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ORIGINAL ARTICLE

Review of NTRK Fusion-Positive Non-Small Cell Lung Cancer

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Abstract

NTRK (neurotrophic tyrosine receptor kinase) gene fusions are genetic alterations that can drive cancer development, including in lung cancer. The incidence of neurotrophic myosin receptor kinase (NTRK) fusions in NSCLC is extremely low, with reports of approximately 0.2%. By reviewing the literature, we will learn about the NTRK gene family, the distribution of NTRK fusions in tumors, its detection methods, the treatment and resistance mechanism of targeted drugs, so that clinicians can have a deeper understanding of NTRK fusion lung cancer.

Keywords: NTRK fusion | NSCLC | NTRK family | Testing methods | Drug resistance mechanism

Introduction

In recent years, the incidence of lung cancer has been steadily increasing, with reports suggesting that the incidence rate of lung cancer has surpassed that of breast cancer and prostate cancer, ranking first worldwide. Targeted therapy has become one of the main treatment strategies for lung cancer, especially for patients with positive driver genes. However, in NSCLC, EGFR mutation is the most common type. Literature suggests that in Asia, the detection rate of lung cancer is about 40% for EGFR[1], and targeted drugs for EGFR are relatively numerous and mature. In recent years, research into targeted drugs for other mutations in lung cancer, such as ALK, MET, RET, and KRAS, has also been increasing, and promising results have been achieved. NTRK fusion is extremely rare in NSCLC, with a reported incidence of about 0.2%[2]. The author, engaged in clinical work related to lung tumors for five years, encountered one case of NTRK mutation, where the patient could afford entrectinib treatment, resulting in a good therapeutic effect. This study aims to raise awareness among clinical medical workers about NTRK mutations in lung cancer, the efficacy of targeted drugs on these mutations, and to summarize relevant knowledge about NTRK through a literature review.

2.Review of NTRK Mutations

2.1 | NTRK Family

The NTRK family is part of a transmembrane tyrosine kinase responsible for neuronal development. This receptor family includes TRKA, TRKB, and TRKC, which are encoded by the NTRK1, NTRK2, and NTRK3 genes, respectively. These receptors have intracellular kinase domains, transmembrane regions, and extracellular binding domains [3]. The binding of neurotrophic factors and the activation of TRK lead to receptor dimerization, followed by activation of the intracellular domains and recruitment of cytoplasmic scaffolding proteins, which in turn activate downstream signaling pathways through MAPK, PI3K, and/or PKC[4]. Although these three receptors are highly

homologous, they each have preferred ligands. The NTRK1 gene is located on chromosome 1q21-q22, and the protein it encodes has the highest affinity for nerve growth factor. The NTRK2 gene is located on chromosome 9q22.1, and its corresponding encoding protein has the highest affinity for neurotrophin-4 and brain-derived neurotrophic factor. The NTRK3 gene is located on chromosome 15q25, and the protein it encodes has the highest affinity for neurotrophin-3[3]. Cancer is primarily driven by NTRK gene fusions. NTRK fusions result from intrachromosomal or interchromosomal rearrangements, where the 3' sequence of NTRK1, NTRK2, or NTRK3 integrates with the 5' sequence of other genes. The resulting fusion proteins containing TRK kinases form ligand-independent activation through various mechanisms, including abnormal dimerization and increased TRK kinase expression[4], leading to uncontrolled cancer cell proliferation(Figure 1).

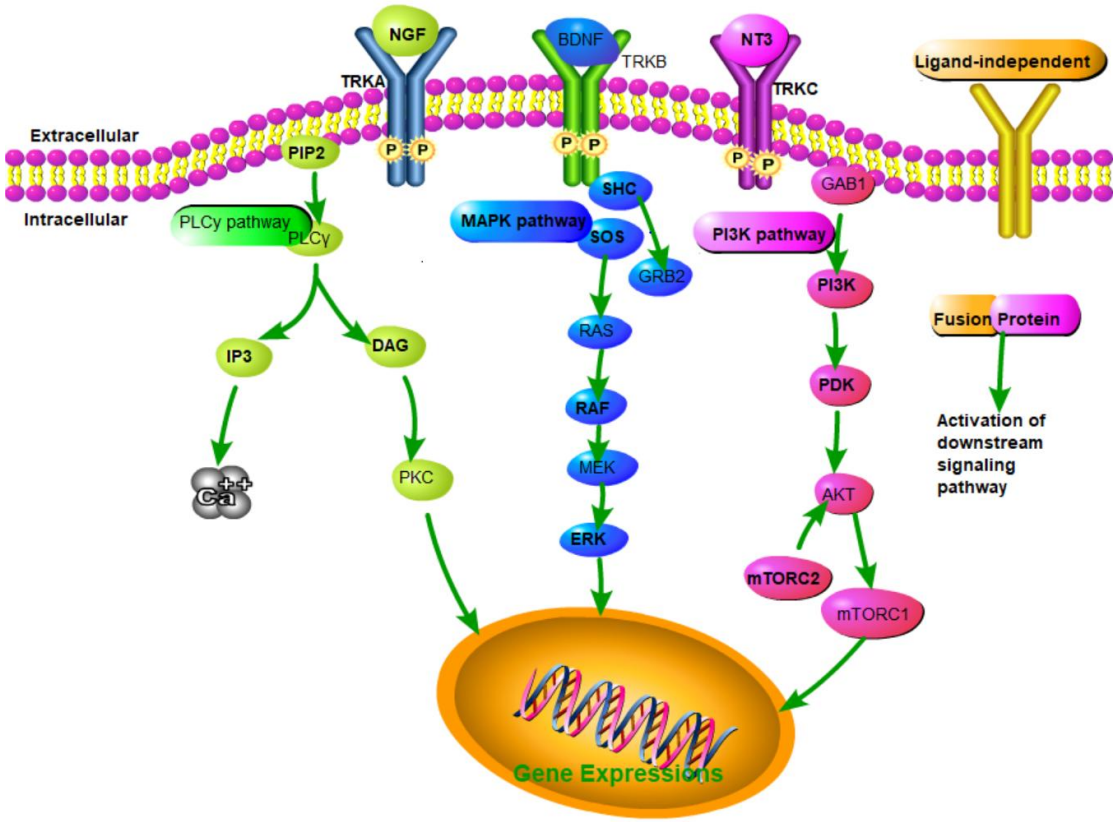

Figure1.The left portion of the TRK protein encoded by NTRK binds to neurotrophic factors, inducing dimerization and phosphorylation of TRK receptors, and activating downstream signaling of PI3K, RAS/MAPK/ERK, and PLC-gamma; The right part is Trk fusion oncoprotein signaling pathway. The two are different: the fusion protein has no ligand binding to the corresponding domain, so the downstream signaling pathways (PKC, MAPK, PI3K) are ligand-independent receptor activation and uncontrolled activation, leading to tumorigenia

2.2 | NTRK Gene Fusions in Cancer Types

NTRK gene fusions are common in adult and pediatric malignancies. These fusions are reported to be detected in less than 1% of common solid tumors, while in some rare tumors, it is much more common. As shown in Table 1, the distribution of NTRK gene fusions in lung tumors is presented.

Table 1 Distribution of NTRK gene fusion in lung cancer

NTRK gene	Gene fusion	Type of lung cancer
NTRK1	SQSTM1	NSCLC[5]
	RFWD2	Large cell neuroendocrine lung cancer[6]

	CD74	Adenocarcinoma[7]
	TPR	Adenocarcinoma[8]
	TPM3	Adenocarcinoma[9]
	MPRIP	Adenocarcinoma[7]
	IRF2BP2	Adenocarcinoma[8]
	TFG	NSCLC[8]
	F11R	NSCLC[8]
	NCOR2	Adenocarcinoma[10]
NTRK2	TRIM24	Adenocarcinoma[11]
	STRN	NSCLC[8]
	SQSTM1	Adenocarcinoma[9]
NTRK3	EML4	NSCLC[8]
	RBPMS	NSCLC[8]
	ETV6	Adenocarcinoma[8]
	SLITRK3	Lung squamous carcinoma[12]
	SQSTM1	Lung squamous carcinoma / Neuroendocrine carcinoma [8]

2.3 | Detection of NTRK Fusion in NSCLC

The reported detection rate of NTRK fusions in NSCLC is around 0.1%-0.3%[13], significantly lower than other mutations in NSCLC, such as KRAS (15-25%), ALK (5-7%), RET (1-2%), and ROS-1 (1-2%)[14-16]. Studies have reported that the frequency of NTRK gene fusion in NSCLC is about 0.17% [17], while another report by Rosen et al. indicated 0.16%[18]. In a study by Gatalica, 4,073 lung cancer samples were tested, with only 4 being NTRK-positive, corresponding to an incidence rate of about 0.1%[19]. A retrospective study conducted by Si X on 7,395 Chinese patients with NSCLC showed that the positive rate of NTRK fusion was 0.59% overall, 0.5% in lung squamous cell carcinoma (4 out of 855), and 0.61% in lung adenocarcinoma (33 out of 5,378)[20]. Other reports suggest that the incidence rate of NTRK1 fusion in NSCLC ranges from 0.07% to 3.3%, NTRK2 ranges from 0.02% to 0.2%, and NTRK3 is around 0.08%[21]. In NSCLC, NTRK fusions tend to exist in a mutually exclusive manner with other fusions or mutations. In a study by Vaishnavi A, 91 NSCLC patients were analyzed, and no other common driver gene mutations, such as EGFR, ALK, KRAS, or ROS-1, were found in those cases with NTRK fusion[22]. Similarly, Farago AF analyzed 11 NSCLC patients with NTRK fusions, and no other common mutations were found[23]. However, some co-mutations, including TP53, NF1, and RB1, were detected, which could contribute to resistance to targeted therapies[24].

In Farago AF's study, most NSCLC patients with NTRK fusions were middle-aged and non-smokers, but fusions were also detected in other age groups and smokers, suggesting that NTRK fusions may not be associated with specific clinical characteristics of NSCLC. However, this study was based on a small retrospective sample, and its results may be biased. Therefore, large-scale, multi-center prospective studies are needed to confirm the clinical relevance of NTRK fusions in NSCLC.

2.4 | Methods of Detecting NTRK Fusion

Several methods are available to detect NTRK fusions, including NGS, IHC, FISH, RT-PCR, and ctDNA testing. Each method has its advantages and limitations.

NGS

Zehir A reported that the MSK-IMPACT sequencing panel could detect mutations in 341 cancer-related genes (recently expanded to 410), including all protein-coding mutations, copy number alterations (CNAs), selected promoter mutations, and chromosomal rearrangements[25]. The high sensitivity and specificity, along with the ability to detect novel fusion genes, are the advantages of DNA sequencing. A. Drilon reported that DNA sequencing could detect resistance mutations to NTRK-targeted drugs. These mutations alter the hydrophilic solvent-exposed portion of the nucleotide-binding loop in the kinase domain, interfering with drug binding spatially and reducing the efficacy of targeted

drugs[26]. However, the limitation of this method is that the short size of the MSK-IMPACT panel reduces coverage of mutated genes, leading to false negatives and lower sensitivity. For example, NTRK3 intronic regions are too long to cover adequately, resulting in false negatives. Therefore, RNA-based NGS testing is the preferred method for detecting NTRK fusions because the large intronic regions have already been spliced out.

In a study by Ryma Benayed, patients with negative results for driver mutations using DNA-based sequencing (MSK-IMPACT) were further analyzed using an RNA panel (MSK-Fusion)[27]. Of the 232 lung adenocarcinoma samples that did not show driver alterations by MSK-IMPACT, 36 cases were found to have positive driver alterations by RNA sequencing, including two cases with NTRK3 fusion and one case with NTRK2 fusion. However, RNA extracted from formalin-fixed paraffin-embedded (FFPE) tissue is prone to fragmentation and degradation, particularly in older samples, requiring strict quality control.

Several commercial companies combine RNA and DNA testing to improve detection rates. For example, ThermoFisher's Oncomine comprehensive assay uses an amplification-based technology that covers 161 cancer-related genes and can detect fusions in all three NTRK genes. According to the company's technical specifications, the test requires only 3 FFPE slides or 10 ng of DNA or RNA. Illumina's TruSight Oncology 500 uses hybrid-capture technology to detect changes in 523 cancer-related genes at the DNA level and sequence RNA transcripts to detect fusions involving any of the 55 genes, including the three NTRK genes[3].

Immunohistochemistry (IHC):
IHC is a method that analyzes protein expression. It is widely used in clinical laboratories due to its affordability, speed, and efficiency. IHC requires only one unstained slide, with a turnaround time of about one day. The most commonly used and well-researched monoclonal antibody is EPR17341 (by Abcam and Roche/Ventana), which detects the expression of TRKA, TRKB, and TRKC proteins and recognizes the C-terminal epitope of the tyrosine kinase domain[28]. However, IHC is not specific to TRK fusion proteins and can also detect wild-type TRK expression, leading to potential false positives. Studies have shown that the sensitivity of IHC for detecting NTRK fusions is 96.7%, with a specificity ranging from 92% to 100%[29]. Solomon et al. found that the IHC detects NTRK1 fusion with a sensitivity of 96%, NTRK2 fusion with a sensitivity of 100%, and NTRK3 fusion with a sensitivity of 79% [3]. IHC is an economical and effective screening tool for detecting NTRK fusions or as an adjunct to nucleic acid testing. The author suggests that both NGS and IHC testing should be performed simultaneously to improve the accuracy of the results.

FISH and RT-PCR:

FISH and RT-PCR have been successfully used in clinical detection of NTRK fusions, especially in tumors with high prevalence, such as mucinous adenoid cystic carcinoma. These methods are particularly effective in identifying ETV6-NTRK3 fusions[30]. FISH and RT-PCR are low-cost but require several working days for detection, and they are largely limited to detecting a single driver gene alteration. Due to the wide variety of NTRK mutations, these methods are rarely used clinically for detection.

Circulating Tumor DNA (ctDNA) Testing

Also known as liquid biopsy, this method detects fragments of tumor DNA that enter the bloodstream as tumor cells proliferate and undergo cell cycle changes. This non-invasive approach can reflect the heterogeneity of both the tumor and its metastases, dynamically monitor treatment efficacy, assess cancer recurrence risk, and analyze the mechanisms of acquired resistance. However, the sensitivity of ctDNA for detecting NTRK fusions in plasma is lower than in tissue[31].

2.5 | NTRK Resistance Mechanisms(Figure 2):

NTRK resistance can be divided into on-target resistance and off-target resistance. On-target resistance refers to resistance mediated by mutations in the TRK kinase domain, while off-target resistance refers to resistance due to the activation of bypass or downstream pathways.

1."On-Target" mechanisms include solvent front mutations, gatekeeper mutations, and mutations at the kinase activation loop xDFG position, which can directly interfere with the binding of drugs to the TRK receptor. For

example, mutations such as NTRKA G595R and TRKC G623R may lead to resistance of the TRK receptor to targeted drugs. In 2016, Russo et al. reported the first case of acquired resistance to an NTRK inhibitor in a patient with liver metastasis of colorectal cancer with LMNA-NTRK1 rearrangement treated with entrectinib, who developed resistance after 4 months. Plasma was collected from the patient for ctDNA sequencing, revealing two mutations, TRKA-G595R and G667C, which were not detected before treatment with entrectinib[32]. Subsequently, Drilon A reported a patient with salivary gland secretory carcinoma, with genetic testing showing ETV6-NTRK3 rearrangement, who developed multiple lung metastases after 10 months of treatment with entrectinib. Testing revealed a new G623R mutation in the lung metastases, where arginine replaced glycine at position 623, leading to structural changes that reduced the binding affinity of the mutated TRKC to entrectinib[33]. To date, most data come from clinical case reports, such as NTRK1 G667S, NTRK1 F589L, and NTRK3 G696A, which have been gradually found to be similar to the above-mentioned targeted drug resistance mechanisms. Due to structural changes, the resulting amino acids prevent the first-generation targeted drugs larotrectinib or entrectinib from binding to the kinase domain.

2."Off-Target" mechanisms (also known as Bypass activation mechanisms): The activation of other signaling pathways, such as the upregulation of KRAS, MET, and the RAS-RAF-MEK pathway, can allow tumor cells to bypass the inhibitory signals of NTRK and continue to proliferate. Cocco E reported a case of a patient with CTRC-NTRK1 fusion-positive pancreatic cancer who developed resistance after 5 months of treatment with larotrectinib. Testing revealed that the patient developed resistance to larotrectinib through acquired BRAF v600E and KRAS G12D mutations, and it was confirmed that the BRAF v600E mutation was independent of changes in the tyrosine kinase domain. In cell lines of NTRK1 fusion-positive pancreatic cancer expressing BRAF v600E treated with second-generation TRK inhibitors[34], the tumor continued to progress for 2 months, suggesting that the activation of the downstream MAPK pathway is hypothesized as a TRK-independent bypass activation mechanism. The patient subsequently received treatment with a combination of RAF and MEK inhibitors, resulting in tumor regression. The second case reported by the author involved a patient with LMNA-NTRK1 fusion-positive colorectal cancer, who initially responded well to larotrectinib but later developed on-target resistance due to the NTRK1 G595R solvent front mutation. The patient then received LOXO-195 and responded well, but resistance re-emerged along with liver metastasis. A biopsy indicated a KRAS G12A mutation, and after resection of the liver metastasis, the patient continued on LOXO-195, but tumor progression was later detected with a KRAS G12D mutation. Additionally, treatment of LMNA-NTRK1 fusion-positive and NTRK1 G595R mutation colorectal cancer cell lines with OXO-195 resulted in the emergence of KRAS G12D mutations, supporting the notion that KRAS pathway activation leads to NTRK resistance. Case 3 reported a patient with PLEKHA6-NTRK1 fusion-positive cholangiocarcinoma who developed resistance after 11 months of treatment with entrectinib, followed by the detection of MET amplification. She received treatment with the MET inhibitor crizotinib, which was effective. Relevant gene mutations in the MAPK pathway are shown in Table 2. In the study by Miho J Fuse[35], NTRK-TKIs were continuously used to treat KM12 cells to establish NTRK-TKI resistant cells, specifically cabozantinib-resistant monoclonal cells, revealing several novel NTRK-TKI resistance mutations in the NTRK1 kinase domain, including G595R, as well as a resistance mechanism mediated by the insulin-like growth factor receptor 1 (IGF1R) bypass pathway. The combination of IGF1R inhibitors (AEW541/OSI906) and cabozantinib was able to reverse resistance in CR20 cells.

Table 2 Mutations in genes related to the MAPK pathway

Patient Number	Tumor Type	Fusion	TRK-Targeted Therapy	Known Resistance and MAPK Alterations
1	Pancreatic cancer	CTRC-NTRK1	Larotrectinib, LOXO-195	BRAF V600E, KRAS G12D

2	Colorectal cancer	LMNA-NTRK1	Larotrectinib, LOXO-195	NTRK1 G595R, KRAS G12A, KRAS G12D
3	Cholangiocarcinoma	PLEKHA6-NTRK1	Entrectinib, LOXO-195	MET amplification
4	Pancreatic cancer	ETV6-NTRK3	PLX7486, LOXO-195	MAP2K1 P124S
5	Pancreatic cancer	TPK-NTRK1	Entrectinib, LOXO-195	NTRK1 G595R, ERBB2 S310F
6	Colorectal cancer	TPM3-NTRK1	Larotrectinib	KRAS G12D, NTRK1 G595R, NTRK1 F589L

Next-Generation Inhibitors for NTRK Fusion Resistance:

Several next-generation NTRK fusion inhibitors targeting resistance to first-generation inhibitors are currently under development. These include LOXO-195 (selitrectinib), TPX-0005, and ONO-5390556, which have demonstrated in vitro activity against many of the above-mentioned TRK mutations[36]. Studies show that these next-generation inhibitors are effective against resistance mediated by secondary mutations in the NTRK kinase domain but are ineffective against resistance mediated by bypass mutations[37,38].

Cocco E's research confirmed the mechanism of resistance to next-generation NTRK inhibitors caused by NTRK xDFG mutations. In case reports of three patients with carcinosarcoma, breast cancer, and colorectal cancer, it was observed that after NTRKA G595R mutations caused resistance to first-generation inhibitors, retesting revealed TRKA G667C or TRKA G667A mutations, suggesting that the NTRKA G667 mutation is one of the reasons for resistance to second-generation inhibitors. In cases 4 and 5, one patient with TPR-NTRK1-positive NSCLC and another with TPM3-NTRK1-positive thyroid cancer were found to have xDFG motif mutations (TRKA G667C, G667S), which led to resistance to larotrectinib and a lack of response to the next-generation TRK inhibitor selitrectinib. This also explains the resistance mechanism to second-generation NTRK inhibitors[39].

However, several studies indicate that NTRK fusion is considered one of the mechanisms of resistance to EGFR-TKIs in NSCLC patients. In a large-scale cohort study of NTRK1 fusion in Chinese lung cancer patients, Hui Xia et al. detected 12 patients with NTRK1 fusion-positive lung cancer, 10 of whom had adenocarcinoma (0.073%)[40]. Of the 12 NTRK1 fusion-positive NSCLC patients, 6 had co-occurring EGFR mutations and had previously been treated with EGFR-TKIs. Among the EGFR-positive patients, two cases had T790M co-mutations, and one had an EGFR C797S co-mutation. Schrock AB's study confirmed that patients with EGFR-mutated lung cancer developed resistance to erlotinib and were later found to have TPM3-NTRK1 fusion[41]. Similarly, Piotrowska Z's research detected TPM3-NTRK1 fusion in patients resistant to the third-generation EGFR-TKI Osimertinib[42]. These findings suggest that NTRK fusion may be one of the resistance mechanisms for EGFR-TKIs.

Wang B's research reported a case of a 51-year-old female with IRF2BP2-NTRK1 fusion-positive lung adenocarcinoma, whose condition stabilized for 16 months after crizotinib treatment[43]. In Hui Xia's report, a 63-year-old female with EGFR 19 del mutation was treated with first-generation TKI gefitinib for 12 months, followed by afatinib for 3 months, but her disease continued to progress. After detecting the EGFR T790M mutation, she was treated with third-generation TKI osimertinib for 15 months before her disease progressed. After osimertinib resistance, EGFR C797S and LMNA-NTRK1 fusions were detected. She was treated with crizotinib combined with osimertinib to control the tumor, and her disease remained stable for 9 months[40]. These studies suggest the potential anti-tumor effect of crizotinib in NTRK fusion-positive NSCLC, and for patients with NTRK fusion-mediated EGFR-TKI resistance, combining EGFR-TKIs with NTRK inhibitors may be a therapeutic option. Further studies are needed to explore the effects of first-generation and next-generation TRK inhibitors on EGFR-TKI-resistant tumors with NTRK fusion to better understand resistance mechanisms.

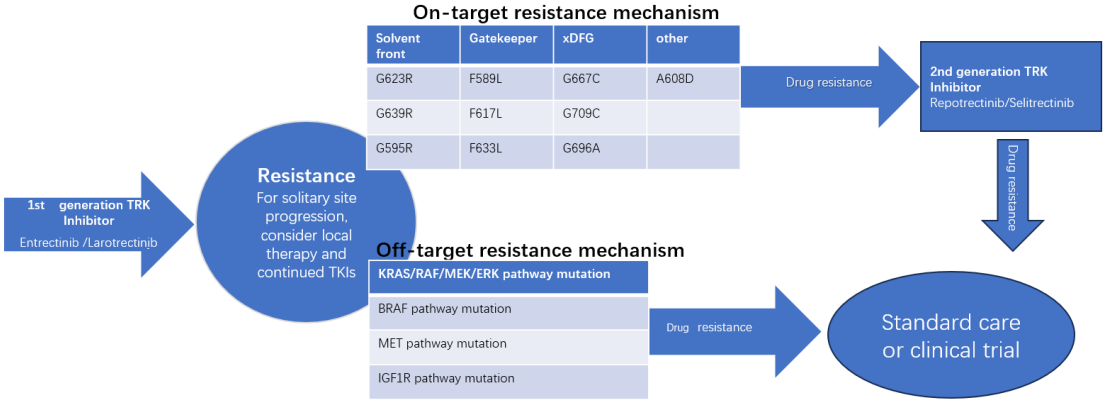

Figure 2.Mechanism of resistance to NTRK fusion inhibitors: For patients with advanced unresectable solid tumors with positive NTRK fusion, the first-generation targeted drugs entrentinib or larotinib should be treated. If local progression occurs after drug resistance, local treatment can be given, while the first-generation targeted drug therapy can be continued. If the first generation of targeted drugs is resistant, no matter the on-target mechanism or off-target mechanism, the second generation of targeted drugs should be given or after another biopsy, if other driver genes are combined, combined therapy can be attempted to control the disease progression. If resistance reappears, standard chemotherapy regimens should be given or participants in clinical trials.

2.6| NTRK Fusion and Immunotherapy:

In recent years, the application of ICIs has significantly prolonged the PFS and OS of lung cancer patients, especially those with NSCLC. Clinically, PD-L1 expression, TMB, and MSI have been identified as predictive biomarkers for ICIs, helping to predict the efficacy of ICIs treatment[44,45]. However, the relationship between NTRK fusion, PD-L1 expression, and TMB is still unclear.

Dan Sha's research shows that the TMB of lung cancer is significantly higher than that of other solid tumors, but the rate of high microsatellite instability (MSI-H) is relatively low[44]. Zhang Lei et al. reported a case of a 60-year-old female with advanced lung adenocarcinoma. NGS testing revealed NCOR2-NTRK1 fusion and high tumor mutational burden (TMB) of 58.58 mutations per megabase, with PD-L1 expression between 20% and 30%[46]. After receiving two cycles of camrelizumab, the patient's disease progressed. Subsequently, the patient switched to the TRK inhibitor larotrectinib, which led to a gradual reduction and eventual disappearance of the lesions. This case suggests that in lung adenocarcinoma with NTRK fusion, PD-L1 positivity, and high TMB, larotrectinib as a targeted therapy is more effective than anti-PD-1 inhibitors. However, there are studies showing that NTRK fusion-positive patients achieved stable disease after receiving ICIs treatment[18]. The comparison of the efficacy of NTRK inhibitors and ICIs, both individually and in combination, requires further exploration to determine the best therapeutic strategy.

3. Conclusion

Combining our research with a review of the current literature, NTRK gene fusions have been found to play a significant driving role in various tumor types. The widespread presence of NTRK fusions in different tumors, along with their close association with malignancy, suggests that NTRK fusion is not only a key diagnostic marker but also an effective therapeutic target. Clinical trials and case studies have demonstrated that targeted therapies, such as TRK inhibitors, show remarkable efficacy in various solid tumors, particularly in patients for whom traditional treatment regimens have been ineffective. However, the emergence of resistance mechanisms and the heterogeneity of treatment responses remain significant challenges in current research.

Future research should focus on exploring the biological mechanisms underlying NTRK fusion, developing novel inhibitors, and optimizing combination therapy strategies to improve overall treatment outcomes and patient prognosis. In

summary, the discovery and application of NTRK fusions represent a major advancement in precision medicine for cancer, providing patients with more treatment options and hope.

Author Contributions

Kede Yuan: conceptualization, writing– original draft.
Chao Wang: methodology.
Kunning Yang: methodology.
Jingyang Huang: visualization.
Xiuxin Mo: visualization
Cunhua Yuan: conceptualization, writing– review and editing.

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Conflict of Interest

The authors declare not to have any conflict of interest.

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