Review Article

Clinical characteristics and targeted therapy of different gene fusions in non-small cell lung cancer: a narrative review

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Background and Objective: Lung cancer is the most fatal malignant tumor in the world. Since the discovery of driver genes, targeted therapy has been demonstrated to be superior to traditional chemotherapy and has revolutionized the therapeutic landscape of non-small cell lung cancer (NSCLC). The remarkable success of tyrosine kinase inhibitors (TKIs) in patients with epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) fusions has shifted the treatment from platinum-based combination chemotherapy to targeted therapy. Although the incidence rate of gene fusion is low in NSCLC, it is of great significance in advanced refractory patients. However, the clinical characteristics and the latest treatment progress of patients with gene fusions in lung cancer have not been thoroughly explored. The objective of this narrative review was to summarize the latest research progress of targeted therapy for gene fusion variants in NSCLC to improve understanding for clinicians.

Methods: We conducted a search of PubMed database and American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and World Conference on Lung Cancer (WCLC) abstracts meeting proceedings from 1 January 2005 to 31 August 2022 with the following keywords "non-small cell lung cancer", "fusion", "rearrangement", "targeted therapy" and "tyrosine kinase inhibitor".

Key Content and Findings: We comprehensively listed the targeted therapy of various gene fusions in NSCLC. Fusions of *ALK*, ROS proto-oncogene 1 (*ROS1*), and rearranged during transfection proto-oncogene (*RET*) are relatively more common than others (*NTRK* fusions, *NRG1* fusions, *FGFR* fusions, etc.). Among *ALK*-rearranged NSCLC patients treated with crizotinib, alectinib, brigatinib, or ensartinib, the Asian population exhibited a slightly better effect than the non-Asian population in first-line therapy. It was revealed that ceritinib may have a slightly better effect in the non-Asian *ALK*-rearranged population as first-line therapy. The effect of crizotinib might be similar in Asians and non-Asians with *ROS1*-fusion-positive NSCLC in first-line therapy. The non-Asian population were shown to be more likely to be treated with selpercatinib and pralsetinib for *RET*-rearranged NSCLC than the Asian population.

Conclusions: The present report summarizes the current state of fusion gene research and the associated therapeutic methods to improve understanding for clinicians, but how to better overcome drug resistance remains a problem that needs to be explored.

Keywords: Non-small cell lung cancer (NSCLC); gene fusion variant; targeted therapy; clinical characteristic

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Introduction

Lung cancer is the most common cause of cancer-related death in the world (1). Non-small cell lung cancer (NSCLC) is responsible for approximately 85% of lung cancer cases. Most patients with lung cancer have reached a state of incurable progression by the time of diagnosis (2). In the past 20 years, continuous molecular biology research has identified a targeted therapy for lung cancer. Anaplastic lymphoma kinase (*ALK*) fusion is the most common gene fusion in lung cancer (3). ROS proto-oncogene 1 (*ROS1*) and rearranged during transfection proto-oncogene (*RET*) fusion are also common in lung cancer, accounting for 1–2% respectively (4,5). Neurotrophic tyrosine receptor kinase (*NTRK*), neuregulin 1 (*NRG1*), fibroblast growth factor receptor (*FGFR*), mesenchymal epithelial transition factor (*MET*), epidermal growth factor receptor (*EGFR*), and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) fusions do not present very frequently. As the first drug used in the treatment of advanced *ALK*-rearranged NSCLC, crizotinib has more benefits than traditional chemotherapy, which can improve the quality of life of patients (*Table 1*) (6-9). The second and third generation drugs, including ceritinib, alectinib, brigatinib, ensartinib, and lorlatinib have also achieved considerable clinical benefits and displayed more advantages than crizotinib (*Table 1*) (10-19). Crizotinib and entrectinib are the first-line drugs for the treatment of *ROS1*-rearranged NSCLC, and it has also been shown that ceritinib, lorlatinib, and taletrectinib are effective in *ROS1* fusion (*Table 1*) (14,20-24). Selpercatinib and pralsetinib are designated for *RET* fusion, and multi-target tyrosine kinase inhibitors (TKIs), such as vandetanib, have a partial effect on NSCLC patients with *RET* fusion (*Table 2*) (25-31). Larotrectinib and entrectinib are highly selective *NTRK* fusion inhibitors with anti-tumor activity in NSCLC, whereas rogaratinib and dovitinib are partly effective in *FGFR*-rearranged NSCLC (*Table 2*) (32-34). Afatinib can inhibit the continuous activation caused by the *NRG1* fusion gene and induce tumor cell death (35). Some NSCLC patients with *MET*, *EGFR*, or *BRAF* fusion have a partial response (PR) to crizotinib, erlotinib, or vemurafenib, respectively (36-40).

Due to the lack of a general summary of the fusion genes and their targeted therapy, this report provides an overview of the treatment of patients with *ALK*, *ROS1*, *RET*, *NTRK*, *NRG1*, *FGFR*, *MET*, *EGFR*, and *BRAF* fusion based on the existing clinical data. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-566/rc).

Methods

On 31 August 2022, a literature search was carried out in the PubMed database and the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the World Conference on Lung Cancer (WCLC) abstracts meeting proceedings. The following search terms were used: "non-small cell lung cancer", "fusion", "rearrangement", "targeted therapy", and "tyrosine kinase inhibitor". Only English articles, published between 1 January 2005 and 31 August 2022, were enrolled in this review (*Table 3*).

Common gene fusions

ALK fusion

ALK is considered a fusion gene of anaplastic large-cell lymphoma, which is a transmembrane receptor tyrosine kinase and belongs to the insulin receptor family (41). About 3–7% of NSCLC patients harbor an *ALK* fusion, mainly the adenocarcinoma subtypes. These cases are mutually exclusive for *KRAS* and *EGFR* mutations (3). In 2007, Soda *et al.* (2) discovered the echinoderm microtubule-associated protein 4 (EML4)-*ALK* fusion in a group of NSCLC patients. In addition, many types of *ALK* fusion, except *ALK*-EML4, have been reported in lung cancer, including KIF5B and KLC1 (42,43).

Crizotinib is a first-generation *ALK* inhibitor that is the first targeted drug for the treatment of NSCLC patients with *ALK* fusion (*Figure 1*). A previous phase I study (PROFILE 1001) evaluated 149 patients with *ALK*-fusion-positive stage III or IV NSCLC. The objective response rate (ORR) was 60.8%, the median progression-free survival (mPFS) was 9.7 months, and the duration of

Table 1 Clinical outcomes in *ALK/ROS1* fusion NSCLC with different therapies

Gene	Article reference	Cases	Therapy	ORR, %	Median PFS, month (95% CI)	Median OS, month (95% CI)
ALK	Camidge, 2012 (6)	149	Crizotinib	60.8	9.7 (7.7–12.8)	NR
	Kim, 2012 (7)	255	Crizotinib	53.0	8.5 (6.2–9.9)	NR
	Shaw, 2013 (8)	173	Crizotinib	65.0	7.7 (6.0–8.8)	20.3 (18.1–NR)
		174	Chemotherapy	20.0	3 (2.6–4.3)	22.8 (18.6–NR)
	Solomon, 2014 (9)	172	Crizotinib	74.0	10.9 (8.3–13.9)	NR
		171	Chemotherapy	45.0	7 (6.8–8.2)	NR
	Peters, 2017 (10)	152	Alectinib	NA	25.7 (19.9–NR)	NR
		151	Crizotinib	NA	10.4 (7.7–14.6)	NR
	Kim, 2017 (11)	112	Brigatinib (A)	45.0	9.2 (7.4–15.6)	NR
		110	Brigatinib (B)	54.0	12.9 (11.1–NR)	NR
	Shaw, 2017 (12)	115	Ceritinib	39.1	6.7 (4.4–7.9)	18.1 (13.4–23.9)
		116	Chemotherapy	6.9	1.6 (1.4–2.6)	20.1 (11.9–25.1)
	Soria, 2017 (13)	189	Ceritinib	72.5	16.6 (12.6–27.2)	NR (29.3–NR)
		187	Chemotherapy	26.7	8.1 (5.8–11.1)	26.2 (22.8–NR)
	Shaw, 2017 (14)	41	Lorlatinib	46.0	9.6 (3.4–16.6)	NR
	Cho, 2019 (15)	73	Ceritinib (450 mg)	78.1	NE (11.8–NE)	NA
		51	Ceritinib (600 mg)	72.5	17.0 (10.1–NE)	NA
		74	Ceritinib (750 mg)	75.7	12.2 (8.2–NE)	NA
	Shaw, 2020 (16)	149	Lorlatinib	76.0	NA	NA
		147	Crizotinib	58.0	9.3 (7.6–11.1)	NA
	Yang, 2020 (17)	147	Ensartinib	52.0	9.6 (7.4–11.6)	NR
	Horn, 2021 (18)	143	Ensartinib	74.0	31.3 (21.8–NR)	NR
		147	Crizotinib	67.0	12.7 (9.2–16.6)	NR
	Camidge, 2021 (19)	137	Brigatinib	71.0	24.0 (18.5–43.2)	NR
		138	Crizotinib	60.0	11.1 (9.1–13.0)	NR
ROS1	Shaw, 2017 (14)	12	Lorlatinib	50.0	7.0 (1.4–13.9)	NR
	Lim, 2017 (20)	32	Ceritinib	62.0	9.3 (0–22.0)	24.0 (5.0–43.0)
		30 (crizotinib-naïve)	Ceritinib	67.0	19.3 (1.0–37.0)	NA
	Wu, 2018 (21)	127	Crizotinib	71.7	15.9 (12.9–24.0)	32.5 (32.5–NR)
	Shaw, 2019 (22)	53	Crizotinib	72.0	19.3 (5.2–39.1)	51.4 (29.3–NR)
	Drilon, 2020 (23)	53	Entrectinib	77.0	19.0 (12.2–36.6)	NR
	Papadopoulos, 2020 (24)	6	Taletrectinib	33.3	4.1 (0.5–14.2)	NE

NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; *ALK*, anaplastic lymphoma kinase; *ROS1*, ROS proto-oncogene 1; A, 90 mg/day; B, 180 mg/day with a seven-day lead-in at 90 mg; NR, not reported; NE, not estimable; NA, not available.

Table 2 Clinical outcomes in other gene fusion NSCLC with different therapies

Gene	Article reference	Cases	Therapy	ORR, %	Median PFS, month (95% CI)	Median OS, month (95% CI)
RET	Drilon, 2016 (25)	26	Cabozantinib	NA	5.5 (3.8–8.4)	9.9 (8.1–NR)
	Yoh, 2017 (26)	19	Vandetanib	47.0	4.7 (2.8–8.5)	11.1 (9.4–NR)
		10 (KIF5B-RET)	Vandetanib	20.0	2.9 (1.1–15.7)	11.1 (3.0–NR)
		6 (CCDC6-RET)	Vandetanib	83.0	8.3 (4.7–8.5)	NR (9.9–NR)
	Lee, 2017 (27)	18	Vandetanib	18.0	4.5	11.6
	Gautschi, 2017 (28)	19	Cabozantinib	37.0	3.6 (1.3–7.0)	4.9 (1.9–14.3)
		11	Vandetanib	18.0	2.9 (1.0–6.4)	10.2 (2.4–NR)
		9	Sunitinib	22.0	2.2 (0.7–5.0)	6.8 (1.1–NR)
	Hida, 2019 (29)	25	Lenvatinib	16.0	7.3 (3.6–10.2)	NE (5.8–NE)
	Drilon, 2020 (30)	105	Selpercatinib	64.0	16.5 (13.7–NE)	NR
		39 (naïve)	Selpercatinib	85.0	NE (13.8–NE)	NR
	Griesinger, 2022 (31)	136	Pralsetinib	59.0	16.5 (10.5–24.1)	NR
		75 (naïve)	Pralsetinib	72.0	13.0 (9.1–NE)	NR
NTRK	Haratake, 2021 (32)	12	Larotrectinib	75.0	28.3 (22.1–NE)	44.4 (36.5–NE)
		10	Entrectinib	70.0	14.9 (4.7–NE)	NR
FGFR	Lim, 2016 (33)	26	Dovitinib	11.5	2.9 (1.5–4.3)	5.0 (3.6–6.4)
	Schuler, 2019 (34)	20	Rogaratinib	5.0	NA	NA

NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; *RET*, rearranged during transfection proto-oncogene; *NTRK*, neurotrophic tyrosine receptor kinase; *FGFR*, fibroblast growth factor receptor; naïve, previously untreated; NR, not reported; NE, not estimable; NA, not available.

Table 3 Search strategy summary

Items	Specification
Date of search	31 August 2022
Databases and other sources searched	PubMed and ASCO, ESMO, WCLC abstracts meeting proceedings
Search terms used	"Non-small cell lung cancer" [All fields] AND ("fusion" [All fields] OR "rearrangement" [All fields]) AND ("targeted therapy" [All fields] OR "tyrosine kinase inhibitor" [All fields])
Timeframe	1 January 2005 to 31 August 2022
Inclusion and exclusion criteria	Inclusion criteria: Clinical studies, multicenter studies, case reports and abstracts presented at recent international meetings. Only English-language articles were included
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Two authors independently selected studies and disagreements were discussed and resolved with a third author

ASCO, American Society of Clinical Oncology; ESMO, the European Society for Medical Oncology; WCLC, World Conference on Lung Cancer.

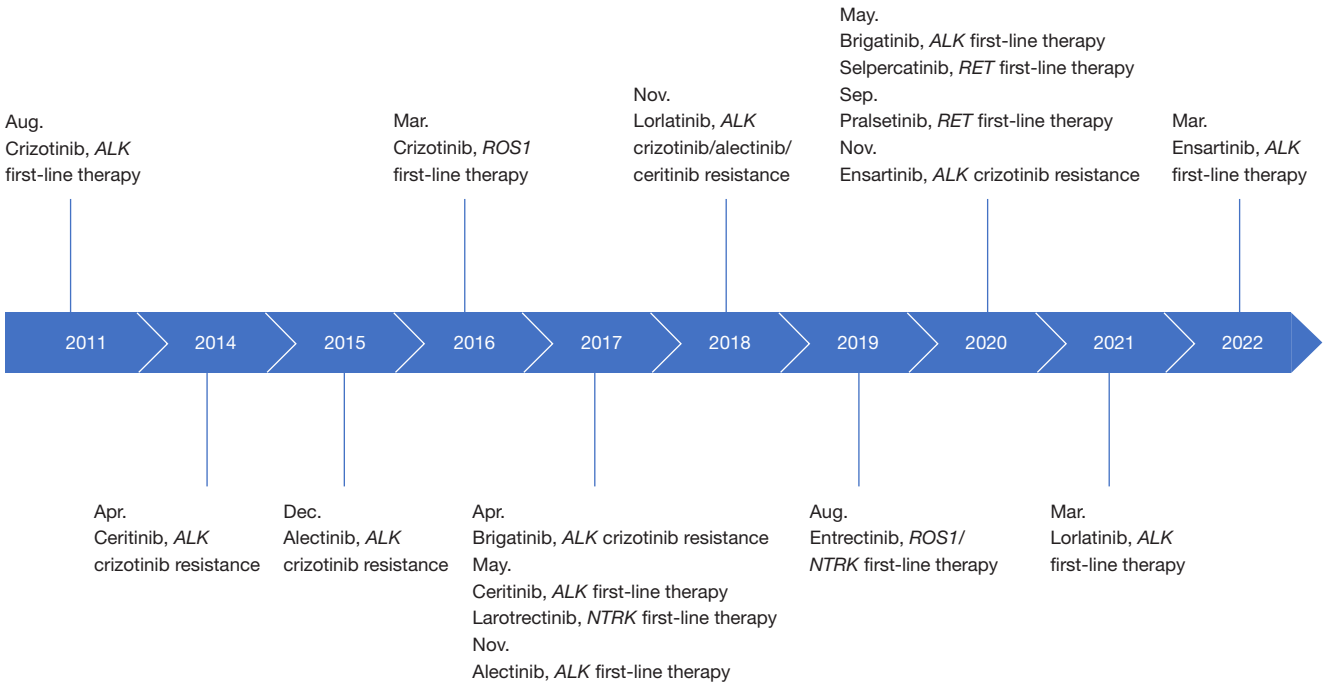

Figure 1 Timeline of targeted drugs' development for the treatment of gene fusion in non-small cell lung cancer. *ALK*, anaplastic lymphoma kinase; *ROS1*, ROS proto-oncogene 1; *RET*, rearranged during transfection proto-oncogene; *NTRK*, neurotrophic tyrosine receptor kinase.

response (DOR) was 49.1 weeks. The efficacy of crizotinib was preliminarily demonstrated, showing that its benefits had no correlation with age, sex, physical status, and previous treatments (6). Subsequently, the PROFILE 1005 trial further confirmed the safety and tolerability of crizotinib. Among patients with advanced *ALK*-fusion-positive NSCLC who received at least 1 first-line systematic treatment, the ORR and mPFS in patients treated with crizotinib were 53% and 8.5 months, respectively. In addition, most of the adverse reactions associated with crizotinib were of grades 1 to 2 (7). The most common treatment-related grade 3–4 adverse reactions were elevated aminotransferase levels and reduced neutrophil levels. In a randomized controlled phase III PROFILE 1007 trial, 347 patients with advanced *ALK*-fusion-positive NSCLC who experienced failure with first-line platinum chemotherapy were randomly assigned to either the crizotinib or standardized treatment group. The results showed that the mPFS in the crizotinib group was longer (7.7 *vs.* 3.0 months), the ORR was higher (65% *vs.* 20%), the symptoms were significantly alleviated, and the overall condition was improved (8). Subsequently, the PROFILE 1014 trial also found that among 343 patients with advanced *ALK*-fusion-positive NSCLC who were not previously treated with chemotherapy, the PFS was significantly prolonged in the crizotinib group (10.9 *vs.* 7.0 months), the ORR was significantly better than chemotherapy (74% *vs.* 45%), yet no significant difference was found in median overall survival (mOS) between the 2 groups, which may be due to the fact that 70% of patients in the chemotherapy group overlapped with the crizotinib group (9). In the study of crizotinib as first-line treatment, Asians treated with crizotinib accounted for 28 to 57%, while non-Asians comprised 43–73% (6,9,10,16,18). In the PROFILE 1014 trial, Asians treated with crizotinib were associated with longer mPFS [hazard ratio (HR): 0.44, 95% CI: 0.30–0.65] than chemotherapy, and the HR of mPFS in non-Asians was 0.53 (95% CI: 0.36–0.76) (9). Additionally, in a cohort study of Chinese patients, the mPFS was 11.1 months (HR: 0.40, 95% CI: 0.29–0.57) (44). Combining the results of these 2 studies, it could be interpreted that crizotinib has a slightly better effect on the Asian population.

The second-generation *ALK* inhibitors ceritinib and alectinib have been shown to be effective against many crizotinib-resistant *ALK*-fusion-positive NSCLC patients, including tumors carrying the L1196M gatekeeper mutation (45). In April 2014, ceritinib was approved by the US Food and Drug Administration (FDA) for the

treatment of metastatic *ALK*-fusion-positive NSCLC patients experiencing progression or harboring intolerance to crizotinib. The randomized phase III trials ASCEND-4 and ASCEND-5 showed that PFS with ceritinib use was significantly longer than that with chemotherapy (16.6 *vs.* 8.1 months and 6.7 *vs.* 1.6 months, respectively), whereas the ceritinib group achieved a better tumor remission rate (12,13). Based on the ASCEND-4 trial results, ceritinib was approved by the FDA as the first-line treatment for NSCLC in May 2017 (46). In studies of ceritinib as first-line treatment, the Asian population accounted for 35–40% of cases, whereas non-Asians comprised 60–65% (13,15). In the ASCEND-4 trial, the mPFS of Asian patients was 26.3 months (HR: 0.66, 95% CI: 0.41–1.06), and the mPFS of non-Asians was 16.4 months (HR: 0.44, 95% CI: 0.30–0.66) (13). Synthesis of the results of this study indicated that ceritinib may have a slightly better effect in the non-Asian population.

The main reason that alectinib is superior to crizotinib and ceritinib is that it can pass through the blood-brain barrier when administered at a large dose. The brain is a common site of recurrence in patients treated with crizotinib, and alectinib is the best choice for patients with central nervous system (CNS) metastasis. The ALEX clinical trial evaluated 303 treatment naïve patients with advanced *ALK*-fusion-positive NSCLC. Oral administration of alectinib (600 mg, twice per day) and crizotinib (250 mg, twice per day) showed that the efficacy of alectinib was significantly better than that of crizotinib. The event-free survival (EFS) of the alectinib group is higher than that of the crizotinib group (68.4% *vs.* 48.7%), and the mPFS was 25.7 and 10.4 months, respectively. CNS progression occurred in 12% of patients in the alectinib group and 45% in the crizotinib group. In addition, Asians comprised 45% of the population and non-Asians made up 55%. Asians treated with alectinib achieved longer mPFS (HR: 0.46, 95% CI: 0.28–0.75) than crizotinib, and the HR of mPFS in non-Asians was 0.49 (95% CI: 0.32–0.76). Therefore, the Asian population treated with alectinib might receive a slightly better effect (10). Based on the patients' good prognosis, alectinib was approved by the FDA in December 2015 for the treatment of metastatic *ALK*-fusion-positive NSCLC with disease progression or intolerance to crizotinib. In November 2017, alectinib was approved as the first-line treatment for patients with *ALK*-fusion-positive NSCLC at a recommended dose of 600 mg twice per day. The 2019 National Comprehensive Cancer Network (NCCN) guidelines recommend it as the first choice for first-line treatment. The updated 2020 ASCO 5-year overall survival (OS) results for the ALEX study showed that the mOS in the alectinib group was significantly better than that in the crizotinib group. A total of 62.5% of patients treated with alectinib as the first-line treatment survived for 5 years, whereas the 5-year OS rate for crizotinib was 45.5% (47).

Brigatinib is an oral TKI that inhibits *ALK* rearrangement. Its inhibitory effect on *ALK* is 12 times higher than that of crizotinib. In a phase II clinical trial for brigatinib, patients were divided into the following 2 groups according to different medication regimens: arm A (90 mg/day) and arm B (180 mg/day with a 7-day lead-in at 90 mg). As evaluated by an independent review committee, the ORR of arms A and B was 45% and 54%, respectively, and the intracranial ORR of patients with measurable brain metastasis was 42% and 67%, respectively. The medication regimen of arm B was more effective compared to that of arm A (11). Based on this experiment, brigatinib was approved by the FDA in April 2017 as the second-line treatment for *ALK*-fusion-positive NSCLC. A recent phase III trial compared the efficacy of brigatinib and crizotinib in the treatment of *ALK*-fusion-positive metastatic NSCLC patients. The results showed that the confirmed ORR was 71% with brigatinib and 60% with crizotinib, whereas the PFS for brigatinib was higher than that for crizotinib (estimated 12-month PFS, 69% *vs.* 43%). In addition, the intracranial ORR was significantly higher than that of crizotinib (78% *vs.* 29%). In first-line treatment, Asians treated with brigatinib accounted for 43% of the population, whereas non-Asians made up 57%. The Asian subgroup achieved longer mPFS (HR: 0.35, 95% CI: 0.20–0.59) than crizotinib, and the HR of mPFS in non-Asians was 0.56 (95% CI: 0.38–0.84). Therefore, brigatinib may have a slightly better effect in the Asian population (19,48). Based on the above results, the 2019 NCCN guidelines recommended brigatinib as the first-line treatment for patients with *ALK*-fusion-positive NSCLC. The 2020 ASCO have previously reported the efficacy and safety of brigatinib in patients treated with alectinib and experiencing progression. The efficacy analysis including 47 patients showed that the ORR was 30% and PFS was 7.3 months. In addition, the adverse reactions to brigatinib were similar to those previously reported. Moreover, brigatinib demonstrated a level of activity against *ALK* kinase domain secondary drug-resistant mutations, such as L1196M, I1171N, G1202R, and V1180L (49).

Ensartinib is a targeted drug originally developed in China. A single-arm, multicenter study in China reported

that the ORR of patients treated with ensartinib was 52% and the mPFS was 9.6 months (17). The eXalt3 study was a global randomized controlled trial which reported that the mPFS of patients with ensartinib was significantly longer than with crizotinib (31.3 *vs.*12.7 months). The 2-year survival rate in the ensartinib group was 78%, indicating that ensartinib may significantly improve the quality of life of ALK-fusion patients. Further, the Asian population accounted for 53.8%, whereas non-Asians made up 46.2%. Asians treated with ensartinib achieved longer mPFS (HR: 0.32, 95% CI: 0.19–0.55) than those treated with crizotinib, and the HR of mPFS in non-Asians was 0.61 (95% CI: 0.34–1.11). It could be seen that ensartinib has a slightly better effect in the Asian population. In March 2022, ensartinib was approved by the National Medical Products Administration (NMPA) for first-line treatment of locally advanced or metastatic ALK-fusion-positive NSCLC (18).

Lorlatinib is a third-generation *ALK* inhibitor that is highly selective for *ALK/ROS1*. In 2017, the results of the first phase I clinical trial on the third-generation *ALK* inhibitor lorlatinib in advanced *ALK/ROS1*-fusion-positive NSCLC were announced. They demonstrated that lorlatinib was effective for patients who have been previously treated with *ALK* inhibitors and developed drug-resistant mutations, such as G1202R. In *ALK*-fusion-positive patients, the ORR for lorlatinib was 46%, and the mPFS was 9.6 months. The ORR for lorlatinib was 50% in patients with *ROS1* rearrangement. This study suggested that lorlatinib is effective in patients with prior first- or second-generation *ALK* inhibitor resistance (14). At present, the phase III clinical trial CROWN on lorlatinib versus crizotinib as the first-line treatment for advanced *ALK*-fusion-positive NSCLC is under way. The Asian population treated with lorlatinib accounts for 44%, and non-Asians comprise 56%. By March 2020, the ORR in the lorlatinib group was 76% and 58% in the crizotinib group. The ORR in patients with measurable intracranial metastases was 82% and 23%, respectively. In addition, 71% of patients who received lorlatinib had a complete intracranial response (16). In November 2018, the FDA approved lorlatinib for the treatment of advanced *ALK*-fusion-positive NSCLC patients who have been previously treated with other *ALK* inhibitors. A phase II study reported by 2020 ASCO evaluated the use of third-generation *ALK*-TKI lorlatinib in advanced NSCLC patients experiencing only intracranial progression after the *ALK*-TKI treatment. A total of 22 patients were included. The results showed that the best intracranial ORR was 59%, intracranial disease control rate (DCR) was 95%, and 1-year intracranial PFS was 81%. Preliminary data showed a satisfactory lorlatinib efficacy in the treatment of brain metastasis (50).

ROS1 fusion

ROS1 can express a rare tyrosine kinase associated with *ALK*, which belongs to the insulin receptor family. In similarity to other tyrosine kinase receptors, the *ROS1*-fusion-positive gene can also activate signal transduction pathways for cell growth and survival. About 1–2% of NSCLC patients have a *ROS1* fusion (51,52). To date, more than 100 types of lung cancer have been reported to have *ROS1*-fusion-positive partners, including CD74, EZR, and SLC34A2.

In 2014, the results for the phase I PROFILE 1001 study on crizotinib for advanced *ROS1*-fusion-positive NSCLC were first reported (53). On 11 March 2016, the FDA expanded the crizotinib indication and approved it for the treatment of metastatic NSCLC with *ROS1* fusion. Shaw *et al.* have reported the updated data for this study in 2019, with a median duration of treatment of 22.4 months in 53 patients. The ORR was 72%, the mPFS was 19.3 months, and the mOS was 51.4 months. Among the study population, Asians treated with crizotinib as first-line treatment accounted for 40%, whereas non-Asian made up 60%. The ORR of the Asian and non-Asian subgroups were 71.4% and 71.9%, respectively. It could be seen that the effect of crizotinib may be similar in the Asian and non-Asian populations with *ROS1*-fusion-positive NSCLC (22). Wu *et al.* assessed the efficacy of crizotinib in East Asian populations with *ROS1*-positive advanced NSCLC in 2018. The phase II clinical study included 127 patients with advanced *ROS1*-fusion-positive NSCLC, which was detected by reverse transcription-polymerase chain reaction (RT-PCR). The ORR for crizotinib was 71.7%, and the mPFS was about 15.9 months (21). In 2017, a phase II clinical study on ceritinib for advanced *ROS1*-fusion-positive NSCLC was announced. A total of 32 patients with *ROS1* fusion were enrolled in the study, of which 28 were evaluated. The resulting ORR for ceritinib was 62%, and the mPFS was 9.3 months. In patients who had not been treated with crizotinib before, the ORR for ceritinib was 67%, and the mPFS was 19.3 months. This study showed that ceritinib had a good clinical effect in a multi-line treatment of *ROS1* fusion in advanced NSCLC (20). Entrectinib is a multi-target inhibitor of *ALK/ROS1* tyrosine kinase and is also effective in the treatment of

NSCLC with *ROS1* fusion. The results of 2 phase I clinical trials on entrectinib, ALKA-372-001 and STARTRK-1, showed that the ORR for previously untreated NSCLC with *ROS1* fusion was as high as 77%, and that its mPFS was 19 months (23). However, patients treated with crizotinib did not respond to entrectinib (22). Taletrectinib is a new, effective, and selective TKI of *ROS1* and *NTRK* that can cross the blood-brain barrier. Phase 1 clinical data for taletrectinib in the treatment of advanced solid tumors in the United States were published in 2020. The confirmed ORR was 33.3% among the 6 patients with crizotinib-refractory *ROS1*-fusion-positive NSCLC (24).

RET fusion

RET fusion is common in non-smoking lung adenocarcinoma (LUAD) patients. Its incidence rate in NSCLC is 1–2% (5). To date, at least 50 *RET* fusion variants have been identified, of which KIF5B-*RET* and CCDC6-*RET* are the most common (54,55).

At present, selpercatinib and pralsetinib are designated for *RET* fusion. The efficacy of multi-target TKIs, such as vandetanib and lenvatinib, in the treatment of *RET*-fusion-positive NSCLC is mediocre. New *RET* inhibitors are currently being developed with encouraging preliminary results. The outcomes of a phase II clinical study demonstrated that the ORR for vandetanib in patients with recurrent or metastatic NSCLC with *RET* fusion after platinum-containing dual-drug chemotherapy resistance development was only 18%, whereas the mPFS was 4.5 months, and the mOS was 11.6 months. In addition, 5 patients with KIF5B-*RET* did not achieve a response. It should be highlighted that the treatment response varies with the location of *RET* fusion (27). The LURET study showed that the efficacy of vandetanib in the treatment of NSCLC with CCDC6-*RET* fusion was significantly better than that of KIF5B-*RET* fusion, with effective rates of 83% and 20% and mPFS of 8.3 and 2.9 months, respectively (26). The results of another phase II clinical trial showed that the mPFS for cabozantinib in the treatment of NSCLC with *RET* fusion was 5.5 months. The Asian population treated with cabozantinib as first-line treatment accounted for 21%, whereas non-Asians made up 79% (25). The ORR for lenvatinib in the treatment of NSCLC with *RET* fusion was 16%, the DCR was 73%, and the mPFS was 7.3 months (29). Another retrospective analysis with the largest sample size of NSCLC cases with *RET* fusion from all over the world showed that the most common *RET* fusion subtype was KIF5B-*RET*, accounting for about 72% of cases. The mPFS for patients treated with *RET* inhibitors was 2.3 months. The ORR values for patients treated with cabozantinib, vandetanib, and sunitinib were 37%, 18%, and 22%, respectively. Lenvatinib and nintedanib also showed a curative effect, but no effect was observed after treatment with sorafenib, alectinib, and regorafenib (28). Another new type of highly selective *RET* inhibitor, selpercatinib, has also attracted attention because of its outstanding efficacy. Selpercatinib is the first approved *RET* fusion targeted drug (30). The LIBRETTO-001 study evaluated 105 patients in the posterior line, and their ORR was 64%. The fusion partner gene and the number of lines or types of treatment previously received did not affect the efficacy, and the mPFS was 16.5 months. In the same study, 39 patients in the initial treatment cohort had an ORR of 85%, whereas the mPFS was not evaluated. In addition, the Asian population who received selpercatinib as first-line treatment accounted for 18%, whereas non-Asians comprised 82% (30). Pralsetinib is another specific therapeutic drug for *RET* fusion. The ARROW trial evaluated 136 patients in the posterior line treatment and 75 in first line, for whom the ORRs were 59% and 72%, respectively. The mPFS of treatment-naïve patients was 13.0 months, whereas it was 16.5 months in posterior line treatment group. Additionally, the Asian population who received pralsetinib as first-line treatment accounted for 34%, whereas non-Asians comprised 66% (31).

Uncommon gene fusions

NTRK fusion

NTRK fusion is present in a variety of solid tumors, including frequent occurrences in some rare tumors. It also accounts for a certain proportion of common tumors, such as lung, breast, thyroid, and colorectal cancers (52). The most common types of *NTRK* gene fusion are ETV6-NTRK3 and TPM3-NTRK1 (56). The approval of drugs for this target may bring new hope to patients with different cancers, and authoritative guidelines for various cancers suggest that as long as tumors carry the *NTRK* gene fusion, appropriate targeted drugs can be considered for use, including larotrectinib and entrectinib. Larotrectinib is the first pan-TRK selective inhibitor in clinical development. In a study that analyzed 3phase I/II clinical trials, eligible participants were *NTRK* fusion-positive patients with locally progressive or metastatic solid tumors, who had received standard treatment and were in good health, and 12 of

whom had lung cancer. The ORR for patients with NSCLC treated with larotrectinib was up to 75%, the mPFS was 28.3 months, and drug safety was controllable. The mOS was 44.4 months (32,57,58). A prior study on entrectinib summarized phase 1 and 2 clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2). As of 31 March 2018, it contained 10 different tumor types and 19 different tissue types in 54 patients with metastatic or locally advanced solid tumors. The median follow-up time was 12.9 months (interquartile range: 8.77–18.76). Of the 54 patients, 31 cases (57%) achieved an ORR. The median DOR was 10 months (59). Among 54 patients with *NTRK* fusion gene-positive solid tumors, 10 had NSCLC. The ORR for NSCLC was 70% and the mPFS was 14.9 months. Taletrectinib, repotrectinib, and selirectinib are currently under development as next-generation TRK inhibitors (32).

NRG1 fusion

NRG1 is a new and possibly effective carcinogenic driving gene. Compared to other common driving mutations, the prevalence of NRG1 fusion in lung cancer is relatively low. In one study, NRG1 fusion was detected in 25 out of 9,592 NSCLC cases (0.26%), where CD74 and SDC4 have been reported to be the most common fusion partners in lung cancer (60). *NRG1* is a member of the EGF ligand family and can transduce its signal through *HER/ERBB* family receptor tyrosine kinases. Targeting *HER2* and *ERBB3* fusions has become an effective treatment strategy *in vitro* (61). At present, the target inhibitors are mainly small molecule TKIs aimed at *EGFR/HER2* fusions, including afatinib, lapatinib, neratinib, and tarloxitinib. Gay *et al.* first reported cases of effective targeted therapy for *NRG1*-fusion-positive NSCLC in 2017. Neither *ERBB* receptor activation mutation nor copy number change was found in any patient before or after treatment with afatinib. Their experience suggests that patients with *NRG1*-fusion-positive NSCLC may benefit from treatment with afatinib and possibly other *ERBB*-targeted therapies (60). Tarloxotinib is a PAN-*ERBB* inhibitor, which shows stronger and longer-lasting anti-tumor activity than afatinib in xenografts derived from CLU-*NRG1* patients. A phase II study is currently under way in NSCLC patients with *HER2*-activating mutations and solid tumors with *NRG1* or *ERBB* fusion (62).

FGFR fusion

FGFR is a type of transmembrane tyrosine kinase receptor. Its family includes 4 *FGFR* receptor subtypes (*FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4*) and up to 18 fibroblast growth factor ligands (63). The *FGFR1* fusion is relatively rare. Its overexpression causes excessive activation of the FGFR signaling pathway and further induces normal cell carcinogenesis. The *FGFR2* fusion is mainly concentrated in cholangiocarcinoma. The *FGFR3* fusion occurs in gliomas and bladder cancer. The *FGFR4* fusion is even rarer. *FGFR* gene fusion can activate the kinase region and induce the formation and development of many kinds of tumors. Small molecule inhibitors targeting the *FGFR* fusion gene can significantly inhibit tumorigenesis (64). *FGFR* fusions have occurred in about 1% of patients with NSCLC and 2–3.5% of patients with squamous cell lung cancer (SCC) (65). Outcomes of the first phase II trial that evaluated AZD4547 as a targeted treatment in patients with *FGFR*-altered SCC showed that AZD4547 had minimal activity in predominantly *FGFR1/FGFR3*-amplified cohort. Very few patients had *FGFR* fusions. Therefore, conclusions regarding efficacy in this subpopulation can be drawn after further study (66). A phase II study evaluated the efficacy of dovitinib in 26 patients with SCC. The median DOR was 2.5 months, the ORR was 11.5%, and the DCR was 50% in 3 patients with a PR (33). One patient achieved a PR after treatment with rogaratinib in a clinical trial including 20 patients with *FGFR*-fusion-positive NSCLC (34).

MET fusion

MET is located on the long arm of human chromosome 7. Its protein product is hepatocyte growth factor (HGF) tyrosine kinase receptor, which has tyrosine kinase activity and is related to a variety of oncogene products and regulatory proteins. It is also involved in the regulation of cell signal transduction and cytoskeleton (67). A case report published in 2017 documented the first case of identification and treatment of *MET* fusion in NSCLC. It evaluated the patient's tumor response to crizotinib treatment. The fusion gene was detected by next-generation sequencing (NGS) based on anchored multiplex PCR, identifying the HLA-DRB1-*MET* fusion, which had not been previously reported. The patient showed a significant response to crizotinib, which is a small molecular TKI with anti-*HGFR* activity (36). A novel gene fusion variant *MET*–ATXN7L1 was identified in a patient with LUAD. The patient had displayed a PR to crizotinib (37). Previous cases have also shown the efficacy of crizotinib in NSCLC patients with *MET* fusions (68-70). In September 2018,

Zhu *et al.* reported the first case of *EGFR*-TKI-resistant *MET*-UBE2H fusion in a patient with LUAD. It showed significant and lasting anti-tumor response after the use of crizotinib and achieved a sustained PR. This fusion gene exhibits a new type of drug resistance to *EGFR*-TKI (71).

EGFR fusion

EGFR is a member of the epidermal growth factor receptor family, which is widely distributed on the surface of mammalian epithelial cells, fibroblasts, glial cells, keratinocytes, and other cells, and plays an important role in the physiological processes of cell growth, proliferation, and differentiation (72). In September 2014, the *EGFR* fusion gene was reported for the first time in the analysis of RNA-seq data for nearly 7,000 cancer genome map samples. A new *EGFR* fusion was found in low-grade gliomas, and its fusion partner was SEPT14 (73). In 2016, Konduri *et al.* described 5 patients with NSCLC with *EGFR* fusion that experienced significant and sustained anti-tumor responses to treatment with erlotinib (74). The first case of *EGFR* fusion in China was reported in January 2018, where the patient exhibited a PR to erlotinib (38). In June 2018, Xu *et al.* first reported the epidemiological data for the *EGFR* fusion gene in a Chinese NSCLC patient at the ASCO annual meeting. Out of 2,410 NSCLC samples, only 2 (0.08%) patients diagnosed with LUAD had a new type of *EGFR*-RAD51 and *EGFR*-SEPT14 fusion. Those 2 patients had PRs to erlotinib and icotinib, respectively (75).

BRAF fusion

BRAF is a member of the RAF gene family of human chromosome 7q34, which is located on the serine/threonine kinase downstream of *KRAS* in the "RAS-RAF-MEK-ERK" signaling pathway and plays an important role in the MAPK signaling pathway (76). In 2005, the AKAP9-*BRAF* fusion as a new mechanism of activating the MAPK signaling pathway was reported for the first time in thyroid cancer, which opened a new chapter in the study of *BRAF* fusion (77). In 2016, Ross *et al.* found that 0.2% (8/4,013) of patients with NSCLC were harboring *BRAF* fusions. All NSCLC cases with *BRAF* fusions were adenocarcinomas or had adenocarcinoma features. *BRAF* fusions have not been observed in squamous or small cell lung cancers (76). Unfortunately, there are no data on *BRAF* inhibitors used in patients with lung cancer with *BRAF* fusion. In 2019, Zhu *et al.* reported a case of a patient with *TRIM24-BRAF*-fusion-positive NSCLC who received vemurafenib. The patient was considered to have a PR, and the PFS was 3.5 months (39).

There are other rare fusion genes in lung cancer, such as *HER2*, *KRAS*, *AKT1*, and *RAF1* (41,78-80). Based on the rapid development of NGS and whole-exon gene sequencing, more new fusion variants in lung cancer will be identified. Their clinical characteristics and treatment methods will have to be further explored and studied in clinical practice.

Conclusions

At present, many studies are investigating new gene targets for fusion mutations in NSCLC. Continuous reports on fusion genes show that they play an important role in carcinogenesis. With more in-depth study of different fusion variations, medical precision in targeting therapy of fusion variants in NSCLC will become more and more significant. The detection of gene fusion and the emergence of TKIs bring hope for NSCLC patients. Although gene fusion is rare in NSCLC, it is of great significance in advanced refractory patients. The present report summarizes the current state of fusion gene research and the associated therapeutic methods. How to better overcome drug resistance remains an urgent problem, in addition to many unknowns and challenges that require continuous exploration.

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Footnote

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