]

With advances in detection technology, molecular targets beyond EGFR have been gradually identified. Oncogenic targets with an incidence of ≤5% are classified as rare targets.[7] Although the incidence of rare mutations is low compared to common targets like EGFR, the large population of lung cancer patients means the actual number of those with rare mutations is significant. These patients often face challenges, including the lack of targeted therapies, poor response to standard chemotherapy, poor prognosis, and increased susceptibility to recurrence and metastasis. Additionally, the low frequency of these mutations complicates the ability to conduct large-scale randomized clinical trials. Currently, targeted therapies for rare mutations primarily include small-molecule drugs and monoclonal antibodies, with kinase inhibitors representing the main class of small-molecule drugs. Kinases can be categorized into tyrosine kinases (eg, EGFR, HER2, MET, ALK, RET, ROS1), serine/threonine kinases (eg, BRAF), and dual-specific kinases (eg, MEK).[7] Corresponding targeted therapies have undergone extensive clinical studies, with some already approved for clinical use and others still in the research phase but showing significant efficacy (Table 1). In the context of immunotherapy, immune checkpoint inhibitors (ICIs) have become the standard treatment for stage IV lung cancer without targeted mutations. However, their use in treating lung cancer with driver mutations remains controversial, with low response rates often observed in first-line therapy. As a result, it remains uncertain whether the use of molecularly targeted agents, ICIs, or chemotherapy has good efficacy in NSCLC patients with specific oncogenic driver gene mutations. This review will explore the latest advancements in therapeutic drugs for oncogenic driver mutations.

ROS1 Rearrangement

In 1987, a ROS1 gene fusion (FIG-ROS, now known as GOPC-ROS1) was first identified in the U118MG glioblastoma cell line. Subsequent studies demonstrated the oncogenic potential of this fusion in gliomagenesis. In 2007, the ROS1 gene was also found in a small subset of NSCLCs. The ROS1 gene, located on chromosome 6q22,[64] belongs to the insulin receptor family of receptor tyrosine kinases (RTKs) and promotes tumor proliferation through the activation of the PI3K-AKT-mTOR, VAV3, JAK-STAT, and MAPK-ERK pathways[65–67] (Figure 1). ROS1 rearrangement is found in approximately 2.6% of NSCLC,[68] with a higher prevalence among females, younger individuals, and non-smokers.[69,70] Compared to traditional chemotherapy with platinum plus pemetrexed, targeted therapy against ROS1 rearrangement has significantly improved patient prognosis and quality of life. Currently, three ROS1 inhibitors are approved for clinical use: crizotinib (approved by the FDA in 2016),[71] entrectinib (approved by the FDA in 2019),[72] and repotrectinib (approved by the FDA in 2023).[73]

Crizotinib is a TKI against multiple targets, including ROS1, ALK and MET. It selectively binds to the ATP-binding site of tyrosine kinases, blocking their phosphorylation and subsequent activation of downstream signaling pathways, thereby inhibiting tumor cell growth and invasion.[74] In the phase I/II AcSe study, crizotinib was administered to patients with ROS1-rearrangement NSCLC, resulting in an ORR of 47.2%, a median progression-free survival (mPFS) of 5.5 months, and a median overall survival (mOS) of 17.2 months.[8] Two other studies, EUCROSS and METROS, also demonstrated significant anti-tumor activity of crizotinib in patients with ROS1-positive advanced NSCLC.[9,10] The predominant site of disease progression in patients with ROS1-positive NSCLC was brain metastases, likely due to crizotinib's low blood-brain barrier penetration rate, despite its strong anti-tumor activity. Furthermore, nearly 36% of patients with ROS1-positive NSCLC had baseline brain metastases. Consequently, future research should focus on developing ROS1-TKIs with improved blood-brain barrier penetration capabilities.[64]

Entrectinib is an oral multi-target inhibitor of ROS1, ALK and pan-tropomyosin receptor kinase (TRK) that effectively penetrates the blood-brain barrier and demonstrates central nervous system (CNS) activity. Its anti-ROS1 activity was found to be 40-fold more potent than that of crizotinib in vitro.[75] A comprehensive analysis based on prospective, global, multicenter datasets (STARTRK-1, STARTRK-2, and ALKA-372-001) demonstrated that entrectinib had a favorable DCR in the CNS and other systems in patients with advanced ROS1-positive NSCLC. The data showed an mPFS of 19 months and a median effective duration of 24.6 months, surpassing the median duration of response (mDoR) of crizotinib therapy (19.7 months). In 20 patients with CNS metastases, the intracranial response rate was 55%

Table 1 Key Randomized Trials in Advanced Oncogene-Driven NSCLC

Rare Oncogenic Mutation	Rate (%)	Drug	Trial ID	N	Efficacy					Reference
					ORR (%)	mOS(mo)	mPFS (mo)	DCR (%)	mDoR (mo)	
ROS1 rearrangement	2.6	Crizotinib	NCT02034981	37	47.2	17.2	5.5	83.3	NA	[8]
			NCT02183870	30	70.0	NA	20.0	90.0	NA	[9]
			NCT02499614	26	65.0	NA	22.8	85.0	21.4	[10]
		Entrectinib	NCT02097810; NCT02568267; EudraCT 2012–000148-88	53	77.0	NA	19	NA	24.6	[11]
		Lorlatinib	NCT01970865	21	62.0	NA	NA	NA	25.3	[12]
		Ceritinib	NCT01964157	32	62.0	NA	9.3	81.0	NA	[13]
		Repotrectinib (TPX-0005)	NCT03093116	71	79.0	NA	35.7	NA	34.1	[14]
BRAF mutation	2.1	Vemurafenib	NCT01524978	54 pretreated	37.0	15.4	6.1	NA	NA	[15]
				8 naive	37.5	NA	12.9	NA	NA	
			AcSe	96	44.8	10.0	5.2	NA	NA	[16]
		Vemurafenib	EURAF	24	53.0	10.8	5.0	85.0	NA	[17]
		Dabrafenib		9			NA			
		Sorafenib		1			NA			
		Dabrafenib	NCT01336634	78	33.1	12.7	5.5	58.0	9.6	[18,19]
		Dabrafenib +trametinib		57	66.7	18.2	10.2	80.7	9.8	[19–21]
		Dabrafenib +trametinib		36	64.0	12.7	10.9	75.0	10.2	[20]
		Encorafenib+binimetinib	NCT03915951	59 naive	75.0	NA	NA	64.0	NA	[22]
				39 pretreated	46.0	NA	9.3	41.0	16.7	
NTRK fusion	<1%	Larotrectinib	NCT02122913 NCT02637687 NCT02576431	153	79.0	44.4	28.3	NA	35.2	[23]
		Larotrectinib	NCT02122913 NCT02576431	15	73.0	40.7	35.4	NA	33.9	[24]
		Entrectinib	NCT02097810 NCT02568267 EudraCT 2012–000148-88	54	57.0	NA	11.2	NA	10.4	[25]
		Entrectinib	NCT02097810 NCT02568267 EudraCT 2012–000148-88	22	63.6	NA	14.9	NA	19.9	[26]
		Entrectinib	NCT02568267	31	64.5	NA	NA	NA	NA	[27]

(*Continued*)

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Table 1 (Continued).

Rare Oncogenic Mutation	Rate (%)	Drug	Trial ID	N	Efficacy					Reference
					ORR (%)	mOS(mo)	mPFS (mo)	DCR (%)	mDoR (mo)	
RET fusion	1–2	Selpercatinib (Loxo-292)	NCT03157128	105 pretreated	64.0	NA	16.5	NA	17.5	[28]
				39 naive	85.0	NA	NA	NA	NA	
			NCT03157128	69 naive	84.0	NA	22.0	NA	20.2	[29]
				247 pretreated	61.0	NA	24.9	NA	28.6	
		Pemetrexed+ platinum-based +pembrolizumab	NCT04194944	83	65.0	NA	11.2	NA	11.5	[30]
		Selpercatinib +pembrolizumab		129	84.0	NA	24.8	NA	24.2	
		Pemetrexed+ platinum-based ±pembrolizumab	NCT04194944	159	63.0	NA	11.2	NA	12.0	
		Selpercatinib ±pembrolizumab		102	84.0	NA	24.8	NA	24.2	
		Pralsetinib	NCT03037385	27 naive	70.0	NA	9.1	85.0	9.0	[31]
				87 pretreated	61.0	NA	17.1	91.0	NA	
			NCT03037385	75 naive	72.0	NA	13.0	91.0	NA	[32]
				136 prior platinum-based chemotherapy	59.0	NA	16.5	90.0	22.3	
MET mutation	3	Tepotinib	NCT02864992	164 naive	57.3	21.3	12.6	NA	46.4	[33]
				149 pretreated	45.0	19.3	11.0	NA	12.6	
		Capmatinib	NCT02414139	28 naive	67.9	20.8	12.4	NA	12.6	[34]
				32 naive	65.6	NA	10.8	NA	NA	
				69 pretreated	40.6	13.6	5.4	NA	9.7	
				31 pretreated	51.6	NA	6.9	NA	8.4	
		Savolitinib	NCT02897479	70	47.1	12.5	NA	81.4	NA	[35]
		Crizotinib	NCT02034981	28	36.0	8.1	2.4	39.0	NA	[8]
			NCT02499614	26	27.0	5.4	4.4	69.0	3.7	[10]
		Amivantamab	NCT02609776	36	33.0	NA	6.7	58.3	NA	[36]

KRAS G12C mutation	2.8	Sotorasib	NCT03600883	59	32.2	NA	6.3	88.1	NA	[37]
				124	37.1	NA	6.8	80.6	11.1	[38]
		Sotorasib	NCT04303780	169	28.1	10.6	5.6	82.5	8.6	[39]
		Docetaxel		151	13.2	11.3	4.5	60.3	6.8	
		Adagrasib	NCT03785249	15	53.3	NA	11.1	NA	16.4	[40]
			NCT03785249	112	42.9	12.6	6.5	NA	8.5	[41]
		Nivolumab	NCT01673867	292	19.0	12.2	2.3	NA	NA	[42]
		Docetaxel		290	12.0	9.4	4.2	NA	NA	
HER2 mutation	2.3	T-DM1	NCT02675829	18	44.0	NA	5.0	NA	4.0	[43]
			NCT02675829	49	51.0	NA	5.0	NA	4.4	[44]
			JapicCTI-194620	22	38.1	8.1	2.8	52.4	3.5	[45]
		T-DXd	NCT03505710	91	55.0	17.8	8.2	92.0	9.3	[46]
		Pyrotinib	NCT02834936	60	30.0	14.4	6.9	NA	6.9	[47]
			ChiCTR1800020262	78	19.2	10.5	5.6	74.4	9.9	[48]
		Poziotinib	NCT03066206	90	27.8	NA	5.5	70.0	5.1	[49]
			NCT03318939	70	41.0	NA	5.6	73.0	5.7	[50]
ALK rearrangement	3.8	Crizotinib	NCT01154140	172	74.0	NA	10.9	NA	11.3	[51]
		Pemetrexed+ platinum-based		171	45.0	NA	7.0	NA	5.3	
		Crizotinib	NCT00932451	173	65.0	NA	7.7	NA	32.1	[52]
		Pemetrexed/docetaxel		174	20.0	NA	3.0	NA	24.4	
		Ceritinib	NCT01828099	189	72.5	NA	16.6	NA	23.9	[53]
		Pemetrexed/docetaxel		175	26.7	NA	8.1	NA	11.1	
		Ceritinib	NCT01828112	115	39.1	NA	5.4	76.5	NA	[54]
		Pemetrexed/docetaxel		116	6.9	NA	1.6	36.2	NA	
		Brigatinib	NCT02737501	137	71.0	NA	24.0	NA	33.2	[55,56]
		Crizotinib		138	60.0	NA	11.1	NA	13.8	
		Alectinib	NCT02075840	152	82.9	NA	25.7	NA	48.2	[57,58]
		Crizotinib		151	75.5	57.4	10.4	NA	23.3	
		Alectinib	NCT02604342	79	50.6	NA	10.9	NA	NA	[59]
		Pemetrexed/docetaxel		40	2.5	NA	1.4	NA	NA	
		Ensartinib	NCT02767804	143	74.0	NA	25.8	NA	NA	[60]
		Crizotinib		147	67.0	NA	12.7	NA	27.3	
		Lorlatinib	NCT01970865	198	47.0	NA	NA	NA	NA	[61]
		Lorlatinib	NCT03052608	149	76.0	NA	NA	NA	NA	[62]
		Crizotinib		147	58.0	NA	9.3	NA	11.0	
NRG1 fusion	0.1–0.4	Seribantumab	NCT04383210	12	30.0	NA	NA	90.0	NA	[63]

Abbreviations: ORR, objective response rate; mOS, median overall survival; mPFS, median progression-free survival; DCR, disease control rate; mDOR, median duration of response; mo, month; NA, not applicable.

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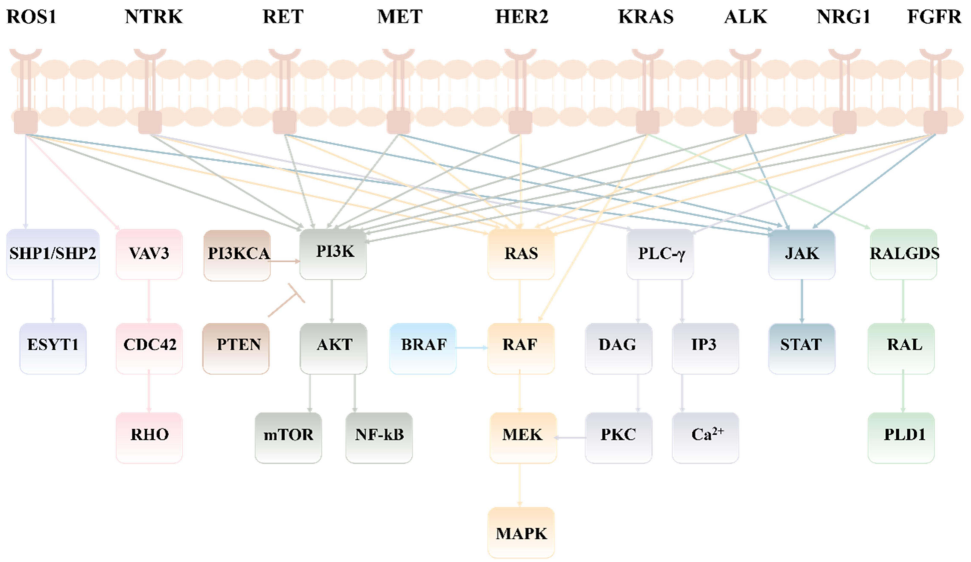

Figure 1 Key signaling pathways of oncogenic driver genes in non-small cell lung cancer. Each of the RTKs activates several downstream signaling molecules, leading to diverse cellular responses. SHP1/SHP2 signaling leads to activation of ESYT1. VAV3 controls the RHO family GTPase via CDC42. The PI3K pathway is activated by various RTKs, leading to AKT phosphorylation and downstream effects on mTOR and NF-kB signaling, modulated by PTEN. The RAS-RAF-MEK-ERK/MAPK cascade is initiated by several RTKs, progressing through BRAF and RAF to activate MEK and eventually MAPK. The PLC-γ pathway regulates intracellular signaling molecules such as DAG, PKC, IP3, and Ca2+. The JAK-STAT pathway is another critical branch, resulting in the activation of STAT proteins. RALGDS signaling controls the RAL GTPase and its effector PLD1. This complex network coordinates various cellular processes including proliferation, survival, migration, and differentiation. Arrowheads indicate activation, while flat-head lines represent inhibitory signals.

and the median intracranial DoR was 12.9 months.[64] This gives entrectinib an advantage over crizotinib, with overall manageable and mostly grade 1 toxicity that was reversible.[74]

Repotrectinib (TPX-0005) is a low molecular weight, multi-target TKI that targets ROS1, TRK and ALK. Phase I/II clinical trials showed that repotrectinib exhibited durable antitumor activity with a mDoR of 34.1 months and a mPFS of 35.7 months in patients who had not received prior ROS1 TKI therapy, regardless of prior chemotherapy. Repotrectinib was similarly effective in patients with ROS1-positive NSCLC who had received at least one prior ROS1 TKI therapy. In comparison, entrectinib had an mDoR of 20.5 months and an mPFS of 15.7 months, while crizotinib had an mDoR of 24.7 months and an mPFS of 19.3 months.[14]

In addition to the three approved and marketed drugs mentioned above, several other targeted drugs have shown significant efficacy in clinical studies. Lorlatinib is a potent oral inhibitor of ALK and ROS1 with activity against crizotinib- and ceritinib-resistant mutations (G2032R, D2033N, and S1986Y) and the ability to penetrate the blood-brain barrier. In a Phase II study enrolling patients with ROS1-positive NSCLC, including those who had not been treated with a TKI and those pretreated, lorlatinib achieved an mPFS of 21.0 months and an ORR of 61.5% in treatment-naive patients, compared with an mPFS of 8.5 months and an ORR of 26.5% in patients pretreated with crizotinib. Surprisingly, in treatment-naive patients with brain metastases, the ORR was 66.7%. Lorlatinib has been reported to be effective against resistance caused by activation of bypass signaling, though it has limited efficacy in patients with G2032R mutation.[12] Ceritinib is an ALK inhibitor with potential anti-ROS1 rearrangement activity. Regardless of prior crizotinib treatment, ceritinib has shown significant efficacy in clinical trials, with favorable intracranial responses and manageable safety profiles in patients with brain metastases.[13] Cabozantinib is a multi-targeted TKI that targets MET, RET, and ROS1. Sun et al reported the clinical efficacy of cabozantinib in four patients with ROS1-positive NSCLC who were resistant to crizotinib and ceritinib. Patients in the cabozantinib group had a PFS of 4.9 to 13.8 months.[74] Brigatinib is a multi-targeted inhibitor of ROS1 and ALK with activity against multiple resistant ROS1 mutations. A study showed that brigatinib had treated TKI-naive patients and crizotinib-resistant patients with ROS1-positive NSCLC had ORRs of 37% and 29% in the overall population and crizotinib-resistant subgroup, respectively.[76] In a case report, brigatinib maintained efficacy even after the patient had received multiple ROS1-TKIs.[77] According to in vitro experiments, brigatinib is ineffective against NSCLC with the G2032R mutation but shows substantial anti-tumor efficacy against those with the L2026M mutation.[74]

Little is known about the effects of ICIs on ROS1-mutant NSCLC. A retrospective study showed that anti-PD-(L)1 antibody monotherapy was poorly active, with only one out of six patients achieving a short-term response rate (ORR of 17%).[78]

BRAF Mutation

Ulf Rapp et al first described v-raf and its association with cancer in 1983 as a mouse retroviral oncogene with a mammalian cell homolog called CRAF.[79] In 1984–1985, BRAF was discovered to be related to CRAF.[80,81] BRAF mutations occur in 2.1% of NSCLC cases and can be categorized into V600 and non-V600 codon mutations.[68] BRAF belongs to the RAF group of serine/threonine kinases and is involved in cell proliferation and differentiation through the MAPK signaling pathway[82,83] (Figure 1). Precision-targeted therapies significantly enhance the prognosis of BRAF mutation-positive NSCLC patients compared to standard paclitaxel-based chemotherapy.[84] Currently, FDA-approved targeted agents for BRAF mutations include dabrafenib in combination with trametinib,[85] and encorafenib in combination with binimetinib.[86]

Vemurafenib (PLX4032) is a V600-BRAF mutation inhibitor.[87] In the VE Basket trial, vemurafenib treatment yielded an ORR of 37% among BRAF V600E-mutated NSCLC patients, with consistent ORR in treatment-naive and previously treated groups. Median overall survival (mOS) was not reached and 15.4 months, while mPFS was 12.9 and 6.1 months, respectively.[15] Another study evaluating vemurafenib monotherapy in BRAF V600 and non-V600 mutated NSCLC reported an ORR of 44.8% and mPFS of 5.2 months in the V600 group, whereas no tumor response was observed in the non-V600 group, with an mPFS of 1.8 months.[16] Vemurafenib monotherapy demonstrates efficacy specifically in BRAF V600-mutant NSCLC, with limited activity against non-V600 mutations. The EURAF cohort further validates the antitumor activity of vemurafenib and dabrafenib in advanced BRAF-mutant lung cancer.[17]

Dabrafenib is an ATP-competitive BRAF inhibitor.[88] A phase II clinical trial found that dabrafenib monotherapy in patients with metastatic BRAF V600-mutated NSCLC who had received prior systemic therapy with an ORR of 33.1% and a DCR of 58%. Dabrafenib in combination with trametinib provided substantial clinical benefit and durable responses, demonstrating comparable efficacy in both treatment-naive (ORR=63.9%, mDoR=10.2 months) and previously treated (ORR=68.4%, mDoR=9.8 months) groups. Combination therapy with dabrafenib and trametinib significantly improved outcomes in NSCLC patients harboring BRAF V600E mutations, surpassing the efficacy of dabrafenib monotherapy irrespective of prior treatment history.[18–20]

Despite initial effectiveness, BRAF inhibitor monotherapy is limited by acquired resistance mechanisms that reactivate the MAPK pathway. To mitigate resistance activation, BRAF monomer inhibitors are combined with downstream MEK inhibitors, enhancing efficacy and tolerability.[89] Encorafenib and binimetinib inhibit tumor proliferation by blocking ERK signaling in the MAPK pathway.[88] In a phase II clinical trial, the combination of encorafenib and binimetinib showed significant antitumor activity in BRAF-mutant NSCLC patients, achieving ORRs of 75% and 46%, mDoR of not reached and 16.7 months, and mPFS of not reached and 9.3 months in treatment-naive and previously treated groups, respectively.[22] Compared to dabrafenib combined with trametinib, the combination of encorafenib and binimetinib demonstrated significantly better efficacy in both treatment-naive patients and those who had received prior therapy. Regarding adverse effects, nearly all patients experienced side effects of varying severity. However, those treated with encorafenib and binimetinib had significantly less pyrexia, while the rates of gastrointestinal and constitutional toxicities were similar between the two drug combinations.[90]

Data on the efficacy of anti-PD-(L)1 antibodies in patients with BRAF-mutated NSCLC are limited and conflicting. One retrospective study reported that anti-PD-(L)1 antibody monotherapy exhibited low clinical activity in patients with BRAF-mutated NSCLC, with an ORR of 24% and a mPFS of 3.1 months.[78] The benefit of treatment in patients with BRAF V600-mutant tumors may be particularly limited, with one study reporting an ORR of only 9% and a time to progression on ICIs of 1.9 months.[91] However, a large study involving NSCLC patients treated with anti-PD-(L)1 antibody monotherapy reported an ORR of 62% for patients with BRAF-mutated NSCLC. This study also demonstrated that patients with BRAF V600-mutant tumors had a longer mPFS and OS compared to those with non-V600 mutations (9.8 months vs 5.4 months and 20.8 months vs 14.9 months, respectively).[92]

For patients with BRAF V600-mutated NSCLC, the optimal first-line treatment remains unclear. Combination therapy with dabrafenib and trametinib may be preferable to ICIs based on available data, but anti-PD-(L)1 antibody monotherapy (in patients with PD-L1 TPS ≥50%) or chemoimmunotherapy, with or without bevacizumab (regardless of PD-L1 status), are also reasonable options. Additionally, evidence from melanoma research supports the use of upfront immunotherapy. In a phase III

trial involving treatment-naive patients with advanced BRAF V600-mutant melanoma, those who received dual ICI therapy (nivolumab plus ipilimumab) followed by BRAF-targeted therapy (dabrafenib plus trametinib) had better OS than those who received the therapies in the reverse sequence (72% vs 52% at two years).[93]

NTRK Fusion

NTRK fusions were first reported in a case of colorectal cancer in 1982. Since then, over 80 different NTRK gene fusions involving various ligands have been identified across a wide range of tumors in both adults and children,[94] occurring in less than 1% of NSCLC cases.[95] NTRK genes encode the TRK proteins, pivotal in embryonic development and maintaining normal nervous system function. NTRK fusion drives various solid tumors in adults and children, promoting tumor proliferation by activating the MAPK, PI3K, and PKC pathways[96,97] (Figure 1). Larotrectinib[98] and entrectinib[72] have both gained FDA approval for the treatment of patients with NTRK fusion-positive tumors.

Larotrectinib, an oral small molecule highly selective for pan-TRK inhibition, was first approved in the US in November 2018 for locally advanced or metastatic solid tumors containing NTRK fusions without acquired resistance mutations.[95] A comprehensive analysis of three clinical trials (LOXO-TRK-14001, SCOUT, and NAVIGATE) found that larotrectinib was highly active in TRK fusion-positive lung cancer, achieving an ORR of 75% with notable CNS efficacy.[23] Compared to chemotherapy and immunotherapy, larotrectinib elicited rapid, significant, and durable responses.[24] Combined analyses from trials NCT02576431 and NCT0212291 showed an ORR of 83% in patients with TRK fusion-positive lung cancer treated with larotrectinib monotherapy and 80% in those with CNS metastases.[99]

Entrectinib, an oral selective inhibitor of TRK, ROS1 and ALK tyrosine kinases, was initially approved in Japan in June 2019 for advanced or recurrent adult and pediatric NTRK fusion-positive solid tumors.[95] Pooled data from STARTRK-1, STARTRK-2 and ALKA-372-001 trials highlighted entrectinib's significant antitumor and CNS activity. Monotherapy in metastatic or locally advanced NTRK fusion-positive tumors achieved an ORR of 57%, an mDoR of 10.4 months, an mPFS of 11.2 months, and the ORR for patients with lung cancer was 70%.[25] In patients with baseline CNS disease (n=6), four showed intracranial responses, including two complete responses (CR) and two partial responses (PR), with one stable disease (SD).[100] The ORR in NSCLC patients with no prior TRK inhibitor therapy was 63.6%. The mDoR, mPFS and mOS were 19.9 months, 14.9 months and not reached, respectively.[26] Further analyses across various solid tumors with positive NTRK fusion reported an ORR of 61.3%, mDoR of 20.0 months, mPFS of 13.8 months, and mOS of 37.1 months. The ORR for the NSCLC subgroup was 64.5%.[27] In conclusion, entrectinib has clinically significant antitumor activity in NTRK fusion-positive patients, especially against CNS tumors and metastases.

RET Fusion

In 1985, Takahashi used DNA from human lymphoma cells to transform NIH3T3 cells. By analyzing the transformed daughter cells, he discovered a new gene activated by rearrangement with other genes, which he named the RET gene due to this rearrangement during the transformation process.[101] Located on chromosome 10q11.2, RET encodes a RTK that triggers downstream MAPK, JAK-STAT, and PI3K-AKT-mTOR signaling pathways, promoting tumor cell proliferation[102] (Figure 1). RET fusions occur in approximately 1–2% of NSCLC cases.[28] Prior to the development of specific RET inhibitors, treatment primarily involved multi-kinase inhibitors, which were less targeted and associated with significant side effects, limiting their efficacy. The FDA has approved selpercatinib[103] and pralsetinib[104] for the treatment of RET fusion-positive NSCLC patients.

Selpercatinib (Loxo-292) is an oral, highly selective RET inhibitor effective against wild-type and multiple mutant or fusion RET subtypes.[105,106] In a phase I/II trial, selpercatinib monotherapy for RET fusion-positive NSCLC showed an ORR of 64% in pretreated patients and 85% in treatment-naive patients. Among patients with measurable CNS metastases at enrollment, 91% achieved an objective intracranial response.[28] Updated data indicated ORRs of 84% and 61% in treatment-naive and pretreated groups, respectively, with mPFS of 22 and 24.9 months.[29] A comparative study found that selpercatinib monotherapy resulted in longer mPFS and DoR compared to platinum-based combination combined with pemetrexed, with or without pembrolizumab. The intracranial ORR was 82%, suggesting favorable efficacy against CNS metastases.[30] This highlights the significant antitumor activity of selpercatinib in patients with RET fusion-positive lung cancer, including in first-line therapy, post-platinum-based chemotherapy, and those with brain metastases.

Pralsetinib (BLU-667) is another potent, oral and selective RET inhibitor for metastatic RET fusion-positive NSCLC. Pralsetinib was well tolerated and showed clinical activity, including intracranial response, in patients with RET fusion-positive NSCLC in the phase I/II ARROW study. The ORR was 61% in pretreated patients and 70% in treatment-naive patients.[31] More recently, updated data reported ORRs of 72% in treatment-naive and 59% in pretreated patients, with mDoR not reached and 22.3 months, and mOS of 13 and 16.5 months, respectively. Tumor shrinkage was observed in all treatment-naive patients and 97% of pretreated patients. Among those with measurable intracranial metastases, the intracranial response rate was 70%. In all patients with RET fusion-positive NSCLC, 7% discontinued due to treatment-related adverse events (TRAEs).[32] In conclusion, pralsetinib has shown clinically meaningful and durable responses in advanced RET fusion-positive NSCLC in both primary and standard refractory populations, including intracranial efficacy, with a manageable safety profile.

A single retrospective study demonstrated significant efficacy of anti-PD-1 antibody monotherapy in patients with previously treated RET-fusion NSCLC, reporting an ORR of 37.5%, a mDoR of 12.1 months, and a mPFS of 7.6 months.[107] However, at least two other retrospective studies showed poor efficacy, with ORRs below 10% and mPFS of less than 3.5 months.[78,108] These findings suggest that the efficacy of immunotherapy in patients with this subtype of mutation remains uncertain.

MET Mutation

The MET gene was first identified in 1984 as a MET-TPR fusion in a human osteosarcoma cell line. In 1996, Natali et al discovered that MET was overexpressed in several cancers and associated with poor prognosis. It was not until 2005 that somatic mutations in the MET gene were first reported in NSCLC.[109] The MET gene, also known as the hepatocyte growth factor receptor (HGFR), is present in approximately 3% of NSCLC cases.[68] It encodes a RTK for hepatocyte growth factor (HGF), which, upon binding to the MET receptor, activates several downstream signaling pathways, including RAS-RAF-MEK-MAPK, PI3K-AKT, STAT, and NF-κB. These pathways are involved in cell proliferation, differentiation, and survival[110] (Figure 1). C-MET mutations mainly consist of MET exon 14 skipping (METex14, 2%–4%), MET amplification (METamp, 1%–6%), MET overexpression (20%–25%) and MET fusion (0.2%–0.3%).[111] The first MET TKI to receive FDA approval was tepotinib,[112] followed by capmatinib.[113] Savolitinib is currently approved only in China for patients who have progressed or are intolerant after platinum-based chemotherapy.[114]

Tepotinib is a highly selective MET inhibitor. The VISION phase II clinical trial evaluated tepotinib for MET-positive patients with advanced NSCLC who had not previously received a MET inhibitor. With the median follow-up time of 32.6 months, the ORR was 51.4%, the mDoR was 18 months, the mPFS was 11.2 months, and the mOS was 19.6 months. Among patients who had received prior platinum-based therapy or ICIs, the ORR was 45.0%, the mDoR was 12.6 months, the mPFS was 11.0 months, and the mOS was 19.3 months. Treatment-naive patients showed an ORR of 57.3%, mDoR of 46.4 months, mPFS of 12.6 months, and mOS of 21.3 months.[33] The efficacy of tepotinib was consistent across different MET mutation types and concomitant MET AMP.[115] The efficacy of tepotinib was similar regardless of prior treatments, with consistent ORR among patients who had received prior platinum-based chemotherapy, immunotherapy, and platinum-based combination immunotherapy. The mDoR was 12.4 months, the mPFS was 11.0 months in platinum-pretreated patients, and the mDoR was 9.5 months, the mPFS was 10.9 months in patients previously treated with ICIs.[116] The intracranial response rate was 66.7% in patients with baseline brain metastases.[33] In conclusion, tepotinib showed clinically relevant outcomes in both naive and pre-treated patients with MET-mutated NSCLC. In patients with baseline brain metastases, tepotinib showed solid systemic and intracranial outcomes with comparable clinical benefit to patients without baseline brain metastases. Moreover, tepotinib was well tolerated and resulted in a low rate of TRAE discontinuation.

Capmatinib is another selective MET inhibitor. In the GEOMETRY-mono1 trial, capmatinib monotherapy in MET-positive NSCLC patients with prior first/second-line therapy resulted in an ORR of 40.6%, mDoR of 9.7 months, mPFS of 5.4 months, and mOS of 13.6 months. Among second-line therapy patients, the ORR was 51.6%, mDoR was 8.4 months, and mPFS was 6.9 months. Treatment-naive patients had an ORR of 67.9%, mDoR of 12.6 months, mPFS of 12.4 months, and mOS of 20.8 months. An extended cohort of treatment-naive patients showed an ORR of 65.6% and mPFS of 10.8 months.[34] This study found that capmatinib exhibited significant antitumor activity in advanced NSCLC

with MET mutation, particularly in treatment-naive patients, with no significant differences between MET mutation types and concomitant MET AMP.[117]

Savolitinib is also a MET inhibitor. In a phase II clinical trial involving METex14 NSCLC patients, with a median follow-up of 28.4 months, the mOS of 12.5 months; in patients with brain metastases, the mOS was 17.7 months.[118] The ORR was 47.6%, and the DCR was 81% in the pretreated group. In the treatment-naive group, the ORR was 46.4%, and DCR was 82.1%.[35] These results indicate that savolitinib has clinically meaningful antitumor activity, regardless of prior therapy or the presence of brain metastases.

Although crizotinib is not approved for treating NSCLC patients with METex14 mutation, it is commonly used in clinical practice.[119] The phase II AcSe trial showed modest efficacy with an ORR of 36%, mPFS of 2.4 months, and mOS of 8.1 months.[8] In the METROS, an Italian multicenter phase II trial, patients with MET-positive NSCLC treated with crizotinib exhibited the ORR of 27%, the mPFS of 4.4 months, and the mOS of 5.4 months.[10] In conclusion, these trials suggest that while crizotinib can induce tumor shrinkage in some MET-regulated NSCLC tumors, its overall impact on the clinical course of MET-mutated NSCLC patients is limited.

Amivantamab is a bispecific antibody that targets both the EGFR and MET, exhibiting a higher affinity for MET (40 pM) compared to EGFR (1.4 nM), along with immune cell-guiding activity. In the MET-2 arm of the CHRYSALIS Phase I trial, the amivantamab cohort demonstrated a response rate of 33% and a mPFS of 6.7 months. Among patients who experienced TRAEs, 12% had their dose reduced, and 5% discontinued treatment. The most common TRAEs included infusion-related reactions (69%, 5% of ≥ grade 3), rash (7% of ≥ grade 3), impetigo, and peripheral edema, none of which reached grade 3 severity.[36] Despite these encouraging results with amivantamab and manageable toxicity, the optimal treatment sequence is still under study.

Similar to other oncogenic factors, such as BRAF, evidence regarding the efficacy of ICIs in patients with MET-positive NSCLC is limited and controversial. Studies indicate that the clinical activity of ICI monotherapy for this genotype is relatively low. Although some cases have reported durable responses,[107,120] at least three other retrospective studies have shown ORRs of less than 20% and mPFS of less than 5.0 months.[78,92,120] Based on this data, MET TKIs may be the preferred treatment for patients with MET-positive NSCLC.

KRAS G12C Mutation

In the 1960s, Harvey and Kirsten et al discovered the mouse tumor genes HRAS and KRAS, which are carried by retroviruses similar to rous sarcoma virus (RSV). In 1982, Weinberg et al identified HRAS in human bladder cancer cells, making RAS the first human tumor gene to be discovered.[121] Activated KRAS proteins activate downstream pathways, including RAF-MEK-ERK, PI3K-AKT-mTOR, and RALGDS-RAL pathways, driving cell differentiation and proliferation[122] (Figure 1). Approximately 2.8% of NSCLC patients harbor the KRAS G12C mutation[68]. Historically, treatments for KRASG12C mutant patients have shown limited efficacy with immunotherapy and chemotherapy, but KRAS G12CI inhibitors have yielded promising results in NSCLC.[123] The FDA approved sotorasib (AMG510) in May 2021 and adagrasib (MRTX849) in December 2022 for the treatment of NSCLC with the KRAS G12C mutation.[124,125]

Sotorasib is the first approved KRAS G12C inhibitor. A phase II study assessed its efficacy in NSCLC patients with KRAS G12C mutations, in the second/third-line settings, sotorasib had an ORR of 37.1%, mDoR of 11.1 months, and mPFS of 6.8 months.[38] The phase III CodeBreaK 200 study compared sotorasib to docetaxel in pretreated NSCLC patients. In the docetaxel group, the mPFS was 4.5 months, ORR was 13.2%, DCR was 60.3%, mDoR was 6.8 months, and mOS was 11.3 months. In contrast, the sotorasib group showed an mPFS of 5.6 months, ORR of 28.1%, DCR of 82.5%, mDoR of 8.6 months, and mOS of 10.6 months. Although sotorasib did not significantly improve OS compared to docetaxel, its toxicity and intracranial activity suggest it is a better option.[39]

Adagrasib is another KRAS G12C inhibitor that demonstrated its efficacy in the phase I KRYSTAL-1 trial,[40] leading to a phase II study. Adagrasib was used to treat patients with KRAS G12C mutated NSCLC, with an ORR of 42.9%, mDoR of 8.5 months, mPFS of 6.5 months, and mOS of 12.6 months.[41] Updated 2023 data extended the mOS to 14.1 months with a median 2-year survival rate of 31%.[126] Additionally, the phase III KRYSTAL-12 trial is evaluating adagrasib versus docetaxel in patients with advanced NSCLC harboring KRAS mutations.[127]

ICIs demonstrate clinical efficacy in patients with KRAS-mutated NSCLC. In the initial phase III trial of ICI-based immunotherapy for NSCLC, nivolumab monotherapy significantly improved OS compared to docetaxel in patients with KRAS mutations.[42] A pooled analysis of data from 12 registrational trials indicated that patients with untreated advanced KRAS G12C mutations had an ORR of 33% when treated with ICIs alone, without chemotherapy.[128] The efficacy of ICIs in patients with KRAS-mutant NSCLC has been further supported by multiple retrospective studies.

HER2 Mutation

In 1979, Schechter et al discovered a new oncogene in rat cells, naming it neu. They later identified that neu shares structural similarities with the previously discovered ERBB2 gene, leading to its alternative designation as ErbB-2. The protein encoded by the ERBB2 gene in humans resembles the structure of the human epidermal growth factor receptor, which is why neu is also referred to as HER2.[129] It forms a dimer with the receptor, and activates the RAS-RAF-MEK-ERK and PI3K-AKT signaling pathways to promote tumor cell proliferation[130] (Figure 1). The incidence of HER2 mutation in NSCLC is approximately 2.3%[68]. The FDA has approved trastuzumab (T-DXd) for the treatment of adult patients with inoperable or metastatic NSCLC with HER2 mutations who have previously received systemic platinum-based therapy, marking the first approved treatment for HER2-mutated lung cancer.[131]

Pyrotinib is an irreversible small molecule inhibitor of EGFR, HER2 and HER4 receptors. A phase II trial showed that platinum-pretreated patients with HER2-mutated advanced NSCLC treated with pyrotinib had an ORR of 30%, an mPFS of 6.9 months, and an mOS of 14.4 months. Subgroup analysis indicated that pyrotinib benefitted all patients, irrespective of brain metastases or HER2 mutant subtypes.[47] Another phase II clinical trial using pyrotinib as first-line or later-line treatment, the ORR was 19.2%, mPFS was 5.6 months, mDoR was 9.9 months, and mOS was 10.5 months.[48] These studies suggest that pyrotinib has clinical efficacy in HER2-mutated advanced NSCLC, although its efficacy in second-line treatment remains unclear. Currently, the phase III study (NCT04447118) is ongoing to evaluate the efficacy of pyrotinib versus docetaxel in platinum-pretreated advanced non-squamous NSCLC with HER2 mutation.[132]

Poziotinib is a novel covalent irreversible EGFR and HER2 receptor inhibitor. The phase II study ZENITH20 evaluated the efficacy of poziotinib monotherapy in HER2-mutated NSCLC. In this trial, the ORR was 27.8%, the DCR was 70%, the mPFS was 5.5 months, and the mDoR was 5.1 months. Poziotinib was efficacious regardless of prior therapy, CNS metastases, or HER2 mutation type. However, 97.8% of patients experienced TRAEs, leading to dose reduction and discontinuation in 76.7% and 13.3% of patients, respectively.[49] The ZENITH20-4 trial showed an ORR of 41%, a DCR of 73%, an mPFS of 5.6 months, and an mDoR of 5.7 months, with improved tolerance due to dose adjustments.[50]

Antibody-drug conjugates (ADCs) are a class of antitumour medicines that effectively extend the therapeutic window by precisely delivering cytotoxic chemicals into cancer cells.[133] T-DM1 is an ADC. A clinical study evaluating T-DM1 in HER2-mutated NSCLC was terminated early due to poor efficacy, with the ORR of 6.7% and the mPFS of 2.0 months.[134] However, a phase II basket trial demonstrated better efficacy: patients (n=18) treated with T-DM1 had an ORR of 44%, an mPFS of 5.0 months, and an mDoR of 4.0 months.[43] In the expanded clinical trial (n=49), the ORR was 50%, the mPFS was 5.0 months and the mDoR was 4.4 months.[44] Another phase II clinical trial reported the ORR was 38.1%, while mPFS and mDoR were only 2.8 and 3.5 months, respectively, for HER2-mutated NSCLC treated with T-DM1.[45] Overall, despite some short-term efficacy, the benefit of T-DM1 in advanced NSCLC with HER2 mutations appears limited in duration.

T-DXd is a relatively new anti-HER2 ADC. The phase II DESTINY-Lung01 study evaluated the efficacy and safety of T-DXd in HER2-mutated relapsed or refractory NSCLC, with the ORR of 55%, the mPFS of 8.2 months, the mDoR of 9.3 months, and the mOS of 17.8 months. It also showed efficacy in patients with brain metastases, with an mPFS of 7.1 months and mOS of 13.8 months.[46] The phase III trial DESTINY-Lung04 is currently ongoing, which compares the efficacy and safety of T-DXd monotherapy with chemotherapy in combination with pembrolizumab as first-line treatment for HER2-mutated advanced NSCLC.[135] In conclusion, T-DXd showed unprecedented efficacy and a manageable safety profile in HER2-mutated NSCLC.

The clinical benefit of immunotherapy in patients with HER2-mutated lung cancer is limited, with ORRs ranging from 7% to 27% and a mPFS of approximately 2 months.[78,107]

ALK Rearrangement

ALK was first identified in a subtype of anaplastic large cell lymphoma (ALCL), hence the name anaplastic lymphoma kinase (ALK). Before the discovery of ALK rearrangement in NSCLC, multiple types of ALK rearrangement have been identified in diffuse large B cell lymphoma and inflammatory myofibroblastic tumor, demonstrating that ALK is a potent oncogene.[136,137] ALK rearrangement is observed in about 3.8% of NSCLC.[68] ALK induces malignant transformation through the activation of pathways such as MAPK, PI3K-AKT, and JAK-STAT[138] (Figure 1). Five ALK inhibitors (alectinib,[139] brigatinib,[140] ceritinib,[141] crizotinib,[142] and lorlatinib[143]) have been approved by the FDA for ALK mutation-positive NSCLC.

Crizotinib is the first-generation ALK TKI. Two Phase III clinical trials showed the superior clinical efficacy of crizotinib compared to pemetrexed in combination with platinum-based chemotherapy in patients with advanced ALK-rearranged NSCLC.[51,52] Among patients who had not received platinum-based therapy, the PFS was significantly longer in the crizotinib group compared to the chemotherapy group (median value of 10.9 months vs 7.0 months).[51] However, resistance to crizotinib has led to the development of second/third-generation ALK TKIs that cover most secondary ALK mutations and effectively penetrate the blood-brain barrier to treat patients with brain metastases.

Ceritinib is the second-generation ALK TKI. The phase III ASCEND-04 trial showed a significant improvement in mPFS for ceritinib compared to pemetrexed combined with platinum-based chemotherapy in patients with ALK-rearranged lung adenocarcinoma (16.6 months vs 8.1 months).[53] The ASCEND-05 trial compared ceritinib to single-agent chemotherapy in patients with advanced ALK-rearranged NSCLC who had previously progressed following crizotinib and platinum-based doublet therapy, showing a significant improvement in mPFS compared with chemotherapy (5.4 months vs 1.6 months, respectively).[54] Comparison of crizotinib and ceritinib revealed a significant advantage for ceritinib in terms of PFS (25.2 months vs 10.8 months), but not in terms of OS.[144]

Brigatinib is another ALK TKI. Patients treated with brigatinib had a significantly longer median PFS compared to those treated with crizotinib (24.0 months vs 11.1 months), and the intracranial response rate was significantly higher in the brigatinib group (78% vs 29%).[55,56]

Alectinib, also a second-generation ALK TKI, significantly prolonged the mPFS in the ALEX study compared to crizotinib group (25.7 months vs 10.4 months). Alectinib also significantly reduced CNS progression events (12% vs 45%).[57] The phase III ALUR study compared the efficacy of alectinib with chemotherapy in patients with advanced metastatic ALK-rearranged NSCLC who had received prior platinum-based chemotherapy and crizotinib. Alectinib showed a mPFS of 10.9 months compared to 1.4 months in the chemotherapy group, with a CNS ORR of 66.7% in the alectinib group versus 0% in the chemotherapy group.[59]

Ensartinib, another second-generation ALK TKI, was evaluated in the phase II eXalt3 trial. Patients treated with ensartinib had a significantly better PFS compared to those treated with crizotinib (25.8 months vs 12.7 months), and the intracranial response rate was higher in the ensartinib group (63.6% vs 21.1%).[60]

Lorlatinib is a third-generation ALK TKI. In a phase II study, lorlatinib was used to treat patients with advanced NSCLC with ALK rearrangement, with an ORR of 47%.[61] The phase III CROWN trial compared lorlatinib with crizotinib, demonstrating improvements in PFS, ORR, intracranial response rate, time to intracranial progress, and DoR in the lorlatinib group. The 3-year PFS of 64% for lorlatinib compared to 19% for crizotinib. Among patients without brain metastases, intracranial progression occurred in 1% of patients in the lorlatinib group versus 23% in the crizotinib group.[145]

NRG1 Fusion

In 1997, the first mutation of the NRG1 gene was discovered. Two years later, it was identified as a fusion phenomenon, with the fusion partner gene of NRG1 initially confirmed as DOC4, along with the discovery of the NRG1 break site. By 2014, a series of partner genes fused with the NRG1 gene were identified in NSCLC, including CD74, SLC3A2, and VAMP2. By 2021, NRG1 gene fusions had also been found in ovarian cancer, prostate cancer, and endometrial cancer, garnering widespread attention.[146] NRG1 fusion occurs in non-squamous NSCLC at an incidence of about 0.1–0.4% and in more than 5% of invasive mucinous adenocarcinomas.[147] NRG1 proteins bind to cell surface HER3 receptor and

promote tumor cell proliferation by activating the PI3K-AKT-mTOR and MAPK signaling pathways[148] (Figure 1). Patients with NRG1 fusion usually do not respond well to chemotherapy, chemoimmunotherapy, or ICIs. However, treatment with HER2 inhibitors (indirect) or HER3 inhibitors (direct) may be an important way to stop tumor growth.[149]

Zenocutuzumab,[146,150] a HER2/HER3-targeting bispecific monoclonal antibody, and seribantumab,[63] an anti-HER3 monoclonal antibody, have shown encouraging efficacy in targeting NRG1-rearranged solid tumors, including NSCLC, and both are currently in phase II clinical trials (NCT02912949, NCT04383210).[151,152]

FGFR Mutation

Fibroblast growth factor (FGF) is a family of peptide growth factors with at least 23 different members found. FGF1 and its receptor FGFR regulates key biological processes such as cell proliferation and differentiation and promotes the growth and angiogenesis of various tumors, including lung or breast cancer.[153] FGFR promotes tumor cell proliferation through the activation of PI3K-AKT, STAT, PKC, and RAS-MAPK pathways[154] (Figure 1). The mutation rate of FGFR in NSCLC is about 1%.[155] Currently erdafitinib has been approved by the FDA for patients with urothelial carcinoma with FGFR mutation,[156] and pemigatinib, infigratinib, and futibatinib are approved for the treatment of patients with cholangiocarcinoma with FGFR mutation.[157–159]

Although most FGFR-targeting medications are still in preclinical testing or clinical research, numerous innovative therapies have been developed, including TKIs, selective inhibitors, and monoclonal antibodies like lenvatinib and dovitinib. The FGFR1 inhibitor ponatinib significantly inhibited the growth of primary lung cancer cells in vitro in NSCLC cell lines that expressed high levels of FGFR1. Moreover, in NSCLC patients with higher FGFR2/3 expression levels, erlotinib responded when combined with bevacizumab. A study showed that erdafitinib led apoptosis in FGF-dependent human squamous cell carcinoma NCI-H1581 and NCI-H520 cells by inhibiting FGF/FGFR.[160]

PI3KCA Mutation

In 1985, M. Whitman and L. Cantley first discovered a phosphatidylinositol kinase capable of phosphorylating inositol cyclo-3-OH to produce phosphatidylinositol 3,4,5-trisphosphate (PIP3). They defined this new kinase as phosphatidylinositol-3-kinase (PI3K), marking the official beginning of PI3K research.[161] Studies have demonstrated that PI3K overactivation of the downstream AKT-mTOR pathway mediates the development of a variety of malignant tumors, with PTEN being a key negative regulator of PIK3CA-activated PI3K-AKT-mTOR[162,163] (Figure 1). The mutation rate of PI3KCA in NSCLC is about 2–5%, being more common in squamous cell lung carcinoma (33%–37%) than in adenocarcinoma (5%–6%).[164]

Currently, many PI3K inhibitors are in different stages of preclinical studies and early clinical trials. Pan-class I PI3K inhibitors include pictilisib (GDC-0941), PX-866, buparisib (BKM120), pilaralisib (XL-147), GNE-317, etc. Unfortunately, trials of buparisib alone, buparisib in combination with gefitinib, and PX-866 in combination with docetaxel have not shown any efficacy.[165–167] Specific PI3K inhibitors have also been studied by Langer CJ et al. Taselisib, a selective PI3K inhibitor, was administered as monotherapy to patients with PI3K-positive lung cancer in the phase II LUNG-MAP trial, but the group was closed due to ineffectiveness.[168]

DDR2 Mutation

Discoidin domain receptors (DDRs) were classified as orphan receptors in the early 20th century. In 1997, Shrivastava et al described DDR as a non-integral collagen-binding receptor that requires collagen to initiate cellular responses. DDR is activated upon collagen binding.[169] To date, dysregulation, mutations, and differential expression of DDRs have been reported in various cancers. DDR2 mutations occur in approximately 4% of squamous NSCLCs and have been shown to promote the growth of lung squamous cell carcinoma cells.[164] Miao et al demonstrated that DDR2 mutants enhance lung squamous cell carcinoma cell proliferation and increase migration and invasion in the absence of collagen stimulation.[170] Additionally, the V582E and L595P mutants of the DDR2 gene induce DDR2 activation and promote cell growth and tumor progression by binding to collagen ligands.[171] While some DDR2 mutations function as oncogenic drivers, some studies suggest that DDR2 may exert inhibitory effects on cancer cells stimulated by fibrocollagen.[172] Although the

physiological and pathological functions of DDRs are well documented, their specific signaling pathways and molecular mechanisms require further exploration and validation.

Several DDR kinase inhibitors have been identified, such as dasatinib, imatinib, and nilotinib, and other BCR-ABL inhibitors.[173] Clinical trials of dasatinib were terminated due to intolerable toxicity and poor efficacy.[174] However, the combination of dasatinib with Src kinase inhibitors has been shown to reduce toxicity and improve the efficacy of dasatinib.[175] Currently, the role of DDR2 as a therapeutic target is not yet fully understood. As basic research continues to advance and genetic screening and personalized tumor therapy become more widespread, it is anticipated that more DDR2 inhibitors will be developed and applied in clinical settings.

Future Directions

With advancements of tumor molecular biology, more and more novel anti-tumor drugs have emerged, leading to significant breakthroughs in the treatment of patients with NSCLC. Traditional cytotoxic drugs have only modestly improved the survival rates of NSCLC patients. However, the identification of oncogenic driver genes has profoundly impacted cancer prognosis and treatment. The FDA has approved several targeted therapies for patients with mutations in oncogenic factors such as EGFR, ALK, ROS1, BRAF, MET, RET, FGFR, and NTRK. Additionally, the development of next-generation TKIs and immunotherapeutic agents has further enhanced treatment outcomes, allowing some patients to achieve long-term survival. Most clinical studies indicate that patients with oncogene mutations may experience greater survival benefits from targeted therapy compared to those receiving chemotherapy or immunotherapy. As a result, targeted therapy has become the preferred first-line treatment option for patients with oncogenic mutations.

Despite significant advancements, several challenges remain in the targeted therapy of NSCLC that require urgent attention. First, patients receiving targeted therapy or immunotherapy often develop drug resistance, leading to disease progression or relapse. For instance, crizotinib, the first ALK TKI approved for treating ALK-positive NSCLC, initially demonstrates promising efficacy (Table 1). However, nearly all patients eventually develop resistance and experience disease progression within one year, often in the brain or other parenchymal regions. Overcoming resistance remains a critical barrier to the long-term success of targeted therapies. Therefore, it is essential to explore new therapeutic targets, investigate resistance mechanisms, and develop novel drugs or strategies to address this issue. Second, while targeted therapies can provide durable responses and prolonged survival for some patients, they may also lead to an increased incidence of adverse effects. A meta-analysis of 31 randomized controlled trials evaluating TKIs in NSCLC treatment found that 27 of the studies reported TRAEs, with the most common being hypertension, fatigue, rash, and gastrointestinal disturbances.[176] Addressing these side effects and enhancing drug safety are focal points of current research. Identifying the underlying mechanisms of these adverse reactions and discovering biomarkers that predict their occurrence can inform future mechanism-based treatment approaches, ultimately improving patient quality of life. Additionally, the combination of immunotherapy, targeted therapy, and chemotherapy is an emerging area of research. Determining whether oncogene-positive NSCLC patients can benefit from immunotherapy is a hot topic in lung cancer treatment. Therefore, there is still a lot of work to be done to achieve true precision medicine.

In conclusion, the identification of oncogenic driver genes in NSCLC has revolutionized the treatment landscape and significantly improved patient prognosis. Precision-targeted therapies have become the first-line treatment option for NSCLC. However, there is still a long way to go in the fight against malignant tumors. Continued exploration of new therapeutic targets and innovative treatment strategies will be essential for advancing anti-tumor therapy, making it more precise and effective.

Abbreviations

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; NCCN, National Comprehensive Cancer Network; NGS, next generation sequencing; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; mPFS, median progression-free survival; ORR, objective response rate; mOS, median overall survival; DCR, disease control rate; mDOR, median duration of response; mo, month; NA, not applicable; RTK, receptor tyrosine kinase; TRK, tropomyosin receptor kinase; CNS, central nervous system; CR, complete response; PR, partial response; SD, stable disease; TRAE, treatment-related adverse event; HGFR,

hepatocyte growth factor receptor; HGF, hepatocyte growth factor; RSV, rous sarcoma virus; METex14, MET exon 14 skipping; METamp, MET amplification; ICI, immune checkpoint inhibitor; ADC, antibody-drug conjugate; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; FGF, fibroblast growth factor; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PI3K, phosphatidylinositol-3-kinase; DDR, discoidin domain receptor.

Consent for Publication

All authors reviewed and approved the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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