Research Progress on Resistance Mechanisms and Post-Resistance Treatment of Targeted Therapy in Non-Small Cell Lung Cancer

Ziyuan Gao [1, †, *], Yuzhu Chen [2, †]

[1] School of Medicine, Xi'an Jiaotong University, Xi'an Shaanxi, 710049, China

[2] Department of Oncology, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing 101149, China

* Corresponding Author: Ziyuan Gao (Email: gzy042813@163.com)

† Two authors have made equal contributions to this article

Abstract. Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related mortality worldwide, and about 60% of the advanced cancer stage patients carry particular molecular mutations that model potential targets in terms of targeted therapy. Gene mutations such as EGFR, MET, and ALK are key drivers of NSCLC. Targeted drugs against these mutations, including EGFR-TKIs, MET-TKIs, and ALK-TKIs, have significantly improved patient prognosis. However, acquired resistance remains a significant challenge, with mechanisms involving secondary target mutations, bypass activation, and phenotypic transformation. This review summarizes the resistance mechanisms of targeted therapy in NSCLC and corresponding therapeutic strategies, aiming to provide new insights for post-resistance treatment.

Keywords: Non-small Cell Lung Cancer (NSCLC); Targeted Therapy; EGFR-TKIs; Acquired Resistance.

1. Introduction

Lung cancer is the most frequent cancer-related mortality worldwide, and non-small cell lung cancer (NSCLC) represents 80%85 of the cases [1]. Molecular advances have driven targeted therapy forward; around 60% of advanced NSCLC patients carry actionable mutations [2]. The most prevalent, which occur in 50 percent of Asian and 10 percent to 16.6 percent of Caucasian patients, are EGFR mutations [3]. EGFR-TKIs have markedly improved outcomes, evolving through generations to counter resistance—notably the T790M mutation with third-generation agents. However, acquired resistance remains a major clinical challenge.

MET alterations occur in ~7% of NSCLC cases, with Type I MET-TKIs offering targeted inhibition [4]. ALK rearrangements, more common in young non-smokers, promote tumorigenesis via downstream signaling [5]. ALK-TKIs have also advanced generationally.

Despite improved outcomes, acquired resistance—through secondary mutations, bypass activation, or phenotypic transformation—limits long-term efficacy. These mechanisms are important to understand and come up with post-resistance. This review is a summary of resistance in NSCLC targeted therapy and responsive therapies.

2. Resistance Mechanisms

2.1 Resistance Mechanisms to EGFR-TKIs

Resistance to EGFR-TKIs is classified as primary or acquired. Acquired resistance further divides into EGFR-dependent and independent mechanisms. EGFR-dependent resistance primarily involves secondary mutations reducing drug binding affinity, notably T790M conferring resistance to first- and second-generation TKIs [6], and C797S driving resistance to third-generation agents like osimertinib [7]. EGFR-independent resistance commonly arises through bypass activation, such as MET amplification (5%–10% of cases) activating PI3K-AKT via HER3 dimerization [8-10], or other

mechanisms including HER2 amplification, RAS-MAPK pathway activation, and oncogenic fusions. Histological transformation, e.g., to SCLC, occurs in 5%–10% of patients, often with RB1/TP53 loss [8-11].

2.2 Resistance Mechanisms to Other Targeted Drugs

For MET-TKIs, resistance involves MET-dependent mutations (e.g., D1228, Y1230) or amplification, and MET-independent mechanisms like RAS/MAPK or PI3K/AKT activation or EGFR/HER2 bypass [12, 13]. ALK-TKI resistance includes ALK-dependent compound mutations (e.g., G1202R+L1196M) and ALK-independent bypass activation; the 2024 ASCO CROWN study reported lorlatinib resistance primarily involving MAPK/PI3K/RTK pathway alterations and cell cycle abnormalities [14].

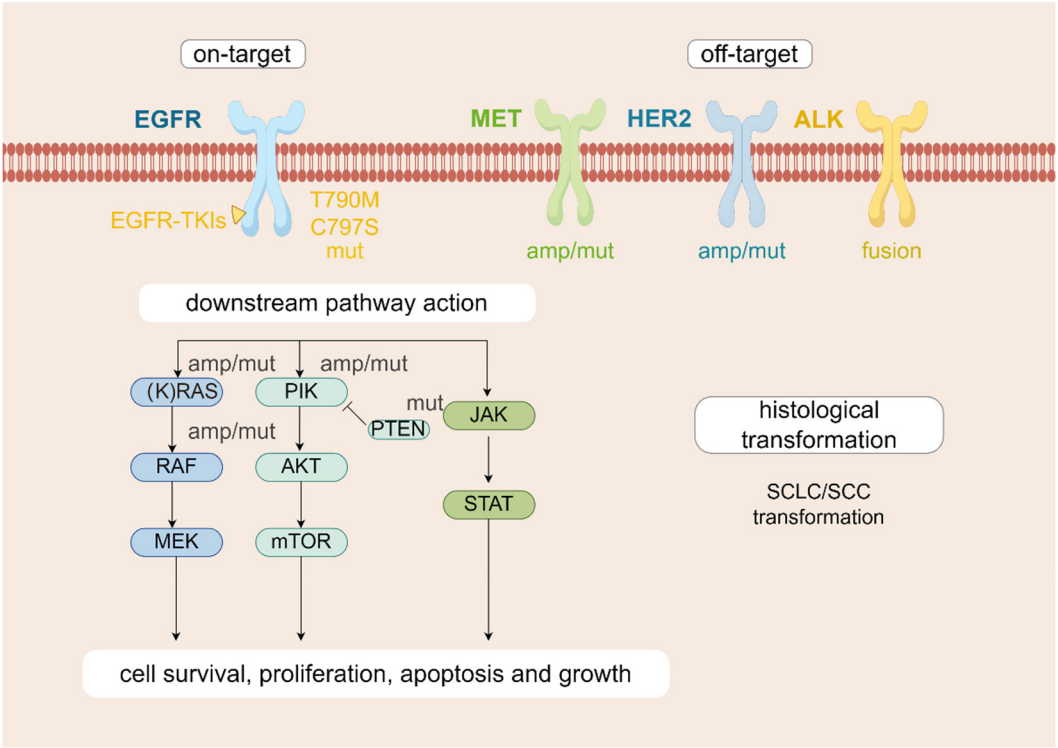

Figure 1. illustrates the acquired resistance mechanisms to EGFR-TKIs, categorized into EGFR-dependent and independent. Mutations (e.g., T790M, C797S) are part of the EGFR-dependent mechanisms, which decrease drug binding. EGFR-independent pathways include bypass resistance (ex, MET amplification, HER2 amplification, ALK fusion) and aberrant downstream signalling (ex, PI3K/AKT/mTOR, RAS/RAF/MEK/ERK), which facilitates the survival of cancer cells, their growth, and anti-apoptosis. It is also important that there should be a histological change (e.g., NSCLC to SCLC/SCC).

3. Post-Resistance Treatment

3.1 Treatment After EGFR-TKI Resistance

EGFR-TKIs are currently used as first-line therapy of advanced MSG of the lung (ETS), which is positive on tested for epidermal growth factor receptor (EGFR). The progression that occurs after the resistance can be categorised into oligoprogression, intracranial progression, and extensive progression. The first Asia-Pacific consensus, based on the third-generation resistance of the two types of origin medicine, of the use of drugs targeted at a gene controller (EGFR-TKI), recommendation by the guidelines of China in the medical sciences (CSCO) recommends customized mode of the method.

3.1.1 Strategies for Oligoprogression and Intracranial Progression

For oligoprogression, local therapies (e.g., radiotherapy, surgery, radiofrequency ablation) combined with continued EGFR-TKIs are recommended, with studies showing improved PFS and OS compared to EGFR-TKIs alone. For intracranial progression, treatment (surgery or systemic therapy) is guided by the number and size of brain metastases.

3.1.2 Strategies for Extensive Progression

Biopsies after third-generation EGFR-TKI resistance identify mechanisms in some patients, but 30%-50% remain unclear.

3.1.2.1 Treatment for Defined Resistance Mechanisms

For defined resistance mechanisms, treatment strategies are highly targeted. Fourth-generation EGFR-TKIs, including BDTX-1535, are active in EGFR-dependent resistance, which includes the C797S mutation, where the phase II trial (NCT05256290) recorded a response rate (ORR) of 42% [15]. The conventional treatment is platinum chemotherapy. For EGFR-independent resistance, combination therapies are selected based on the specific mechanism: osimertinib combined with MET-TKIs is recommended for MET amplification [16, 17]; trastuzumab deruxtecan (T-DXd) has shown significant activity against HER2 amplification, as evidenced in the DESTINY-Lung02 trial [18]; dabrafenib plus trametinib is an established strategy for BRAF V600E mutations, with five-year follow-up data showing 5-year OS rates of 19% in pretreated and 22% in untreated patients [19, 20]. Combinations targeting downstream pathways are under active investigation.

3.1.2.2 Treatment for Undefined Resistance Mechanisms

Another future strategy with respect to patients of unspecified resistance mechanisms is antibody-drug conjugates (ADCs). In a phase II trial (HERTHENA-Lung01), HER23-DXd (patritumab deruxtecan) was discovered to have an ORR and a median progression-free survival (mPFS) of 29.8 and 5.5 months, respectively [21].ADCs targeting TROP2, including datopotamab deruxtecan (Dato-DXd), have also shown clinical response in phase III trials. The conventional chemotherapy based on platinum has its limitations, but it is still at the backbone of treatment. The combination of lazertinib, amivantamab, and chemotherapy showed potential in a small study [22], while immunotherapy combined with EGFR-TKIs is not recommended due to safety concerns [23]. Regimens combining immunotherapy, chemotherapy, and anti-angiogenesis, such as the ABCP regimen in IMpower150 [24] and sintilimab-based combinations in ORIENT-31 [25], have shown efficacy in selected populations.

3.2 Treatment After Other TKI Resistance

Strategies for MET-TKI and ALK-TKI resistance reference EGFR-TKI approaches, tailored to progression patterns and mechanisms.

3.2.1 Treatment After MET-TKI Resistance

Management depends on the resistance type and clinical context. MET-dependent resistance (20%-35% of cases) [12, 13] may respond to sequential MET-TKIs, leveraging differential sensitivity between type I/II inhibitors [29]. The VISION trial confirmed tepotinib's efficacy in METex14-mutant NSCLC [30]. MET-independent resistance involves alternative pathways (e.g., RAS/MAPK, PI3K/AKT) or bypass activation (e.g., EGFR/HER2) [12, 13, 29, 31], potentially requiring combination strategies. For undefined mechanisms (25%-47%), platinum chemotherapy, immunotherapy, or anti-angiogenic therapy are standard options.

Table 1. Data summary of clinical trials in EGFR mutant metastatic NSCLC cases progressing on EGFR inhibitors

Generation	Resistance type	Reference	Study name	Phase	Treatment arm	Efficacy	Safety
First/Second Generation	T790M	[26]	APOLLO (NCT02981108)	II	Almonertinib	**mPFS:**12.4mo **ORR:**68.9% **DCR:**93.4%	The incidence of grade 3 and above adverse events is low, and the safety is good.
Third Generation	C797S	[15]	NCT05256290	II	BDTX-1535	**ORR:**42%	Most AEs are mild or moderate, and the researchers did not observe new safety signals.
	MET	[16]	ORCHARD	II	osimertinib + savolitinib	**ORR:**41%	Grade ≥ 3 AE: 30% SAE: 30%
		[17]	INSIGHT2	II	osimertinib + tepotinib	**mPFS:**5.6 mo **ORR:**50% **mOS:**17.8mo	Grade ≥ 3 AE: 34% SAE: 29%
	HER2	[18]	Destiny-Lung02 (NCT04644237)	II	T-DXd, DS-8201	**mPFS:** 5.4mg/kg group:10.0mo 6.4mg/kg group:12.9mo **ORR:** 5.4mg/kg group:49% 6.4mg/kg group:56% **mOS:** 5.4mg/kg group:19.0mo 6.4mg/kg group:17.3mo	Grade ≥ 3 AE: 5.4mg/kg group:39.6% 6.4mg/kg group:60.0%
	BRAF	[19, 20, 27]	BRF113928	II	A:Dabrafenib monotherapy B:Dabrafenib+ Trametinib (treated patients) C:Dabrafenib+ Trametinib (untreated patients)	**mPFS:** A:5.5mo B:9.7mo C:10.9mo **ORR:** A:33% B:63.2% C:64%	A: Common adverse events include fever, fatigue, nausea, and skin-related toxicities. B: Adverse events of combination therapy include fever, diarrhea, nausea, and rash, but they are generally controllable. C: Similar to cohort B.
	Undefined (HER3)	[21]	HERTHENA-Lung01	II	Patritumab deruxtecan(HER3-DXd: U3-1402)	**mPFS:**5.5 mo **ORR:**29.8% **mOS:**11.9 mo	Grade ≥ 3 TEAE: 64.9% SAE: 40%
	Undefined (TROP2)	[28]	TROPION-Lung01	III	A:Dato-Dxd B:Docetaxel	**mPFS:** A: 4.4 mo B: 3.7 mo **ORR:** A:26.4% B:12.8%	Grade ≥ 3 TRAE: A: 25%; B: 41% Serious TRAE: A: 10%; B: 12%
	Undefined	[22]	CHRYSALIS-2	Ib/II	Amivantamab +Lazertinib +Carboplatin+ Pemetrexed	The **ORR** reached 50%. The **mPFS** of 11 patients was 14.0 months.	The most common grade ≥ 3 TEAEs include neutropenia (70%), thrombocytopenia (25%), and fatigue (25%).
	Undefined	[24]	IMpower150	III	Atezolizumab +Bevacizumab + Carboplatin+Paclitaxel **(ABCP)** Atezolizumab + Carboplatin+Paclitaxel **(ACP)** compared with the standard treatment Bevacizumab+ Carboplatin+Paclitaxel **(BCP)**	**mPFS:** ACP:6.9mo BCP:6.9mo ABCP:10.2mo **mOS:** ACP:19.0mo BCP:18.1mo ABCP:29.4mo	The incidences of grade 3-4 treatment-related adverse reactions were 56.8%, 55.8%, and 66.7% respectively.
	Undefined	[25]	ORIENT-31	III	A:sintilimab+IBI305+chemo B: sintilimab+ chemo C: chemo	**mPFS:** A: 7.2 mo B: 5.5 mo C: 4.3 mo	Grade ≥ 3 TRAE: A: 56% B: 41% C: 49%

3.2.2 Treatment After ALK-TKI Resistance

Therapeutic strategies include sequential ALK-TKIs, combination therapies, or local intervention for oligoprogression. ALK-dependent resistance, particularly compound mutations involving G1202R, often retains sensitivity to next-generation agents like lorlatinib [32-36]. ALK-independent resistance, frequently involving bypass activation of MAPK, PI3K, or RTK pathways as reported in the 2024 ASCO CROWN study [14], may benefit from combination approaches such as ALK-TKIs with MEK inhibitors [37, 38]. Lorlatinib demonstrates notable intracranial activity [39], while brigatinib offers efficacy against specific mutations and bypass mechanisms [40].

Table 2. Data summary of clinical trials in MET and ALK mutant metastatic NSCLC cases progressing on MET and ALK inhibitors

Generation	Resistance type	Reference	Study name	Phase	Treatment arm	Efficacy	Safety
First Generation	MET-TKIs	[41]	NCT02414139	II	Capmatinib	**mPFS:** Untreated patients: 9.69 mo Treated patients: 5.42 mo **ORR:** Untreated patients: 67.9% Treated patients: 40.6% **mOS:** Untreated patients: 20.82 mo Treated patients: 13.56 mo	The safety is good, and most adverse events are mild to moderate.
		[30]	NCT02864992	II	Tepotinib	In the overall patient population, **the ORR** of Tepotinib was 51.4%, **the mDOR** was 18.0 months, **the mPFS** was 11.2 months, and **the mOS** was 19.6 months.	Most adverse events are mild to moderate, and the incidence of grade 3 and above adverse events is 28.2%.
Second Generation	ALK-TKIs	[39]	NCT01970865	II	Lorlatinib	Among patients who had received ≥ 1 second-generation ALK-TKI, **the ORR** reached 39.6%, **the mDoR** was 9.6 months, **the mPFS** was 6.6 months, and **the mOS** was 20.7 months.	Common adverse events include hypercholesterolemia, hypertriglyceridemia, and peripheral neuropathy, and most of them are grade 1-2.
		[40]	NCT02737501	II	Brigatinib	Among patients who had received Crizotinib treatment, **the ORR** was 53%, and **the mPFS** was 16.7 months.	Common adverse events include nausea, diarrhea, headache, and cough, and most of them are grade 1-2.

4. Discussions

Targeted therapy significantly improves NSCLC management, yet acquired resistance remains a critical barrier. This review synthesizes key resistance mechanisms and evolving strategies, emphasizing that effective post-resistance treatment requires personalized approaches based on molecular profiling and clinical context. While next-generation TKIs, ADCs, and combination therapies show promise in extending survival, TKI-immunotherapy combinations remain limited by safety concerns and insufficient evidence.

Beyond genetic alterations, emerging research highlights non-genetic mechanisms driving resistance. Drug-tolerant persister (DTP) cells evade therapy through epigenetic and signaling adaptations [42], while dysregulated ferroptosis, controlled by GPX4, SLC7A11, and NRF2, represents another key resistance pathway. Targeting DTP populations and modulating ferroptosis offer novel therapeutic opportunities to re-sensitise tumors to treatment. Future advances will depend on elucidating these mechanisms and integrating multidisciplinary strategies to overcome resistance and improve long-term outcomes.

5. Conclusion

Targeted therapy has transformed NSCLC treatment by improving precision and patient outcomes, yet acquired resistance continues to limit long-term efficacy. This review summarizes the principal resistance mechanisms and corresponding strategies, underscoring the necessity of mechanism-guided therapy. The integration of next-generation TKIs, ADCs, and rational combinations provides promising paths to extend survival after resistance development. Future success will rely on targeting non-genetic mechanisms such as DTP cells and ferroptosis, advancing personalized multimodal strategies to overcome resistance and improve prognosis in NSCLC ultimately.

Declarations

Ethics approval and consent to participate: Not applicable.
Consent for publication: Not applicable.

Author Contributions

Yuzhu Chen: Data curation; Resources; Writing, review & editing.
Ziyuan Gao: Writing – review & editing.

Competing Interests

The authors declare that there is no conflict of interest.

Availability of Data and Materials

Not applicable.

References

[1] Bray, F., et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018. 68(6): p. 394-424.

[2] Alduais, Y., et al., Non-small cell lung cancer (NSCLC): A review of risk factors, diagnosis, and treatment. Medicine (Baltimore), 2023. 102(8): p. e32899.

[3] Wu, L., et al., Development of EGFR TKIs and Options to Manage Resistance of Third-Generation EGFR TKI Osimertinib: Conventional Ways and Immune Checkpoint Inhibitors. Front Oncol, 2020. 10: p. 602762.

[4] Michaels, E. and C.M. Bestvina, Meeting an un-MET need: Targeting MET in non-small cell lung cancer. Front Oncol, 2022. 12: p. 1004198.

[5] Herbst, R.S., D. Morgensztern, and C. Boshoff, The biology and management of non-small cell lung cancer. Nature, 2018. 553(7689): p. 446-454.

[6] Yun, C.H., et al., The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci U S A, 2008. 105(6): p. 2070-5.

[7] Patel, H., et al., Recent updates on third generation EGFR inhibitors and emergence of fourth generation EGFR inhibitors to combat C797S resistance. Eur J Med Chem, 2017. 142: p. 32-47.

[8] Yu, H.A., et al., Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res, 2013. 19(8): p. 2240-7.

[9] Engelman, J.A., et al., MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science, 2007. 316(5827): p. 1039-43.

[10] Bean, J., et al., MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci U S A, 2007. 104(52): p. 20932-7.

[11] Lee, J.K., et al., Clonal History and Genetic Predictors of Transformation Into Small-Cell Carcinomas From Lung Adenocarcinomas. J Clin Oncol, 2017. 35(26): p. 3065-3074.

[12] Recondo, G., et al., Molecular Mechanisms of Acquired Resistance to MET Tyrosine Kinase Inhibitors in Patients with MET Exon 14-Mutant NSCLC. Clin Cancer Res, 2020. 26(11): p. 2615-2625.

[13] Guo, R., et al., MET Exon 14-altered Lung Cancers and MET Inhibitor Resistance. Clin Cancer Res, 2021. 27(3): p. 799-806.

[14] Solomon, B.J., et al., Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. J Clin Oncol, 2024. 42(29): p. 3400-3409.

[15] ClinicalTrials.gov. A Study of BDTX-1535 in Patients With Glioblastoma or Non-Small Cell Lung Cancer. 2022 2025-3-25]; Available from: https://clinicaltrials.gov/study/NCT05256290.

[16] Yu, H.A., et al., Biomarker-Directed Phase II Platform Study in Patients With EGFR Sensitizing Mutation-Positive Advanced/Metastatic Non-Small Cell Lung Cancer Whose Disease Has Progressed on First-Line Osimertinib Therapy (ORCHARD). Clin Lung Cancer, 2021. 22(6): p. 601-606.

[17] Wu, Y.L., et al., Tepotinib plus osimertinib in patients with EGFR-mutated non-small-cell lung cancer with MET amplification following progression on first-line osimertinib (INSIGHT 2): a multicentre, open-label, phase 2 trial. Lancet Oncol, 2024. 25(8): p. 989-1002.

[18] Goto, K., et al., Trastuzumab Deruxtecan in Patients With HER2-Mutant Metastatic Non-Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial. J Clin Oncol, 2023. 41(31): p. 4852-4863.

[19] Planchard, D., et al., Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. Lancet Oncol, 2016. 17(5): p. 642-50.

[20] Planchard, D., et al., Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol, 2017. 18(10): p. 1307-1316.

[21] Yu, H.A., et al., HERTHENA-Lung01, a Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in Epidermal Growth Factor Receptor-Mutated Non-Small-Cell Lung Cancer After Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Platinum-Based Chemotherapy. J Clin Oncol, 2023. 41(35): p. 5363-5375.

[22] Lee, S.H., et al., MA13.06 Amivantamab, Lazertinib Plus Platinum-based Chemotherapy in EGFR-mutated Advanced NSCLC: Updated Results from CHRYSALIS-2. Journal of Thoracic Oncology, 2023. 18(11): p. S146-S147.

[23] Hartmaier, R.J., et al., Osimertinib + Savolitinib to Overcome Acquired MET-Mediated Resistance in Epidermal Growth Factor Receptor-Mutated, MET-Amplified Non-Small Cell Lung Cancer: TATTON. Cancer Discov, 2023. 13(1): p. 98-113.

[24] Nogami, N., et al., IMpower150 Final Exploratory Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC Patient Subgroups With EGFR Mutations or Metastases in the Liver or Brain. J Thorac Oncol, 2022. 17(2): p. 309-323.

[25] Lu, S., et al., Sintilimab plus chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer with disease progression after EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): second interim analysis from a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med, 2023. 11(7): p. 624-636.

[26] Soria, J.C., et al., Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med, 2018. 378(2): p. 113-125.

[27] Odogwu, L., et al., FDA Approval Summary: Dabrafenib and Trametinib for the Treatment of Metastatic Non-Small Cell Lung Cancers Harboring BRAF V600E Mutations. Oncologist, 2018. 23(6): p. 740-745.

[28] Ahn, M.J., et al., Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study. J Clin Oncol, 2025. 43(3): p. 260-272.

[29] Fujino, T., et al., Foretinib can overcome common on-target resistance mutations after capmatinib/ tepotinib treatment in NSCLCs with MET exon 14 skipping mutation. J Hematol Oncol, 2022. 15(1): p. 79.

[30] Kato, T., et al., Efficacy and safety of tepotinib in Asian patients with advanced NSCLC with MET exon 14 skipping enrolled in VISION. Br J Cancer, 2024. 130(10): p. 1679-1686.

[31] Jamme, P., et al., Alterations in the PI3K Pathway Drive Resistance to MET Inhibitors in NSCLC Harboring MET Exon 14 Skipping Mutations. J Thorac Oncol, 2020. 15(5): p. 741-751.

[32] Shiba-Ishii, A., et al., Analysis of lorlatinib analogs reveals a roadmap for targeting diverse compound resistance mutations in ALK-positive lung cancer. Nat Cancer, 2022. 3(6): p. 710-722.

[33] Shaw, A.T., et al., ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer. J Clin Oncol, 2019. 37(16): p. 1370-1379.

[34] Gainor, J.F., et al., Molecular Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in ALK-Rearranged Lung Cancer. Cancer Discov, 2016. 6(10): p. 1118-1133.

[35] Dagogo-Jack, I., et al., Treatment with Next-Generation ALK Inhibitors Fuels Plasma ALK Mutation Diversity. Clin Cancer Res, 2019. 25(22): p. 6662-6670.

[36] Yoda, S., et al., Sequential ALK Inhibitors Can Select for Lorlatinib-Resistant Compound ALK Mutations in ALK-Positive Lung Cancer. Cancer Discov, 2018. 8(6): p. 714-729.

[37] Crystal, A.S., et al., Patient-derived models of acquired resistance can identify effective drug combinations for cancer. Science, 2014. 346(6216): p. 1480-6.

[38] Hrustanovic, G., et al., RAS-MAPK dependence underlies a rational polytherapy strategy in EML4-ALK-positive lung cancer. Nat Med, 2015. 21(9): p. 1038-47.

[39] Kim, D.W., et al., Brigatinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. J Clin Oncol, 2017. 35 (22): p. 2490-2498.

[40] Felip, E., et al., Intracranial and extracranial efficacy of lorlatinib in patients with ALK-positive non-small-cell lung cancer previously treated with second-generation ALK TKIs. Ann Oncol, 2021. 32(5): p. 620-630.

[41] Wolf, J., et al., Capmatinib in MET exon 14-mutated non-small-cell lung cancer: final results from the open-label, phase 2 GEOMETRY mono-1 trial. Lancet Oncol, 2024. 25(10): p. 1357-1370.

[42] Sadida, H.Q., et al., Epigenetic modifications: Key players in cancer heterogeneity and drug resistance. Transl Oncol, 2024. 39: p. 101821.