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Targeted Therapy in NSCLC: A Comprehensive Review of Molecular Drivers and Treatment Strategies

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Abstract

Non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related mortality worldwide, with its management increasingly guided by molecular profiling and targeted therapies. This review comprehensively examines current treatment standards for NSCLC, focusing on the evolving landscape of targeted therapies tailored to specific oncogenic driver mutations, including EGFR, ALK, ROS1, MET, KRAS, RET, BRAF, NTRK, and HER2. We highlight the efficacy, resistance mechanisms, and clinical trial outcomes of tyrosine kinase inhibitors (TKI) and other targeted agents, emphasizing their impact on progression-free survival (PFS) and overall survival (OS). The integration of these therapies into clinical practice has transformed patient outcomes, particularly in advanced-stage disease. However, challenges such as acquired resistance and toxicity profiles necessitate ongoing research into combination strategies and next-generation inhibitors. This work underscores the importance of precision medicine in NSCLC and outlines future directions for optimizing therapeutic approaches.

Aim of Study: The aim of this review is to provide a comprehensive and up-to-date synthesis of current targeted therapy options for NSCLC, with a focus on molecularly defined subtypes. By analyzing the efficacy, resistance mechanisms, and clinical outcomes associated with various targeted agents, including TKI and emerging treatments, this review seeks to support clinicians and researchers in optimizing treatment strategies for patients with advanced NSCLC.

Keywords: non-small cell lung carcinoma, molecular targeted therapy, tyrosine kinase inhibitors, gene expression profiling.

1. Introduction

Lung cancer, particularly NSCLC, is a heterogeneous disease with diverse molecular subtypes that influence prognosis and treatment response. Over the past two decades, the identification of oncogenic drivers such as EGFR mutations, ALK rearrangements, and KRAS alterations has revolutionized therapeutic strategies, shifting the paradigm from conventional chemotherapy to targeted therapies. This review provides an in-depth analysis of the current targeted therapy options for NSCLC, organized by molecular alterations. We discuss the clinical efficacy

of first-, second-, and third-generation TKI, antibody-drug conjugates (ADC), and emerging agents, supported by pivotal clinical trials. Additionally, we explore resistance mechanisms and innovative approaches to overcome them, including combination therapies and novel inhibitors. By synthesizing the latest evidence, this work aims to serve as a resource for clinicians and researchers navigating the complex and rapidly evolving field of NSCLC treatment.

2. Materials and Methods

A search of the PubMed and Google Scholar databases was conducted using relevant keywords to find available studies published up to May 5, 2025. Only articles written in English were included. A preliminary selection of titles and abstracts was made, followed by a full-text review of the relevant publications.

3. Results

Current Targeted Therapy Options for NSCLC

The management of lung cancer varies depending on several clinical and pathological factors, including:

- patient age,
- tumor grade,
- histological subtype and molecular characteristics,
- anatomical location,
- presence of lymphovascular invasion,
- tumor size,
- disease extent,
- patient's ability to tolerate treatment,
- pleural involvement,
- and individual patient preferences.

NSCLC may be treated with surgical resection, radiotherapy, chemotherapy, targeted therapy, immunotherapy, or a combination of these approaches. In early-stage disease, surgical resection is generally the preferred initial treatment, as NSCLC tends not to metastasize at this stage. Early surgical intervention can significantly prolong survival if the tumor is localized.

However, the majority of patients are diagnosed at advanced stages, where surgery provides minimal benefit. In cases involving larger tumors or lymph node involvement, multimodal therapy—incorporating surgery, chemotherapy, and radiotherapy—is often recommended. For patients with stage IV NSCLC who are not eligible for targeted therapies or immunotherapy, platinum-based chemotherapy regimens (e.g., cisplatin or carboplatin) remain the primary treatment option. Unfortunately, median survival in this group rarely exceeds 12 months.

Numerous oncogenic driver mutations have been identified in NSCLC, enabling the use of specific molecularly targeted therapies tailored to these genetic alterations. Common targets include:

- EGFR (epidermal growth factor receptor), particularly exon 20 insertions,
- ALK (anaplastic lymphoma kinase),
- ROS1 (proto-oncogene tyrosine-protein kinase ROS),
- BRAF (B-Raf proto-oncogene, serine/threonine kinase),
- RET (rearranged during transfection),
- MET (mesenchymal-epithelial transition factor, especially exon 14 skipping mutations),
- KRAS (Kirsten rat sarcoma viral oncogene homolog, especially G12C mutations),
- HER2 (human epidermal growth factor receptor 2),
- NTRK (neurotrophic tyrosine receptor kinase).

The introduction of TKI has dramatically changed the treatment landscape for patients with advanced or metastatic NSCLC harboring these molecular alterations. Targeted therapy with TKI is now considered the standard of care for appropriately selected patients.

Molecular targeted therapy

3.1. EGFR mutation

The epidermal growth factor receptor (EGFR) mutation was the first oncogenic driver identified in NSCLC, and it remains the most common molecular alteration in this disease. EGFR mutations are present in approximately 10–15% of Caucasian patients and in up to 50% of Asian populations.

EGFR belongs to the HER family, which includes HER1 (EGFR), HER2, HER3, and HER4. These transmembrane receptors exist as inactive monomers that become activated through homodimerization or heterodimerization upon ligand binding. Receptor activation triggers complex intracellular signaling cascades that regulate cellular proliferation and survival. Aberrant activation or dysregulation of EGFR signaling contributes to tumorigenesis and malignant transformation.

For patients with EGFR-mutated NSCLC, treatment typically involves one of three generations of TKI:

- First-generation (e.g., erlotinib, icotinib, gefitinib),
- Second-generation (e.g., afatinib, dacomitinib),
- Third-generation (e.g., osimertinib).

3.1.1. First-generation TKI

First-generation EGFR TKIs, including gefitinib, erlotinib, and icotinib, function by reversibly inhibiting the ATP-binding site of the EGFR tyrosine kinase domain, thereby blocking downstream signaling pathways. These agents demonstrated superior response rates compared to conventional cytotoxic chemotherapy in treatment-naïve patients with activating EGFR mutations.

However, acquired resistance inevitably develops in most cases, with the T790M point mutation accounting for approximately 60% of resistance mechanisms.

- **Gefitinib**

Multiple clinical trials—such as IPASS, First-SIGNAL, WJTOG-3405, and NEJ002—have validated the efficacy of gefitinib in East Asian patients with advanced EGFR-mutant NSCLC.

In the IPASS study (n=1217), among 261 patients harboring EGFR mutations, gefitinib significantly improved PFS compared to carboplatin-paclitaxel chemotherapy (ORR(objective response rate): 71.2% vs. 47.3%; HR(hazard ratio = 0.48; 95% CI: 0.36–0.64; $p < 0.001$). The most notable benefits in PFS were observed in patients with exon 19 deletions and L858R point mutations, as confirmed in First-SIGNAL, NEJ002, and WJTOG-3405. Despite improvements in PFS, no significant OS benefit was observed—likely due to treatment crossover between study arms. [1], [2], [3]

In the ADJUVANT trial, gefitinib as adjuvant therapy in patients with resected stage II–IIIA EGFR-mutant NSCLC demonstrated superior disease-free survival (28.7 vs. 18.0 months; HR = 0.60; $p = 0.0054$) and a more favorable safety profile compared to cisplatin plus vinorelbine. [4]

- **Erlotinib**

Erlotinib significantly extended PFS in patients with EGFR mutations compared to chemotherapy, as shown in the OPTIMAL (13.1 vs. 4.6 months; HR = 0.16; $p < 0.0001$) and EURTAC (9.7 vs. 5.2 months; HR = 0.37; $p < 0.0001$) studies.

Frequent side effects included rash, diarrhea, and elevated liver enzymes, though erlotinib required fewer dose reductions and treatment discontinuations than chemotherapy.

Erlotinib remains FDA approved for first-line, maintenance, and second-line therapy in patients with EGFR exon 19 deletions or L858R mutations. [5], [6]

- **Icotinib**

Icotinib, a first-generation EGFR TKI developed and approved in China, demonstrated non-inferiority to gefitinib in the ICOGEN trial (PFS: 4.6 vs. 3.4 months; HR = 0.84).

In the CONVINCE trial, icotinib showed improved PFS compared to cisplatin/pemetrexed chemotherapy (11.2 vs. 7.9 months; HR = 0.61; $p = 0.006$), although OS differences were not statistically significant.

Due to its efficacy and favorable safety profile, icotinib is widely used as a first-line treatment for NSCLC in China. [7]

Meta-analyses comparing gefitinib, erlotinib, icotinib, and chemotherapy consistently demonstrate that first-generation EGFR TKIs significantly prolong PFS in EGFR-mutant NSCLC. However, OS benefits remain uncertain, largely due to treatment crossover in clinical trials. Nevertheless, these agents continue to be foundational in the molecularly targeted management of NSCLC.

3.1.2. Second-generation TKI

Second-generation EGFR TKIs, such as afatinib and dacomitinib, irreversibly bind to the ATP-binding site of EGFR and related members of the HER family (HER2, HER4), resulting in sustained inhibition of downstream signaling. Unlike first-generation agents, these drugs were developed to overcome resistance mutations, particularly T790M, although clinical efficacy against this mutation was limited. Nonetheless, they demonstrated robust activity against sensitizing EGFR mutations.

- **Afatinib**

Afatinib covalently and irreversibly binds to conserved cysteine residues within the kinase domains of EGFR, HER2, and HER4, blocking tyrosine kinase activity until new receptor proteins are synthesized. Although it was initially designed to address resistance mutations like T790M, clinical trials confirmed that its most significant efficacy lies in treating tumors with sensitive EGFR mutations, notably exon 19 deletions and L858R substitutions.

The LUX-LUNG 3 and LUX-LUNG 6 phase III trials led to afatinib's approval for first-line treatment of patients with metastatic NSCLC harboring EGFR exon 19 or 21 mutations. In a pooled analysis of both trials, patients with exon 19 deletions achieved a significant OS benefit compared to chemotherapy.

- In LUX-LUNG 3, median OS was 33.3 months with afatinib versus 21.1 months with chemotherapy (HR = 0.54; 95% CI: 0.36–0.79; p = 0.0015).[8]
- In LUX-LUNG 6, the corresponding OS was 31.4 vs. 18.4 months (HR = 0.64; 95% CI: 0.44–0.94; p = 0.023). [9]

Importantly, the OS benefit was not observed in the L858R subgroup, suggesting distinct biological behavior and therapeutic response among EGFR mutation types.

Head-to-head comparisons also support afatinib's efficacy. In the LUX-LUNG 7 trial, an international, randomized phase IIb study, 319 treatment-naïve patients with EGFR-mutant advanced NSCLC were assigned to receive afatinib or gefitinib.

- Afatinib achieved a longer median PFS (11.0 vs. 10.9 months; HR = 0.73; p = 0.017) and TTF (median time to treatment failure) (13.7 vs. 11.5 months; HR = 0.73; p = 0.0073) compared to gefitinib. Although afatinib was associated with more frequent adverse events (e.g., diarrhea, rash), treatment discontinuation rates were comparable. [10]

In LUX-LUNG 8, a phase III trial comparing afatinib and erlotinib in advanced squamous cell carcinoma post-platinum therapy, afatinib modestly but significantly improved outcomes:

- PFS: 2.4 vs. 1.9 months (HR = 0.82; p = 0.0427),
- OS: 7.9 vs. 6.8 months (HR = 0.81; p = 0.0077). [11]

Although sensitizing EGFR mutations are rare in squamous NSCLC, EGFR overexpression, seen in up to 82% of cases, may explain responsiveness.

Adverse events, including stomatitis, rash, and diarrhea, were more frequent in the afatinib group. Based on these results, the FDA approved afatinib for both EGFR-mutant metastatic NSCLC and metastatic squamous NSCLC after platinum-based chemotherapy.

- **Dacomitinib**

Dacomitinib is an irreversible pan-HER TKI targeting EGFR (HER1), HER2, and HER4. Despite promising preclinical efficacy, its performance in previously treated NSCLC was modest. [12] In a phase II study, dacomitinib failed to meet the primary OS endpoint in patients who had received one or two prior systemic therapies. [13]

The ARCHER 1009 trial, a phase III comparison with erlotinib in previously treated advanced NSCLC, enrolled patients with varied EGFR statuses. No significant difference in PFS was found:

- Median PFS in both groups was 2.6 months (HR = 0.94; p = 0.229). [14]

In contrast, the ARCHER 1050 trial, which enrolled treatment-naïve EGFR-mutant NSCLC patients without CNS metastases, showed superior outcomes with dacomitinib:

- PFS: 14.7 vs. 9.2 months (HR = 0.59; p < 0.0001),
- OS: 34.1 vs. 26.8 months (HR = 0.76; p = 0.044). [15]

This was the first study to demonstrate a statistically significant OS benefit of a second-generation TKI over a first-generation agent, regardless of EGFR mutation type.

However, dacomitinib was associated with a higher incidence of treatment-related adverse events, particularly:

- Diarrhea (87% vs. 56%),

- Paronychia (62% vs. 20%),
- Dermatitis acneiform (49% vs. 29%),
- Stomatitis (44% vs. 17%).

Grade ≥3 toxicities were more frequent in the dacomitinib arm. Despite its efficacy, tolerability remains a concern. Nonetheless, based on ARCHER 1050, the FDA approved dacomitinib for the first-line treatment of EGFR-mutant metastatic NSCLC.

3.1.3. Third-generation TKI

- **Osimertinib**

Osimertinib is an oral, irreversible third-generation EGFR tyrosine kinase inhibitor specifically designed to target both sensitizing EGFR mutations (such as exon 19 deletions and L858R substitutions) and the resistance-associated T790M mutation, which commonly emerges after treatment with first- or second-generation TKIs. Additionally, osimertinib demonstrates improved CNS penetration, a critical feature given the high incidence of brain metastases in EGFR-mutant NSCLC.

The clinical efficacy of osimertinib in T790M-positive patients was demonstrated in the AURA3 trial, a phase III study that compared osimertinib to platinum-based chemotherapy in patients who had progressed on prior EGFR TKI therapy. Osimertinib significantly prolonged PFS (10.1 vs. 4.4 months; HR = 0.30; 95% CI: 0.23–0.41; $p < 0.001$) and showed a higher ORR: 71% vs. 31%.

Importantly, osimertinib was also associated with a more favorable safety profile compared to chemotherapy. [16]

In the first-line setting, the FLAURA trial compared osimertinib with standard EGFR TKI (gefitinib or erlotinib) in treatment-naïve patients with EGFR-mutant advanced NSCLC. Osimertinib demonstrated superior clinical outcomes, including:

- Median PFS: 18.9 vs. 10.2 months (HR = 0.46; $p < 0.001$),
- Median OS: 38.6 vs. 31.8 months (HR = 0.80; $p = 0.046$).
- Grade 3 or higher adverse events were less frequent in the osimertinib group (42%) than in the comparator group (47%).

Additionally, osimertinib was associated with delayed CNS progression, reflecting its ability to penetrate the blood-brain barrier.[17], [18]

Due to its efficacy across multiple mutation settings—including T790M-positive resistance and newly diagnosed EGFR-mutant disease—and its superior CNS activity, osimertinib is now considered the standard of care for first-line treatment of advanced EGFR-mutant NSCLC.

Ongoing studies such as FLAURA2 and NeoADAURA are further evaluating the role of osimertinib in combination regimens and perioperative settings, respectively, aiming to expand its utility across different stages of NSCLC management.

Despite these findings, the development of resistance ultimately results in treatment failure. The origins of resistance are diverse and involve the occurrence of various mutations, e.g. EGFR exon 20 insertion mutation. [19] . Therefore, conducting a tumor biopsy at the time of disease progression should be considered whenever possible to enhance treatment strategies.

3.1.4. TKI Agents Active in Patients with the EGFR exon 20 insertion mutation

EGFR Exon 20 insertion mutations occur in approximately 4–10% of EGFR-mutant NSCLC cases. Unlike classical EGFR mutations (e.g., exon 19 deletions or L858R), these insertions lead to conformational changes in the EGFR kinase domain that confer resistance to first- and second-generation TKIs (e.g., gefitinib, erlotinib, afatinib). As a result, specialized TKI have been developed to target these alterations.

- Mobocertinib

Mobocertinib is an oral, irreversible TKI designed specifically to target EGFR exon 20 insertion mutations with selectivity over wild-type EGFR.

The EXCLAIM-1 and EXCLAIM-2 trials evaluated mobocertinib, an EGFR exon 20 insertion-targeted TKI, in metastatic NSCLC.

EXCLAIM-1 phase 1/2 trial evaluated treatment outcomes and safety of mobocertinib in patients with previously treated EGFR exon 20 insertion-positive mNSCLC.

- ORR: 28% (95% CI: 20–37%)
- DCR (Disease Control Rate): 78% (95% CI: 69–85%)
- PFS: 7.3 months (95% CI: 5.5–9.2 months)
- Median OS: 24.0 months (95% CI: 14.6–28.8 months)
- Common Adverse Events: Diarrhea (91%), rash (45%), paronychia (38%).

[20]
EXCLAIM-2 phase 3 trial compared mobocertinib with platinum-based chemotherapy in EGFR exon 20 insertion + advanced/metastatic NSCLC.

- Median PFS: 9.6 months (both arms)
- ORR: 32% (mobocertinib) vs. 30% (chemotherapy)
- Median DoR (Duration of Response): 12.0 months (mobocertinib) vs. 8.4 months (chemotherapy)
- Grade ≥3 Adverse Events: Diarrhea (20%), anemia (6%), increased lipase (6%).

The EXCLAIM-2 trial did not meet its primary endpoint, as mobocertinib did not demonstrate superiority over chemotherapy.
[21]

- **Amivantamab**

Amivantamab, a bispecific EGFR-MET antibody, has been approved for treating EGFR exon 20 insertion-mutant NSCLC.

The PAPILLON phase 3 trial compared amivantamab combined with carboplatin and pemetrexed to chemotherapy alone.
Results:

- Median PFS: 11.4 months (amivantamab + chemotherapy) vs. 6.7 months (chemotherapy alone).
- Response Rate: 73% (amivantamab + chemotherapy) vs. 47% (chemotherapy alone).

Safety Profile: Common adverse events included rash, nail toxicity, stomatitis, infusion-related reactions, fatigue, and edema.[22]

The CHRYSALIS-20 phase 1 trial evaluated amivantamab in EGFR exon 20 insertion-mutant NSCLC patients who had progressed on platinum-based chemotherapy.

Results:

- ORR: 40% (95% CI: 29–51%).
- DoR: 11.1 months (95% CI: 6.9–not reached).
- PFS: 8.3 months (95% CI: 6.5–10.9 months).
- Most common adverse events: Rash (86%), infusion-related reactions (66%), paronychia (45%). Grade ≥3 adverse events: Hypokalemia (5%), rash, pulmonary embolism, diarrhea, and neutropenia (4% each).
- Treatment-related dose reductions: 13%.
- Treatment discontinuations: 4%.[23]

These results highlight amivantamab's efficacy in EGFR exon 20-mutant NSCLC, demonstrating robust and durable responses with a manageable safety profile.

- **Poziotinib**

Poziotinib, an irreversible TKI, has demonstrated activity in EGFR exon 20 insertion mutations in NSCLC.

A phase II clinical trial reported an ORR of 32%, with efficacy highly dependent on the location of the exon 20 insertion. Patients with near-loop insertions exhibited an ORR of 46%, whereas those with far-loop insertions showed no response.[24]

The multicohort ZENITH20-2 and ZENITH20-4 phase 2 trials evaluated poziotinib in EGFR exon 20 insertion-mutant NSCLC.
ZENITH20-2 Trial (Previously Treated Patients):

- ORR: 27.8% (95% CI: 18.9–38.2%)
- DCR: 70.0% (95% CI: 59.4–79.2%)
- Median PFS: 5.5 months (95% CI: 3.9–5.8 months)
- Median DoR: 5.1 months (95% CI: 4.2–5.5 months)

- Common Grade ≥3 Adverse Events: Rash (48.9%), diarrhea (25.6%), stomatitis (24.4%)
- Dose Reductions: 76.7% of patients[25]

ZENITH20-4 Trial (Treatment-Naïve Patients):
- ORR: 41% (95% CI: 30–54%)
- DoR: 5.7 months (range: 1.2 to >19.1 months)
- PFS: 5.6 months (range: 0 to >20.2 months)
- Dose Interruptions: 90% (once-daily dosing), 68% (twice-daily dosing)
- Dose Reductions: 79% (once-daily), 64% (twice-daily)
- Common Grade ≥3 Adverse Events: Rash (35%), stomatitis (21%), diarrhea (15%)[26]

Despite its antitumor activity, poziotinib's toxicity profile remains a challenge, with frequent dose reductions required due to adverse effects such as rash, diarrhea, and stomatitis. These findings suggest that precision medicine approaches may be necessary to optimize treatment for EGFR exon 20 mutant NSCLC.

- **Sunvozertinib(DZD9008)**

Sunvozertinib is a selective, irreversible EGFR/HER2 inhibitor optimized for exon 20 insertion mutations.

The WU-KONG1 and WU-KONG6 trials evaluated sunvozertinib in NSCLC patients with EGFR exon 20 insertion mutations.

WU-KONG1 phase I/II trial assessing sunvozertinib in treatment-naïve advanced NSCLC.
- Patient Population: 36 patients with EGFR exon 20 insertions.
- Efficacy: Preliminary results showed promising activity, particularly in patients with baseline brain metastases.
- The most frequent mutation subtypes included 769_ASV (36.1%) and 770_SVD (5.6%)[27]

WU-KONG6 phase II trial enrolling 104 patients with EGFR exon 20 insertions who had progressed after platinum-based chemotherapy.
- ORR: 60.8% across different EGFR exon 20 insertion subtypes.
- Median Follow-Up: 7.1 months
- Median DoR: not yet reached.
- Safety: Common Grade ≥3 adverse events included CPK increase (17.3%), diarrhea (7.7%), and anemia (5.8%). [28]

Approved in China in 2023 for EGFR exon 20 insertions NSCLC.

These results highlight sunvozertinib's potential as a targeted therapy for EGFR exon 20-mutant NSCLC, warranting further investigation in ongoing pivotal studies. High intracranial activity is observed in patients with brain metastases.

- **Furmonertinib (AST2818)**

Furmonertinib is an EGFR TKI originally developed for T790M, now under evaluation for EGFR exon 20 insertions.

The FAVOUR phase 1b trial evaluating furmonertinib in patients with EGFR exon 20 insertion-mutant NSCLC.

Results:

Treatment-Naïve Patients (240 mg QD):
- ORR: 78.6% (95% CI: 59.05%–91.70%)
- DoR: 15.2 months
- Median PFS is still maturing.

Previously Treated Patients:
- 240 mg QD Cohort: ORR of 46.2% (95% CI: 26.59%–66.63%)
- 160 mg QD Cohort: ORR of 38.5% (95% CI: 20.23%–59.43%).

Safety Profile:
- Well tolerated; fewer dose reductions than with poziotinib
- Most common adverse event: Low-grade diarrhea
- No unexpected safety signals identified.[29]

These results highlight furmonertinib's promising efficacy in both treatment-naïve and previously treated patients, with manageable toxicity.

Approved in China for EGFR T790M; being studied for EGFR exon 20 insertions indications.

- **Osimertinib**

Osimertinib is a 3rd-generation EGFR TKI; approved for EGFR T790M and common mutations.
A phase I/II study of osimertinib demonstrates limited activity against EGFR exon 20 insertion; ORR <10% in small retrospective cohorts. Not currently recommended as monotherapy for EGFR exon 20 insertion patients.[30]

- **Afatinib + Cetuximab**

Mechanism: Dual blockade of EGFR via TKI and anti-EGFR antibody.

The Phase II IFCT-1503 ACE-Lung Study evaluated the combination of afatinib, an EGFR TKI, and cetuximab, a monoclonal antibody, as first-line treatment for EGFR-mutant NSCLC.
Results:

- TTF at 9 months: 59.3% (afatinib) vs. 64.9% (afatinib + cetuximab).
- Median TTF: 11.1 months (afatinib) vs. 12.9 months (afatinib + cetuximab).
- PFS and OS: No significant improvement with the combination therapy compared to afatinib alone.
- Safety: Slight increase in grade ≥3 adverse events in the combination group.
- EGFR circulating tumor DNA analysis: Higher allele frequency at baseline was associated with shorter PFS, regardless of treatment received.[31]

The study concluded that adding cetuximab to afatinib did not provide a meaningful clinical benefit in treatment-naïve EGFR-mutant NSCLC, suggesting that further investigation of this combination is not warranted.

- Zipalertinib**(TAS6417)**

Zipalertinib (TAS6417), an oral EGFR TKI, has shown promising antitumor activity in EGFR exon 20 insertion-mutant NSCLC.
The REZILIENT1 phase 1/2 trial evaluating zipalertinib (TAS6417/CLN-081) in EGFR exon 20 insertion-mutant NSCLC.
Results:

- ORR: 39% in patients with prior chemotherapy or EGFR exon 20-targeted therapies.
- DCR: 94%.
- ORR in patients previously treated with amivantamab: 41%.
- DCR in amivantamab-treated patients: 97%.
- PFS: 12 months (for patients previously treated with chemotherapy).
- Safety Profile: rash (80%), paronychia (32%), diarrhea (30%), fatigue (21%). [32]

These findings highlight zipalertinib's potential as a targeted therapy for EGFR exon 20-mutant NSCLC, with further data expected from ongoing clinical evaluations.

3.2. ALK-rearrangement

ALK is a transmembrane receptor tyrosine kinase that plays a crucial role in cellular signaling, influencing pathways such as PI3K-AKT, JAK-STAT, and MAPK. While ALK is primarily active during developmental stages and subsequently silenced in adult tissues, various genetic alterations, including mutations, deletions, and rearrangements, can lead to its pathological reactivation in tumors. The formation of ALK-fusion proteins, resulting from chromosomal rearrangements, promotes dimerization and subsequent activation of the kinase domain, thereby facilitating oncogenic processes through multiple downstream signaling cascades. The most common ALK fusion partner is EML4. [33]

ALK rearrangements are observed in approximately 5% of advanced NSCLC cases, with prevalence ranging from 2% to 7% overall and reaching up to 19% in stage IV disease.[34] These genetic alterations predominantly occur in adenocarcinomas (97%), whereas squamous cell carcinomas account for a smaller proportion (3%).[35] The oncogenic potential of ALK rearrangements underscores their significance in NSCLC pathogenesis, necessitating targeted therapeutic strategies. The identification of ALK gene rearrangements in NSCLC has significantly influenced therapeutic strategies, leading to the development of targeted ALK tyrosine kinase inhibitors. Crizotinib was the first agent approved for the treatment of ALK-positive NSCLC and functions as a multitarget inhibitor, exerting activity not only against ALK but also against MET and ROS1 kinases.

3.2.1. First-generation TKI

- **Crizotinib**

Crizotinib is an oral, small-molecule TKI that targets the ALK, ROS1, and MET receptor tyrosine kinases.

The PROFILE 1014 Phase III trial compared first-line crizotinib versus platinum-based chemotherapy in patients with ALK-positive advanced non-squamous NSCLC. A total of 343 patients were enrolled and randomized. Results:

- PFS: 10.9 months (crizotinib) vs. 7.0 months (chemotherapy)
- This represented a statistically significant improvement with crizotinib (hazard ratio ~0.45, $p < 0.001$).
- ORR: 74% (crizotinib) vs. 45% (chemotherapy)
- OS: Due to a high crossover rate (around 84% of patients in the chemotherapy arm switched to crizotinib after progression), the median OS was not reached in the crizotinib group versus 47.5 months in the chemotherapy group. Adjusted analyses (accounting for crossover) further favored crizotinib.
- Safety profile: Visual disturbances, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), and edema. No unexpected toxicities were reported. [36]

These results established crizotinib as a new standard of care for ALK-positive advanced NSCLC based on its significant improvement in PFS and higher response rates compared to chemotherapy.

However, its limited CNS penetration resulted in suboptimal control of brain metastases, which are common in ALK-positive patients. [37] As a result, second- and third-generation ALK inhibitors were developed to overcome resistance mutations and improve CNS activity.

3.2.2. Second-generation TKI

Ceritinib, alectinib, and brigatinib are more potent than crizotinib and effective against several crizotinib-resistant mutations, including L1196M. These targeted therapies have demonstrated ORR of 50–55% in patients with ALK-positive NSCLC who developed resistance to crizotinib. The reported median PFS for each agent is as follows: ceritinib (6.9 months), alectinib (8.9 months), and brigatinib (15.6 months), based on clinical studies. [38], [39], [40] Importantly, these agents exhibit superior CNS activity, addressing a key limitation of crizotinib.

- **Alectinib**

Alectinib is a highly selective ALK inhibitor with strong CNS activity.

The ALEX phase III trial compared alectinib against crizotinib in treatment-naïve ALK-positive patients. Results:

- Median PFS was significantly prolonged with alectinib (34.8 vs. 10.9 months; HR = 0.43; $p < 0.001$),
- CNS progression was also significantly reduced (12% vs. 45% at 12 months).
- Time to CNS progression: not reached with alectinib vs. 16.6 months with crizotinib.
- Intracranial ORR: 81% in patients with brain metastases.
- Safety: generally well-tolerated; most common AEs were constipation, myalgia, and peripheral edema.

As a result, alectinib became the preferred first-line therapy for ALK-positive NSCLC. [41]

- **Ceritinib**

Ceritinib is a potent ALK inhibitor with activity against several crizotinib-resistant mutations. It also penetrates the CNS, though less effectively than alectinib or brigatinib.

The ASCEND-4 Phase III trial compared ceritinib to platinum-based chemotherapy in previously untreated ALK-positive NSCLC.

Results:

- Median PFS: 16.6 months (ceritinib) vs. 8.1 months (chemotherapy); HR = 0.55; $p < 0.00001$.
- ORR: 72.5% vs. 26.7%.
- CNS activity: improved vs. chemotherapy, but inferior to newer ALK inhibitors.
- Toxicity profile: ceritinib is associated with significant gastrointestinal toxicity, including nausea, diarrhea, and vomiting, often necessitating dose modifications[42].

The ASCEND-5 phase III randomized trial evaluated ceritinib versus standard chemotherapy in patients with ALK-positive advanced NSCLC who had progressed after prior treatment with crizotinib and platinum-based chemotherapy.

Results:

- Median PFS: 5.4 months (ceritinib) vs. 1.6 months (chemotherapy); HR = 0.49; $p < 0.0001$
- ORR: 39.1% (ceritinib) vs. 6.9% (chemotherapy)
- Median OS: 18.1 vs. 20.1 months (not statistically significant)

Ceritinib demonstrated significant superiority in PFS and response rate compared to chemotherapy in the post-crizotinib setting, supporting its role as a second-line agent. [43]

The open-label, multicenter Phase 1b trial explored the combination of ceritinib (ALK TKI) and nivolumab (anti–PD-1 checkpoint inhibitor) in ALK-positive NSCLC patients to evaluate safety, tolerability, and preliminary efficacy of the combination.
Results:

- The combination was not well tolerated. High rates of grade ≥3 hepatotoxicity were observed.
- No clear synergistic effect was demonstrated.
- Clinical development of the combination was discontinued early due to toxicity concerns.

Conclusion: Combining ALK TKI with checkpoint inhibitors, particularly ceritinib and nivolumab, resulted in excessive immune-related toxicity and is not recommended outside of clinical trials. [44]
The Phase 1 dose-escalation study assessed the combination of ceritinib (ALK inhibitor) with trametinib (MEK inhibitor) in patients with ALK-positive NSCLC who had progressed on previous ALK TKI.
Results:

- The combination showed modest activity, including partial responses in heavily pretreated patients.
- However, toxicity was a limiting factor, with common adverse events including diarrhea, rash, fatigue, and elevated liver enzymes.

Conclusion: The dual inhibition of ALK and MEK pathways is biologically rational but presents challenges in tolerability. Further optimization of dosing or drug selection is needed for future development. [45]

- **Brigatinib**

Brigatinib is a highly potent ALK inhibitor with strong activity against a broad range of resistance mutations, including G1202R, and excellent CNS penetration.

ALTA-1L phase III study compared brigatinib vs. crizotinib in treatment-naïve ALK-positive NSCLC patients.
Results:

- Median PFS (by blinded independent review): not reached (brigatinib) vs. 9.8 months (crizotinib); HR = 0.49; $p < 0.001$.
- 1-year PFS rate: 67% (brigatinib) vs. 43% (crizotinib).
- Intracranial ORR: 78% in patients with measurable brain metastases.
- TTF: significantly longer with brigatinib.
- Toxicity profile: Brigatinib is associated with hypertension, elevated CPK, and in some cases, early-onset pulmonary events within the first week, requiring close monitoring.[46]

In light of the limited efficacy of second-generation ALK TKI, recent retrospective analyses have demonstrated that combining ALK inhibition with platinum/pemetrexed-based chemotherapy enhances treatment outcomes. The dual approach resulted in a median PFS of 6.8 months, compared to 3.2 months observed with chemotherapy alone [47]. These findings underscore the potential advantages of sustained ALK inhibition, even in resistant cases. Currently, ongoing clinical trials are investigating the addition of ceritinib to nivolumab (NCT02393625) and ceritinib in combination with trametinib (NCT03087448), aiming to refine therapeutic strategies for patients with ALK-positive NSCLC.

3.2.3 The third-generation TKI:

- **Lorlatinib**

Lorlatinib is a third-generation ALK TKI developed to inhibit a wide range of ALK resistance mutations, including the G1202R mutation, which is known to confer resistance to both first- and second-generation ALK inhibitors. In addition, lorlatinib demonstrates exceptional blood-brain barrier penetration and potent CNS activity.

The CROWN Phase III Trial compared lorlatinib to crizotinib as first-line treatment in treatment-naïve ALK-positive NSCLC.
Results:

- Median PFS: not reached (lorlatinib) vs. 9.3 months (crizotinib); HR = 0.28; $p < 0.001$.
- 12-month PFS rate: 78% (lorlatinib) vs. 39% (crizotinib).
- Intracranial ORR (among patients with measurable brain metastases): 82% (lorlatinib) vs. 23% (crizotinib).
- Time to intracranial progression was significantly delayed with lorlatinib.

- Toxicity profile: Lorlatinib is associated with hyperlipidemia (cholesterol/triglyceride elevation), cognitive effects (e.g., memory or speech disturbances), mood alterations (e.g., depression or irritability). Careful baseline and on-treatment monitoring for neuropsychiatric and metabolic adverse events is recommended. [48], [49], [50]

Lorlatinib is considered the preferred agent in patients with CNS involvement or resistance mutations such as G1202R. It is now approved for both treatment-naïve and previously treated ALK-positive NSCLC.

3.2.4. Next-generation ALK inhibitor

Ensartinib, a next-generation ALK inhibitor, has demonstrated therapeutic efficacy in crizotinib-resistant patients and those who had previously undergone treatment with two or more ALK inhibitors. [51] Similarly, TQ-B3139, a novel ALK TKI, was evaluated in a first-in-human phase I trial, exhibiting promising antitumor activity in patients with advanced NSCLC harboring ALK or ROS1 alterations. [52]

Notably, specific mutations conferring resistance to lorlatinib have been observed to resensitize tumor cells to crizotinib, suggesting that molecularly guided therapeutic approaches could serve as an effective strategy in overcoming resistance mechanisms. This insight underscores the potential of precision oncology in optimizing treatment selection and improving patient outcomes. [53]

Key Resistance Mechanisms to ALK Inhibitors

The use of ALK TKI has significantly improved outcomes in patients with ALK-rearranged NSCLC. However, the emergence of resistance, both on-target and off-target, remains a major limitation to long-term treatment efficacy.[54]

1. On-Target Resistance Mechanisms

On-target resistance is primarily driven by secondary mutations in the ALK tyrosine kinase domain that interfere with drug binding.

- The L1196M gatekeeper mutation is one of the most common mechanisms of resistance to crizotinib, as it causes steric hindrance to drug binding.
- G1202R, a solvent front mutation, is the most problematic mutation for second-generation inhibitors such as alectinib and ceritinib, but it may be overcome by the third-generation ALK inhibitor lorlatinib.
- Other mutations such as C1156Y, G1269A, F1174L, I1171T/N/S, and V1180L alter the structure of the kinase domain, reducing the binding affinity of ALK inhibitors.

[54], [55], [56]

2. ALK Gene Amplification

Amplification of the ALK fusion gene leads to overexpression of the ALK protein, which may overwhelm the inhibitory capacity of ALK-TKIs. [55]

3. Off-Target Resistance Mechanisms

Off-target or bypass resistance mechanisms involve the activation of alternative signaling pathways that sustain cell proliferation independently of ALK signaling .

- Examples include MET amplification, EGFR or KRAS pathway activation, and HER family receptor upregulation.
- Epithelial-to-mesenchymal transition (EMT) has also been associated with drug resistance and a more invasive phenotype.
- Rare cases of histological transformation, such as transformation from NSCLC to small-cell lung cancer (SCLC), have also been observed. [54], [57], [58]

4. Clinical Implications

Crizotinib resistance is typically followed by second-generation TKIs such as alectinib, ceritinib, or brigatinib, depending on the resistance profile. The G1202R mutation in particular requires treatment with lorlatinib. For optimal treatment sequencing, molecular profiling, including liquid biopsy or next-generation sequencing, is crucial to identify specific resistance mutations.[56], [57]

3.3. ROS1-rearrangement

Overview of ROS1 Rearrangements in NSCLC

ROS1 (c-ros oncogene 1) is a receptor tyrosine kinase closely related to ALK. Chromosomal rearrangements involving ROS1 lead to fusion oncogenes that drive tumorigenesis through constitutive kinase activity. ROS1 fusions are identified in approximately 1–2% of NSCLC cases and share clinical characteristics with ALK-positive tumors, more commonly occurring in younger, non-smoking patients with adenocarcinoma histology. [59] The most common fusion partners include CD74, SLC34A2, EZR, and TPM3. All resulting fusion proteins maintain an intact ROS1 intracellular kinase domain, which becomes constitutively activated due to these rearrangements. This active kinase initiates intracellular signaling pathways, including the RAS–RAF-MEK-ERK, PI3K-AKT-mTOR, and JAK-STAT3 pathways, promoting cellular survival and proliferation. [60]

Patients with ROS1-rearranged NSCLC generally show a better response to chemotherapy, particularly to pemetrexed-based regimens compared to tumors with other driver mutations.

ROS1-Targeted Therapies

Due to structural homology between ROS1 and ALK, several ALK inhibitors also show activity against ROS1 rearrangements. However, distinct resistance patterns and CNS efficacy profiles exist, necessitating a tailored therapeutic approach.

- **Crizotinib**

Crizotinib was the first TKI approved for ROS1-rearranged NSCLC based on its potent inhibitory activity against ROS1 kinase.
PROFILE 1001 Phase I trial evaluated crizotinib in a cohort of patients with advanced ROS1-positive NSCLC.
Results:

- ORR: 72% (95% CI: 58–84%)
- Median PFS: 19.2 months
- Median OS: 51.4 months
- Responses were durable and consistent across fusion variants.

Limitations:

- Crizotinib has limited CNS penetration, leading to a high rate of intracranial progression. [61]
- Resistance mutations such as G2032R and D2033N can emerge after prolonged treatment. [62], [63]

- **Entrectinib**

Entrectinib is a multitargeted TKI that inhibits ROS1, NTRK, and ALK and demonstrates superior CNS activity compared to crizotinib.
Integrated Analysis (STARTRK-1, STARTRK-2, ALKA-372-001) investigated the efficacy and safety of entrectinib in locally advanced or metastatic ROS1 Fusion-Positive NSCLC, previously undergone platinum-based chemotherapy.
Results:

- ORR: 77%
- Median PFS: 19.0 months
- Intracranial response rate: 55% in patients with brain metastases

Entrectinib is approved for ROS1-positive NSCLC with or without CNS involvement, offering an advantage over crizotinib in patients with brain metastases. [64]

- **Lorlatinib**

Although primarily developed for ALK-positive disease, lorlatinib exhibits potent activity against ROS1 and some crizotinib-resistant ROS1 mutations, excluding G2032R.
Phase 1–2 Trial on Lorlatinib investigated its efficacy and safety in patients with advanced ROS1-positive NSCLC, including those previously treated with other ROS1 TKIs.
Results:

- ORR: Lorlatinib demonstrated an ORR of 48–50% in patients with prior ROS1 TKI treatment.
- The median PFS ranged from 7.5 to 9.6 months, depending on prior treatment status.
- Intracranial Response: Among patients with brain metastases, the CNS ORR was 55–60%, highlighting its efficacy in treating CNS disease.

- Strong CNS activity, but limited efficacy against solvent-front mutations like G2032R.
- Safety Profile: Lorlatinib was generally well tolerated, but notable adverse effects included: hyper-lipidemia (≥70%), neurocognitive effects (30–35%), edema (25–30%), fatigue (20–25%), conclusion[65]

Lorlatinib demonstrated strong clinical activity in ROS1-positive NSCLC, particularly in patients resistant to previous ROS1 TKIs, and exhibited high CNS efficacy. While adverse effects such as hyperlipidemia and neurocognitive symptoms were observed, the drug maintained an acceptable safety profile. Further phase 3 trials are needed to confirm its efficacy compared to other ROS1 inhibitors.

- **Ceritinib**

Ceritinib is a selective ALK inhibitor that demonstrates activity against the ROS1 kinase. In a Phase II trial involving 32 patients with ROS1-positive NSCLC, ORR was 67%. Notably, two patients who had previously been treated with crizotinib showed no response at all.[66]

Emerging ROS1 Inhibitors

- **Repotrectinib**

Repotrectinib next-generation ROS1/NTRK/ALK inhibitor developed to overcome solvent-front mutations like G2032R and shows potent preclinical and early clinical activity, including CNS efficacy. The power of this drug against ROS1 is over 90 times stronger than that of crizotinib, and it has exhibited effectiveness against ROS1 resistance mutations.[67]

In the TRIDENT-1 Phase II trial, repotrectinib showed:

- ORR: 79% in TKI-naïve patients
- ORR: 39% in patients pretreated with crizotinib
- Intracranial responses: observed even in heavily pretreated patients
- Currently undergoing phase II/III trials and granted Breakthrough Therapy Designation by the FDA. [68]

- **Taletrectinib**

Taletrectinib is another promising ROS1/ALK/NTRK inhibitor active against resistance mutations, including G2032R.

Early data (NCT02279433) demonstrate ORR >70% in TKI-naïve patients and good CNS activity.

Treatment Considerations in ROS1-positive NSCLC

- First-line: Crizotinib remains a standard choice where CNS involvement is absent.
- CNS disease: Entrectinib is preferred due to better intracranial penetration.
- Post-crizotinib progression: Repotrectinib or enrollment in clinical trials is encouraged, especially in cases of G2032R-mediated resistance.

Resistance to ROS1 Inhibitors

- Intrinsic resistance to ROS1 inhibition arises from solvent-front or gatekeeper point mutations in the ROS1 kinase domain, with the ROS1 G2032R mutation being the most prevalent.
- Activation of parallel signaling pathways, such as KRAS, BRAF, or MET. In cases of ROS1-positive NSCLC, the activation of BRAF and KRAS mutations, as well as MET amplification, has been observed in patients treated with crizotinib or lorlatinib. [69], [70]

3.4. MET mutation

MET is a proto-oncogene encoding a receptor tyrosine kinase for hepatocyte growth factor (HGF). Aberrant activation of the **HGF/MET axis** leads to uncontrolled cell growth, survival, invasion, and metastasis. It

triggers a signaling cascade that involves the RAS-RAF, STAT3, and PI3K pathways. Dysregulation of MET signaling in NSCLC occurs through:

1. MET exon 14 skipping mutations - MET degradation, leading to oncogenic overactivation.
2. MET amplification - overexpression of the receptor and downstream signaling.
3. MET overexpression - often assessed by IHC, but its predictive value is less well established.

Among these, MET exon 14 skipping mutations have the strongest predictive value for MET-targeted therapy and occur in ~3–4% of NSCLC cases, particularly in elderly patients and those with pulmonary sarcomatoid carcinoma.

MET Exon 14 skipping

MET exon 14 skipping mutation leads to MET ubiquitination, decreased MET turnover, and enhanced activation of cellular signaling. The activation of the MET pathway leads to an increase in the proliferation of neoplastic cells, prolongs their survival, and can lead to metastasis. [71]

1. Selective MET Inhibitors

Two oral MET tyrosine kinase inhibitors have received FDA approval for MET exon 14-altered NSCLC: capmatinib and tepotinib.

- **Capmatinib**

Capmatinib is a highly selective type I MET inhibitor that blocks ATP binding and inhibits downstream signaling.

The GEOMETRY mono-1 Phase II (2020) multicenter study assessing capmatinib in MET exon 14-altered NSCLC. Patients were stratified into treatment-naïve and previously treated cohorts. [72]

Results:

- Treatment-naïve patients: ORR = 68%, median PFS = 12.4 months
- Previously treated patients: ORR = 41%, median PFS = 5.4 months
- Intracranial responses were observed in patients with brain metastases (ORR = 54.5%).
- Adverse events: peripheral edema, nausea, elevated creatinine.

FDA Approval: May 2020 for MET exon 14-altered advanced NSCLC.

- **Tepotinib**

Tepotinib is another selective MET inhibitor with demonstrated intracranial efficacy.

The VISION Phase II trial evaluated tepotinib in patients with MET exon 14 skipping mutations detected via liquid or tissue biopsy. [73]

Results:

- ORR (independent review): 44%.
- Median DoR: 11.1 months.
- Similar efficacy was observed in both liquid- and tissue-biopsy–detected mutations.
- Intracranial activity: observed in a small subset of patients with brain metastases.
- Common AEs: peripheral edema (63%), nausea, diarrhea.

FDA Approval: February 2021 for MET exon 14-altered NSCLC.

- **Savolitinib (Approved in China)**

Savolitinib approved in China for MET exon 14 NSCLC based on phase II data showing ORR = 49%, better responses in pulmonary sarcomatoid carcinoma subgroup.[74]. Not yet approved by the FDA.

These treatments have transformed the therapeutic landscape for patients with a MET exon 14 skipping mutation, demonstrating impressive and sustained response rates in clinical trials.

2. Non-Selective / Multi-Targeted MET Inhibitors

- **Crizotinib**

Crizotinib (also inhibits ALK/ROS1) tested in the PROFILE 1001 trial has shown modest activity in MET exon 14 cases:

  - ORR = ~32%, PFS 7. 3 months, [75]

- Limited CNS efficacy.

Not FDA-approved for MET indications. Two additional phase 2 AcSé33 and METROS34 trials of crizotinib reported only modest activity of crizotinib in MET exon 14 cases.[76], [77]

- Cabozantinib and glesatinib

Cabozantinib and glesatinib are under investigation, though their clinical utility remains unclear due to broader targets and higher toxicity.

Emerging Agents and Trials

- Sym015: a MET-targeting ADC. This therapy demonstrated impressive efficacy in three treatment-naive patients with this type of mutation of NSCLC, achieving a response rate of 90% and a progression-free survival of 9,2 months. [78].
- REGN5093 is the dual MET antibody that is currently under development for patients with MET-mutation.[79]
- Combination trials: capmatinib + spartalizumab (anti-PD-1) (NCT04323436), tepotinib + osimertinib (NCT03940703) for EGFR TKI resistance with MET amplification.
- In the ongoing SHIELD-1 phase I.trial Elzovantinib a next-generation MET/CSF1R/SRC inhibitor with CNS activity, is being evaluated in patients with MET-driven advanced solid tumors.[80]

Resistance to MET Inhibitors

Resistance mechanisms to MET TKIs include:

1. Secondary MET mutations in the kinase domain (e.g., D1228N, Y1230C) - confer resistance to type I inhibitors.[81]
2. Activation of bypass pathways (e.g., KRAS, EGFR, HER3 amplification).[82]
3. Histological transformation (rarely).[83]

Combination strategies (e.g., MET + EGFR or MET + MEK inhibition) are under investigation to delay or overcome resistance.

3.5. KRAS mutation

KRAS (Kirsten rat sarcoma viral oncogene homolog) is the most frequently mutated oncogene in NSCLC, found in approximately 25–30% of adenocarcinomas, particularly in smokers. KRAS is a small GTPase that functions downstream of EGFR and other receptor tyrosine kinases, regulating key pathways such as:

- MAPK/ERK
- PI3K/AKT
- RalGDS

The KRAS G12C mutation, caused by a glycine-to-cysteine substitution at codon 12, represents around 13% of lung adenocarcinomas, creating a druggable cysteine residue that allowed for the development of covalent KRAS G12C inhibitors. [84]

KRAS G12C

Structural analyses of wild-type KRAS and its mutant variants have identified a unique feature in KRASG12C, where the cysteine-12 residue is positioned near the P2 pocket, a site that exists solely in the inactive KRAS-GDP conformation. This cysteine-12 residue possesses a sulfur-containing side chain, which facilitates the formation of irreversible covalent bonds with small-molecule inhibitors. As a result, KRASG12C remains in its inactive GDP-bound state, thereby suppressing oncogenic signaling pathways.

These findings have driven the development of oral small-molecule inhibitors specifically targeting KRASG12C. Among these agents, sotorasib (AMG 510) and adagrasib (MRTX849) have been approved for clinical application, while several others—including GDC-6036, JDQ443, and JNJ-74699157 (ARS-3248)—remain under investigation in preclinical and clinical trials.

- **Sotorasib**

Sotorasib is a first-in-class selective, irreversible KRAS G12C inhibitor.

In the phase I/II CodeBreaK-100 trial sotorasib assessed in patients with KRASG12C-positive NSCLC.
Results:

- ORR: 37.1%
- DCR: 80.6%
- Median PFS: 6.8 months
- Median OS: 12.5 months
- Common adverse events: diarrhea, nausea, elevated liver enzymes. [85]

- The CodeBreaK-200 phase III trial compared sotorasib vs. docetaxel in second-line setting.
  Results:
  - Median PFS: 5.6 months vs. 4.5 months
  - ORR: 28.1% vs. 13.2% (sotorasib vs. docetaxel)
  - Improved PFS but no significant OS benefit (11. 3 months vs 10. 6. months). [86]

- **Adagrasib**

Adagrasib is a covalent KRAS G12C inhibitor with a longer half-life (~24 hours). FDA accelerated approval (2022) based on KRYSTAL-1 trial.

The KRYSTAL-1 phase II trial (NCT03785249) evaluated activity and safety of adagrasib (MRTX849) in patients with advanced with KRASG12C-positive NSCLC.
Results:

- ORR: 43%
- DCR: 80%
- Median PFS: 6.5 months
- Median OS: 12.6 months
- Notably, intracranial activity was demonstrated in patients with brain metastases.
- Side effects: nausea, vomiting, fatigue, diarrhea, elevated transaminases. [87]

The KRYSTAL-7 phase 2 trial assessed the safety and efficacy of adagrasib in combination with pembrolizumab as first-line treatment for patients with advanced or metastatic KRAS G12C-mutated NSCLC.
Results:

- ORR: 59.3%
- PFS: 27.7 months
- DoR: 26.3 months
- OS: 62%
- Grade ≥3 treatment-related adverse events (TRAEs) occurred in 68% of patients.

The combination of adagrasib and pembrolizumab demonstrates promising efficacy as a first-line treatment in patients with KRAS G12C-mutated NSCLC and high PD-L1 expression, with a manageable safety profile. [88]

KRYSTAL-12 phase 3 trial compared the efficacy and safety of adagrasib vs. docetaxel in patients with previously treated KRAS G12C-mutated advanced or metastatic NSCLC, who had received prior platinum-based chemotherapy and anti–PD-(L)1 therapy.
Results:

- PFS: 5.5 months (adagrasib) vs. 3.8 months (docetaxel)
- ORR: 28.3% (adagrasib) vs 10.0% (docetaxel)
- Adagrasib also demonstrated improved intracranial efficacy compared to docetaxel.
- The safety profile of adagrasib was consistent with previous reports, with no new safety signals observed.

Adagrasib significantly improves PFS and ORR compared to docetaxel in previously treated patients with KRAS G12C-mutated NSCLC, offering a more effective treatment option in this setting. [89]

Ongoing Clinical Trials and Emerging Strategies

To improve efficacy and prevent resistance, several combination trials are ongoing:
1. KRAS G12C inhibitor + SHP2 inhibitor

- SHP2 is a key node upstream of RAS.
- Trials:

- Sotorasib + RMC-4630 (NCT04185883)
- Adagrasib + TNO155 (NCT04330664)

2. KRAS inhibitor + Immune Checkpoint Inhibitor

- KRYSTAL-7 (adagrasib + pembrolizumab, NCT04613596) in first-line setting.
- CodeBreaK 101 (sotorasib + atezolizumab, NCT04185883)
- Goal: overcome immunosuppressive TME in KRAS-mutant NSCLC.

3. KRAS G12C inhibitor + MEK inhibitor

- Dual pathway blockade of RAS–MAPK signaling.
- Studies are exploring combinations such as adagrasib + trametinib.

4. Next-generation KRAS inhibitors

- Target other KRAS mutants:
  - KRAS G12D, G12V, G13D (common in CRC and pancreatic cancer)
- Pan-KRAS inhibitors and PROTAC-based degraders (e.g., MRTX1133 for G12D).

Resistance Mechanisms

1. On-target mutations:
   - Secondary KRAS mutations (e.g., Y96D, R68S, H95) prevent drug binding. [90]
2. Off-target/bypass pathway activation:
   - EGFR, HER2, FGFR, MET amplification.
   - Upregulation of wild-type RAS isoforms (NRAS, HRAS). [91]
   - PI3K-AKT-mTOR and MAPK reactivation.
3. Phenotypic transformation:
   - EMT[92]
   - Small cell transformation (rare).

These mechanisms underscore the need for combination strategies to prevent or overcome resistance.

KRAS G12C inhibitors have changed the therapeutic landscape for a long-undruggable oncogene in NSCLC. While sotorasib and adagrasib demonstrate meaningful clinical benefit, resistance remains a challenge. Combinatorial strategies and next-generation inhibitors are currently under active investigation to broaden efficacy and address resistance mechanisms.

3.6. RET mutation

The RET gene, located on chromosome 10 (10q11.2), encodes a cell surface receptor tyrosine kinase that shares structural similarity with the ALK kinase domain. As a receptor for the Glial Cell Line-Derived Neurotrophic Factor (GDNF) family, RET facilitates neuronal development through its interaction with GFRα, leading to dimerization and autophosphorylation, which subsequently activates RAS, MAPK/ERK, PI3K/AKT, and JAK/STAT signaling pathways.

Mutations in RET result in constitutive kinase activity, independent of ligand binding, thereby disrupting normal cell signaling, growth, and differentiation. Excessive tyrosine kinase activation contributes to uncontrolled cell proliferation, increasing the risk of tumorigenesis.

Genetic rearrangements involving RET have been identified in roughly 1%-2% of lung adenocarcinomas. These alterations are more frequently observed in younger individuals and those with no history of smoking. (Ferrara et al., 2018) Genetic rearrangements involving RET have been identified in roughly 1%-2% of lung adenocarcinomas. These alterations are more frequently observed in younger individuals and those with no history of smoking.

Prior to the development of selective RET inhibitors, treatment options for RET fusion-positive NSCLC were limited, with multi-kinase inhibitors (MKIs) such as cabozantinib and vandetanib offering only modest benefit and significant toxicity due to off-target effects.

- Selpercatinib

Selpercatinib is a highly selective and potent inhibitor of the RET receptor tyrosine kinase with CNS penetration,

In LIBRETTO-001 Phase I/II Trial, the efficacy of Selpercatinib in in patients with RET-altered cancers, including NSCLC.

- Population: 247 patients with RET fusion-positive NSCLC (105 treatment-naïve, 143 previously treated).
- Results:
    - Previously treated: ORR = 64%, median PFS = 17.0 months.
    - Treatment-naïve: ORR = 85%, median PFS not reached at interim analysis.
    - Intracranial response rate: 91%.
- Safety: Common AEs included hypertension, liver enzyme elevations, and diarrhea.
  (Drilon et al., 2019; Nelson-Taylor et al., 2017)

The LIBRETTO-431 phase III trial compared the safety and efficacy of selpercatinib with platinum-based chemotherapy, with and without pembrolizumab in patients with advanced/metastatic RET fusion–positive NSCLC. Enrolled 261 patients across 23 countries.

Results:

- PFS:
    - In the intention-to-treat(ITT) population that received pembrolizumab (ITT-pembro), median PFS was 24.8 months with selpercatinib versus 11.2 months in the control arm (HR 0.465; $p < 0.001$).
    - Similar PFS benefits were observed in the overall ITT population (HR approximating 0.482; $p < 0.001$).

- Clinically meaningful improvements were noted in the ORR and DoR with selpercatinib.
- Selpercatinib significantly prolonged the time to CNS progression (cause-specific HR approximately 0.28).
- **Safety profile:** The treatment-emergent adverse events were generally consistent with those previously reported for selpercatinib and were manageable with dose modifications.

These results support the use of selpercatinib as a first-line targeted therapy for RET fusion–positive NSCLC by demonstrating a substantial, statistically significant improvement in PFS and favorable intracranial activity compared to the standard chemotherapy regimen.

- Pralsetinib

Pralsetinib is a potent and selective RET kinase inhibitor with CNS activity.

ARROW phase ½ trial (NCT03037385) evaluated the safety and efficacy of pralsetinib in RET fusion–positive NSCLC, including as first-line therapy.

- Population: 220 patients with RET fusion-positive NSCLC.
- Results:
    - Previously treated: ORR = 61%, median PFS = 17.1 months.
    - Treatment-naïve: ORR = 70%, median PFS not reached.
    - Intracranial ORR: ~56% (based on subset analysis).
- Safety: Neutropenia, increased ALT/AST, constipation. [96]

The AcceleRET phase 3 trial evaluated pralsetinib against the standard treatment regimen of platinum-based chemotherapy, with or without pembrolizumab. Results highlight pralsetinib's potential as a first-line treatment for RET fusion-positive NSCLC, warranting further investigation in clinical practice. [97]

- Cabozantinib

Cabozantinib is a multikinase inhibitor, has demonstrated activity in RET-rearranged NSCLC.

Phase II open-label, single-arm trial, evaluated cabozantinib in patients with advanced RET-rearranged NSCLC.

ORR: 28%, with partial responses observed in patients with various RET fusions, including KIF5B–RET, TRIM33–RET, and CLIP1–RET.

The median PFS: 5.5 months

The median OS: 9.9 months.

Although cabozantinib has shown antitumor activity, its nonselective nature leads to off-target adverse effects, necessitating dose reductions in 73% of patients due to drug-related toxicities. Given the emergence of selective RET inhibitors such as selpercatinib and pralsetinib, cabozantinib is not the standard of care but remains an option for patients who progress on RET-selective TKIs.

Further research is needed to better understand resistance mechanisms and optimize treatment strategies for RET-positive NSCLC. [98]

Next-Generation RET Inhibitors

- Enbezotinib(TPX-0046): RET/SRC inhibitor with activity against RET G810 mutations.[99]
- LOXO-260: Selective RET inhibitor targeting resistance mutations.[100]

Resistance Mechanisms

Despite strong initial responses, resistance to RET inhibitors may emerge:

- On-target mutations: Solvent front mutations (e.g., RET G810C/S/R) reduce binding affinity.
- Off-target mechanisms:
  - MET amplification
  - KRAS mutations
  - PI3K pathway activation
- Phenotypic alterations: Rare histologic transformations or EMT-like features.
  [101]

Selective RET inhibitors significantly improved outcomes of RET fusion-positive NSCLC, offering high response rates and durable control with improved tolerability. Resistance through on-target mutations and bypass signaling remains a challenge. Ongoing trials and novel agents are under development to address these resistance pathways and improve long-term outcomes.

3.7. BRAF mutation

The BRAF gene encodes a serine/threonine kinase involved in the MAPK (RAS-RAF-MEK-ERK) signaling pathway, which regulates cell growth and survival. Activating BRAF mutations are present in approximately 1.5–3% of NSCLC cases—primarily in adenocarcinomas. [102]

- The most common BRAF mutation in NSCLC is V600E, a substitution at position 600 that leads to constitutive kinase activation., drive uncontrolled cell growth and proliferation. This site in the pathway has become a significant therapeutic target for drug treatments using BRAF inhibitors. [103]
- Non-V600E mutations (e.g., G469A, D594G) are less common and may behave differently, often less responsive to BRAF inhibition.

BRAF V600E

Single-agent BRAF inhibitors showed modest activity in BRAF-mutant NSCLC. Greater efficacy has been achieved by combining BRAF inhibitors with MEK inhibitors, targeting downstream components of the pathway to delay resistance. [104]

- **Dabrafenib Monotherapy**

Arm A of BRF113928 open-label trial

- ORR: 33%
- Median PFS: 5.5 months
- DoR limited compared to combination therapy
- Led to development of combination strategy to improve durability and prevent MAPK reactivation.

[105]

- **Dabrafenib plus trametinib**

The BRF113928 Phase 2 multicenter, open-label trial evaluated dabrafenib alone and in combination with trametinib.

- Population: 93 patients with BRAF V600E-mutant NSCLC. Previously treated cohort (n=57). Treatment-naïve cohort (n=36).

Results:

- Previously treated: ORR: 63%

Median PFS: 9.7 months
Median OS: 18.2 months

- Treatment-naïve: ORR: 64%

Median PFS: 10.8 months
Median OS: 17.3 months

- Intracranial response observed in some patients with baseline brain metastases.
- Toxicity profile: Pyrexia, fatigue, nausea, rash. [106]

Ongoing and Emerging Strategies

1. Encorafenib + Binimetinib:

   The PHAROS multicenter trial examined the efficacy of the combination of encorafenib and binimetinib. Promising results:
   - ORR: 75% (treatment-naïve patients); 46% (patients previously received treatment). [107]

   As a result, this combination could potentially serve as a new therapeutic option..
2. Combination with immune checkpoint inhibitors: Based on evidence from melanoma, trials are evaluating dabrafenib/trametinib + PD-1/PD-L1 blockade.
3. Targeting resistance pathways: Trials exploring BRAF/MEK inhibition + PI3K/mTOR inhibitors, CDK4/6 inhibitors, or SHP2 inhibitors.

BRAF V600E is an actionable mutation in NSCLC with effective targeted options. Dabrafenib plus trametinib is the current standard, offering meaningful clinical benefit. Further research is ongoing to address resistance and explore rational combinations, especially with immunotherapy.

Resistance Mechanisms

Despite promising responses, acquired resistance remains a clinical challenge. Mechanisms include:

- Upregulation of RTKs (e.g., EGFR, MET)
- MEK1/2 mutations or amplification
- Alternative splicing of BRAF
- Activation of parallel pathways (e.g., PI3K-AKT)

These suggest potential benefit of triple combinations or alternative pathway blockade. [108]

3.8. NTRK mutation

The NTRK genes—NTRK1, NTRK2, and NTRK3—encode the tropomyosin receptor kinase (TRK) family of proteins (TRKA, TRKB, and TRKC), which are involved in neuronal development and function via the RAS-MAPK, PI3K-AKT, and PLCγ pathways.

- NTRK gene fusions result from chromosomal rearrangements leading to constitutively active TRK fusion proteins, which drive oncogenesis.
- These fusions are rare in NSCLC, found in <1% of cases, but are highly actionable.

Clinical features of lung cancer patients with NTRK gene fusions are comparable to NSCLC with ALK, RET, or ROS1 mutation. They are typically younger and often have a minimal smoking history.

Early-phase trials and preclinical studies suggest that repotrectinib and selitrectinib may exhibit promising efficacy in patients whose disease progression relies on the TRK pathway. [109]

- **Entrectinib**

Entrectinib is an inhibitor targeting TRKA, TRKB, TRKC, ROS1, and ALK and exerts its antineoplastic effects by preventing the phosphorylation of TRK fusion proteins and associated signaling molecules. The efficacy and safety of entrectinib were evaluated in the integrated analysis of three trials (ALKA-372-001, STARTRK-1, STARTRK-2).

Population:

- Total NTRK fusion-positive patients: 54
- NSCLC subgroup: 10 patients

Results (all histologies):

- ORR: 57%
- Median DoR: 10 months
- Median PFS: 11 months
- Median OS: 21 months
- CNS activity confirmed with an intracranial response rate of 50% in patients with brain metastases.

Results(NSCLC-specific):

- ORR: ~70%
- Intracranial responses were observed.
- Toxicity profiles: dysgeusia (47%), constipation (28%), fatigue (28%), diarrhea, peripheral edema, dizziness, paresthesias, and nausea/vomiting. [110]

Given these findings, entrectinib has been approved for treating patients with NTRK fusion-positive solid tumors.

- **Larotrectinib**

Integrated Analysis of three clinical trials NCT02122913, NCT02637687, and NCT02576431 investigated the effectiveness of larotrectinib for treating NTRK fusion-positive patients (all tumor types).

Population:

- Total NTRK fusion-positive patients (all tumor types): 159
- NSCLC subgroup: 10 patients

Results (all histologies):

- ORR: 75% (95% CI: 67–81)
- Median DoR: 49.3 months
- Median PFS: 35.4 months
- Median OS: Not reached at median follow-up of 20 months

Results (NSCLC-specific):

- ORR: ~70%
- Responses were durable and included complete responses.
- Toxicity profiles: increased ALT levels (3%), anemia(2%), and reduced neutrophil count (2%). [111]

Given these promising findings, the FDA approved larotrectinib for use in both adult and pediatric patients with solid tumors possessing NTRK gene fusions.

Second-Generation TRK Inhibitors

- **Selitrectinib**

Selitrectinib is a TRK inhibitor known for its high efficacy against acquired resistance solvent-front and gatekeeper mutations.

Currently under investigation (NCT03215511, NCT03206931).

- **Repotrectinib**

Repotrectinib, a next-generation inhibitor targeting ALK, ROS1, and NTRK., being tested**)** for its efficacy and safety in TRIDENT-1 phase 1 trial (NCT03093116).

The agent has demonstrated high therapeutic activity and tolerability in patients with NTRK gene fusions who had previously received first-generation TKIs, such as entrectinib or larotrectinib.

Notably, repotrectinib has exhibited the capacity to control disease progression mediated by the kinase domain, effectively addressing acquired resistance observed with earlier TRK inhibitors. Among the eight patients treated, three achieved a positive response, yielding an ORR of 50%. Additionally, the drug has maintained a

manageable toxicity profile, with the most frequently reported adverse events being dizziness (57%), dysgeusia (51%), dyspnea (30%), and fatigue (30%). [68]

Resistance Mechanisms

Resistance to first-generation TRK inhibitors can be on-target or off-target:

On-target:

- Mutations in kinase domain (e.g., NTRK1 G595R, G667C, F589L, NTRK3 G623R)
- Prevent inhibitor binding while preserving TRK activity

Off-target:

- Activation of bypass pathways (e.g., MET or EGFR amplification)
- Phenotypic transformation. [112]

NTRK fusion-positive NSCLC, though rare, is highly actionable with dramatic and durable responses to selective TRK inhibitors. Both larotrectinib and entrectinib are recommended as first-line therapy for advanced disease harboring NTRK fusions. Ongoing trials aim to address resistance mechanisms and CNS progression.

3.9. HER 2

HER2 (ERBB2) mutations, particularly HER2 exon 20 insertions, are identified in approximately 2–4% of NSCLC cases. These alterations are more prevalent in non-smokers and are typically mutually exclusive with other oncogenic drivers like EGFR or ALK. HER2 alterations in NSCLC can manifest:

- Mutations: Predominantly HER2 exon 20 insertions.
- Amplification: Increased gene copy number.
- Overexpression: Elevated protein levels detected via immunohistochemistry (IHC). [113]

While HER2-targeted therapies have revolutionized breast and gastric cancers, their application in NSCLC has been more recent and is rapidly evolving.

- Trastuzumab-deruxtecan (T-DXd)

T-DXd is an ADC combining trastuzumab with a topoisomerase I inhibitor.

The DESTINY-Lung01 phase 2 trial tested trastuzumab-deruxtecan in patients with HER2-mutant NSCLC.

Results:

- ORR: 55%
- DoR: 9.3 months
- PFS: 8.2 months [114]
- It is important to note that interstitial lung disease (ILD) as a side effect of T-DXd required immediate diagnosis and management.

These findings led to FDA approval for HER2-mutant NSCLC.

The DESTINY-Lung02 phase 2 evaluate T-DXd at two dosing levels (5.4 mg/kg and 6.4 mg/kg) in patients with HER2-mutant NSCLC.

Results:

- ORR: 49.0%(5.4 mg/kg) and 56.0%(6.4 mg/kg).
- Median treatment duration: 7.7 months (5.4 mg/kg) and 8.3 months (6.4 mg/kg).
- Preliminary Results: Maintained efficacy with improved safety profile.
  [115]

Both trials demonstrated clinically meaningful responses, reinforcing T-DXd’s potential as a treatment for HER2-mutant NSCLC.

The DESTINY-Lung-04 study aims to evaluate T-DXd's predominance in comparison to standart chemotherapy as a first-line treatment.

The ongoing DESTINY-Lung04 phase 3 trial evaluating T-DXd as a first-line treatment for HER2-mutant unresectable, locally advanced, or metastatic NSCLC. The trial compares T-DXd (5.4 mg/kg) with platinum-pemetrexed chemotherapy plus pembrolizumab, enrolling approximately 450 patients. [116]

- Trastuzumab-rezetecan

Trastuzumab-rezetecan is a novel ADC targeting HER2 with a potent cytotoxic payload.

The HORIZON-Lung phase 2 trial evaluating trastuzumab-rezetecan in patients with advanced HER2-mutant NSCLC.

Results:

- ORR: 73%
- Median PFS: Data maturing
- Safety: Common grade 3-4 adverse events included decreased neutrophil and white blood cell counts, anemia, and interstitial lung disease. No treatment-related deaths occurred. [117]

- Pyrotinib

Pyrotinib an oral irreversible pan-HER TKI targeting EGFR, HER2, and HER4.

Phase II trials investigated pyrotinib in patients with advanced NSCLC who had previously been treated with platinum-based therapies.

Results:

- ORR: Up to 53.3% in patients with HER2 exon 20 insertions.
- Median PFS: 6.4 months.
- Safety: Acceptable safety profile; further validation in larger randomized clinical trials is warranted.

The study indicated that the treatment gaine substantial benefit for patients with various HER2 mutations and brain metastases.[118]

The PATHER2 phase II trial investigated the combination of pyrotinib with apatinib in advanced HER2-altered NSCLC patients.

Results:

- ORR: 51,5%
- DCR: 93.9%
- Median DoR: 6.0 months
- Median PFS: 6,9 months
- Median OS: 14,8 months.
- Toxicity profile: The most frequent grade ≥3 treatment-related adverse events included diarrhea (3.0%) and hypertension (9.1%), with no treatment-related deaths reported. [119]

These results suggest that pyrotinib plus apatinib exhibits promising antitumor activity with a manageable safety profile in HER2-altered metastatic NSCL.

The ongoing phase III PYRAMID-1 trial comparing efficacy and safety of pyrotinib to docetaxel in patients with advanced NSCLC harboring a HER2 exon 20 mutation, who have previously been treated with platinum-based chemotherapy (NCT04447118)[120]

- Poziotinib

Poziotinib is an irreversible pan-HER TKI with activity against HER2 exon 20 insertions.

Clinical Evidence:

In a phase II trial involving 30 patients with HER2 exon 20 mutant NSCLC, Poziotinib achieved ORR of 27% and a median PFS of 5.5 months.[121]

The ZENITH20-2 and ZENITH20-4 trials evaluated poziotinib, an irreversible TKI targeting HER2 exon 20 insertion mutations in NSCLC.

ZENITH20-2 Trial (Previously Treated Patients)

Results:

- ORR: 27.8% (95% CI: 18.9–38.2%)
- DCR: 70.0% (95% CI: 59.4–79.2%)
- PFS: 5.5 months (95% CI: 3.9–5.8 months)
- DoR: 5.1 months (95% CI: 4.2–5.5 months)
- Common Grade ≥3 Adverse Events: Rash (48.9%), diarrhea (25.6%), stomatitis (24.4%)
- Dose Reductions Required: 76.7% of patients [25]

ZENITH20-4 Trial (Treatment-Naïve Patients)
Results:

- ORR: 41% (95% CI: 30–54%)
- DoR: 5.7 months (range: 1.2 to >19.1 months)
- PFS: 5.6 months (range: 0 to >20.2 months)
- Dose Interruptions: 90% (once-daily dosing), 68% (twice-daily dosing)
- Dose Reductions: 79% (once-daily), 64% (twice-daily)
- Common Grade ≥3 Adverse Events: Rash (35%), stomatitis (21%), diarrhea (15%) [26]

While poziotinib demonstrated antitumor activity, its toxicity profile remains a limiting factor, requiring frequent dose modifications.

Conclusion: Poziotinib exhibits promising activity in HER2 exon 20 mutant NSCLC, with higher efficacy observed in treatment-naïve patients.

The FDA has concluded that more data from a randomized controlled trial are essential to evaluate the overall risk-benefit analysis before poziotinib can receive approval for use in pretreated patients with NSCLC with HER2 exon 20 insertion mutations.

- Zongertinib (BI 1810631)

Zongertinib is an oral, irreversible HER2-selective TKI.

The BEAMION-Lung01 phase 1b trial evaluating the safety and efficacy of zongertinib in patients with HER2 aberration-positive HER2 m+ NSCLC.
Population: Previously treated HER2-mutant NSCLC patients.
Results:

- ORR: 71%
- CR: 7%
- DCR: 96%
- Median DoR: 14.1 months
- Median PFS: 12.4 months
- Safety profile: Manageable safety profile with low incidence of grade ≥3 drug-related adverse events. [122]

- Zenocutuzumab

On December 4, 2024, the FDA granted first approval for zenocutuzumab, an IgG1 bispecific antibody targeting the human epidermal growth factor receptors HER2 and HER3. The new treatment is targeted at adults with advanced, unresectable pancreatic adenocarcinoma or NSCLC that has undergone previous systemic therapy and disease progression. [123]

- Afatinib

Afatinib is an irreversible pan-HER TKI.

The NICHE phase II trial assessed the clinical activity of afatinib in pretreated patients with advanced NSCLC harboring HER2 exon 20 mutations.
Results:

- ORR: 7.7%
- Median PFS: 15.9 weeks

Lower disease control rate than expected; failed to meet criteria for further clinical testing.
[124]

- ELVN-002

ELVN-002 exhibits potent inhibition of HER2 kinase activity, including various clinically relevant HER2 mutations such as HER2 exon 20 insertions (e.g., YVMA) and point mutations like L755S and S310F. Preclinical studies have demonstrated that ELVN-002 has over 100-fold selectivity for HER2 over EGFR, minimizing off-target effects. In vitro and in vivo models have shown that ELVN-002 effectively inhibits tumor growth in HER2-driven cancers, including intracranial models, suggesting potential efficacy in treating brain metastases.

A first-in-human Phase 1a/1b clinical trial is currently underway to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of ELVN-002 in patients with HER2-altered advanced solid tumors, including HER2-mutant NSCLC. [125]

The trial also includes exploratory cohorts to evaluate ELVN-002 in combination with other HER2-targeted therapies:

- ELVN-002 + Trastuzumab Deruxtecan (T-DXd): For patients with HER2-mutant NSCLC, assessing the safety and preliminary efficacy of the combination. [125]
- ELVN-002 + Trastuzumab Emtansine (T-DM1): For patients with HER2-overexpressing metastatic breast cancer (MBC), evaluating the combination's safety and activity. [125]

- Neratinib

Neratinib is an irreversible pan-HER TKI.

The SUMMIT trial evaluated neratinib in 26 patients with HER2-mutant NSCLC. Results:

- ORR: 4%.
- Notably, the sole responder had an L755S point mutation; no responses were observed in patients with the common Y772_A775dupYVMA exon 20 insertion.

Conclusion: Neratinib shows limited efficacy in HER2-mutant NSCLC, particularly against HER2 exon 20 insertions. [126]

- Dacomitinib

Dacomitinib is an irreversible pan-HER TKI targeting EGFR, HER2, and HER4.
ZENITH20-2 phase II trial tested dacomitinib in patients with HER2-mutant NSCLC.

Results:

- ORR: 11.5%,
- PFS: 3 months. [127]

Conclusion: Dacomitinib has demonstrated modest activity in HER2-mutant NSCLC, with limited efficacy against HER2 exon 20 insertion mutations. Responses were primarily observed in patients with specific mutations such as P780_Y781insGSP and M774delinsWLV. [128]

Ongoing and Emerging Strategies to Overcome Resistance

To address these resistance mechanisms, several therapeutic strategies and clinical trials are underway:

1. Next-Generation HER2 Inhibitors
   - Zongertinib: An experimental Boehringer Ingelheim drug, zongertinib, demonstrated a 71% tumor response rate in patients with advanced HER2-mutated NSCLC, with disease stabilization lasting over a year. [122]
   - ELVN-002: A highly selective, irreversible HER2 inhibitor currently in clinical evaluation for HER2-mutant NSCLC. [129]
2. Combination Therapies
   - HER2 TKIs + mTOR or MEK Inhibitors: Combining HER2-targeted TKIs with inhibitors of downstream pathways aims to block compensatory signaling mechanisms. [129]
   - HER2 TKIs + Checkpoint Inhibitors: Integrating immunotherapy with targeted therapies may provide synergistic effects, improving treatment outcomes. [130]
3. Improved ADCs
   - Next-Generation ADC: Development of ADC with different payloads, enhanced linker stability, and bystander killing effects is being explored to overcome resistance.
4. Biomarker-Guided Therapy
   - Genomic Profiling: Utilizing comprehensive genomic profiling to identify specific HER2 alterations and co-mutations can guide personalized therapy.
   - Circulating tumor DNA analysis can help in the early detection of resistance mutations and guide treatment adjustments.
5. Overcoming ADC Resistance

- Combination with DNA Repair Inhibitors: Combining ADC with agents like PARP inhibitors may enhance efficacy by preventing the repair of ADC-induced DNA damage.
- Efflux Transporter Inhibitors: Targeting efflux transporters may increase intracellular retention of ADC payloads.

Resistance Mechanisms to HER2-Targeted Therapies in NSCLC

Resistance to HER2-targeted therapies in NSCLC can be categorized into several mechanisms:

1. On-Target Resistance
   - Secondary HER2 Mutations: Mutations such as L755S and T798I can alter the HER2 kinase domain, reducing the binding efficacy of TKI.
   - HER2 Protein Downregulation: Loss or reduction of HER2 expression can diminish the effectiveness of ADC like trastuzumab-deruxtecan (T-DXd).
2. Off-Target or Bypass Mechanisms
   - Activation of Alternative Pathways: Upregulation of pathways such as EGFR, MET, IGF1R, or AXL can bypass HER2 dependency, sustaining tumor proliferation.
   - PI3K/AKT or MAPK Pathway Reactivation: Mutations or amplifications in downstream effectors like PIK3CA or loss of PTEN can undermine HER2 blockade.
3. ADC-Specific Resistance
   - Impaired Internalization or Trafficking: Alterations in the internalization process of the HER2-ADC complex can reduce the cytotoxic payload delivery.
   - Efflux Transporter Overexpression: Overexpression of efflux transporters such as ABCB1 can decrease intracellular accumulation of the ADC payload.
   - Resistance to Cytotoxic Payload: Tumor cells may develop resistance to the cytotoxic agents used in ADC, such as topoisomerase I inhibitors in T-DXd.
4. Phenotypic Changes
   - EMT can lead to a more invasive phenotype, contributing to resistance.
   - Histologic Transformation: Rarely, tumors may undergo histologic changes, such as transformation to small cell lung cancer, leading to resistance. [129]

4. Discussion

Advances in molecular profiling have revolutionized the management of NSCLC by enabling the identification of distinct oncogenic drivers and the tailoring of treatment strategies accordingly. As highlighted in this review, targeted therapies—including TKI, ADC, and bispecific antibodies—have markedly improved clinical outcomes in patients whose tumors harbor actionable mutations in genes such as EGFR, ALK, ROS1, MET, KRAS, RET, BRAF, NTRK, and HER2.

The success of first-, second-, and third-generation EGFR TKIs in improving PFS and OS in EGFR-mutant NSCLC has set the stage for subsequent innovations. However, challenges remain—most notably the inevitable development of acquired resistance. Resistance mechanisms, such as the emergence of secondary mutations (e.g., T790M, C797S) and phenotype transformations, necessitate the development of next-generation inhibitors and combination strategies. In a similar vein, the evolution of ALK-directed therapies—from crizotinib to more potent and CNS-penetrant agents like alectinib, brigatinib, and lorlatinib—illustrates how improving drug properties can mitigate specific limitations such as brain metastases and acquired resistance mutations.

Other molecular subsets, including ROS1 and NTRK fusions, have also benefited from targeted treatments that not only achieve high ORR but also demonstrate durable intracranial activity. Agents such as entrectinib and larotrectinib underscore the promise of molecularly targeted therapies even in low-prevalence subgroups. Similarly, breakthroughs observed with KRAS G12C inhibitors, such as sotorasib and adagrasib, affirm that previously “undruggable” mutations can now be exploited therapeutically. Nevertheless, the heterogeneity inherent to KRAS-mutant NSCLC, coupled with complex resistance mechanisms, signals a need for both combinatorial approaches and the exploration of next-generation inhibitors.

Among the emerging targets, alterations in RET, MET, HER2, and BRAF have expanded the therapeutic landscape further. Trials such as LIBRETTO-431, DESTINY-Lung01/02, and CHRYSALIS-20 have collectively demonstrated that selective inhibitors can yield substantial clinical benefits in appropriately selected patients. However, the review also emphasizes the challenges of toxicities, optimal sequencing of therapies, and the need

for dynamic treatment monitoring—often through liquid biopsy or comprehensive genomic profiling—to promptly identify resistance mechanisms and guide therapeutic modifications.
Overall, while the integration of targeted therapies into clinical practice has undoubtedly transformed the treatment paradigm for advanced NSCLC, resistance—the interplay of on-target mutations and bypass signaling pathways—remains the foremost barrier to achieving long-term disease control. This growing complexity calls for a multidimensional approach that combines novel inhibitors, immunotherapies, and robust biomarker-driven strategies.

5. **Conclusions**

The landscape of NSCLC treatment has been profoundly altered by the advent of precision medicine. By aligning therapeutic strategies with individual molecular alterations, clinicians have achieved significant improvements in PFS, OS, and quality of life for selected patients. Targeted therapies against EGFR, ALK, ROS1, MET, KRAS, RET, BRAF, NTRK, and HER2 not only illustrate the effectiveness of these agents in advanced NSCLC but also underscore the importance of continuous genomic characterization to overcome resistance.
Despite these advancements, several challenges remain. Acquired resistance—manifesting through secondary mutations or activation of alternative pathways—limits the durability of current treatment options and necessitates ongoing research into combination regimens and next-generation inhibitors. Furthermore, toxicity profiles and CNS penetration efficacy are key factors that must be addressed to optimize patient outcomes.

In conclusion, precision medicine has emerged as the cornerstone of modern NSCLC management. Continued investment in translational research, innovative clinical trials, and multi-omics profiling will be critical in overcoming current therapeutic limitations. Future treatment paradigms are likely to incorporate combination therapies and personalized monitoring tools, which together promise to further extend survival benefits and improve the quality of life for patients with NSCLC.

These sections synthesize the key points from the review and articulate both the progress made and the challenges that remain in the field of targeted therapies for NSCLC.

6. Disclosure

Author's Contribution:
Conceptualization: VM, KM
Methodology: DL, VM
Formal analysis: KT, KM, MS
Investigation: DW, VK, AM
Writing-rough preparation: IK, DL,
Writing-review and editing: DK, VK, DW,
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