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A Review of Driver Gene Co-mutations in Prognostic Stratification of Targeted Therapy for Non-Small Cell Lung Cancer

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Abstract. EGFR-TKIs have significantly improved the survival outcomes of patients with EGFR-mutant non-small cell lung cancer (NSCLC). However, substantial heterogeneity in treatment efficacy exists among individuals, and conventional single-gene testing has limitations in guiding therapeutic decision-making. This systematic review focuses on the effects of driver gene co-mutations on the prognosis of targeted therapy in EGFR-mutant NSCLC and explores their value in clinical translation. Literature published from 2022 to 2026 concerning co-mutations and prognosis of targeted therapy in EGFR-mutant NSCLC was systematically retrieved from the PubMed database for summarization and analysis. This review found that TP53 is the most prevalent co-mutated gene in EGFR-mutant NSCLC and is strongly associated with poor prognosis under TKI monotherapy. Phase III clinical trials have confirmed that TKI combined with chemotherapy significantly prolongs median progression-free survival compared with TKI monotherapy among patients with EGFR mutations accompanied by tumor suppressor gene co-mutations. NGS multi-gene panels serve as the technical foundation for comprehensive co-mutation assessment. In summary, driver gene co-mutations play a critical role in prognostic stratification for EGFR-mutant NSCLC treatment. Taking co-mutation status into account helps identify high-risk patients who may benefit from intensified treatment, supporting more precise and individualized targeted therapy.

Keywords: EGFR mutation, Non-small cell lung cancer, Co-mutations, Targeted therapy, Prognostic stratification

1. Introduction

Among all typies of lung cancer, non-small cell lung cancer (NSCLC) occupies the largest proportion, especially in East Asian populations, EGFR mutations are one of the most frequently appeared driver gene mutations. The application of EGFR-TKI has significantly improved the survival time of patients harboring these mutations. However, it has been found in clinical practice that even patients with the same mutation type can have significantly different responses to targeted

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therapy and outcomes. Traditional single-gene testing is no longer effective in guiding treatment decisions.

However, with the help of Next-Generation Sequencing (NGS) technology, researchers have discovered that driver gene co-mutations (i.e. other genetic mutations that co-exist with the main driver gene) may be key to explaining these differences. The most common co-mutation gene in EGFR-mutant NSCLC is TP53 and it is proved to be associated with poor prognosis in TKI treatment. In recent years, several studies have systematically evaluated the effect of co-mutations on the efficacy of targeted treatment and explored prognostic stratification models and treatment ooptimization strategies based on co-mutation information.

This systematic search was performed in the PubMed database for literature published between 2022 and 2026 regarding co-mutations and the prognosis of targeted therapy in EGFR-mutant NSCLC, followed by summarization and analysis.

This review systematically reviews the prognostic and translational value of driver gene co-mutations in EGFR-mutant NSCLC, covering their clinical implications, underlying mechanisms, and the technical transition from single-gene to multi-gene panels, along with current challenges in clinical implementation.

2. Prognostic heterogeneity in classic driver gene-targeted therapy

2.1. Heterogeneity of EGFR mutation subtypes in response to targeted therapy

EGFR-TKIs (epidermal growth factor receptor tyrosine kinase inhibitors) are the current standard first-line treatment for EGFR mutations in late-stage NSCLC. However, responses of TKI treatment in various types of EGFR mutations is different, particularly in cases of 19del and L858R point mutations. This indicates that only relying on the EGFR mutation status for stratification may not be sufficient for achieving precise prognostication.

The FLAURA2 trial compared osimertinib plus chemotherapy with osimertinib alone, and found that the combination group gained a longer median PFS (25.5 vs 16.7 months, HR = 0.62, 95% CI 0.49-0.79, P < 0.001) [1]. The benefit was more pronounced in L858R-mutated patients (24.7 vs. 13.9 months) than in those with 19del mutations (27.9 vs. 19.4 months). In addition, patients with baseline CNS metastases also achieved considerably prolonged median PFS with combination therapy (24.9 vs 13.8 months).

Similarly, the third generation of EGFR-TKI trials also demonstrated that aumolertinib had superior PFS over gefitinib (19.3 vs 9.9 months, HR=0.46, 95% CI 0.36-0.60, P<0.0001), accompanied by lower rates of rash and diarrhea [2]. These findings indicate that obvious differences in efficacy and tolerability profiles exist across different generations of EGFR-TKIs.

2.2. Individual variability in EGFR-targeted regimens and the co-mutation challenge at the KRAS G12C locus

In the context of EGFR-mutant NSCLC, the efficacy of different targeted treatment options is notably variable. In the phase III MARIPOSA trial, the combinaton of amivantamab and lazertinib achieved a better PFS than osimertinib (23.7 vs. 16.6 months, HR = 0.70, 95% CI 0.58-0.85, P < 0.001) [3], suggesting that even when targeting the same driver gene, different regimens can yield divergent outcomes. Additionally, among patients with a confirmed response, the median duration of response was also longer in the combination therapy group (25.8 vs. 16.8 months). Accordingly, this

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review hypothesize that factors other than EGFR mutations may regulate therapeutic mechanisms and ultimately affect treatment efficacy.

In patients with KRAS G12C-mutant NSCLC, there is also heterogeneity in the response to treatment. Despite the importance of KRAS G12C inhibitors (such as sotorasib and adagrasib) as significant therapy advances, their effectiveness is limited, and patients' responses and prognoses are also susceptible to influence. The review by Shaverdashvili et al. indicates that this is mainly associated with certain co-occurring gene mutations (such as KEAP1, STK11 and CDKN2A, etc.) and drug resistance driven by these alterations [4]. This suggests that KRAS G12C targeted therapy exhibits individual heterogeneity result from the presence of coexisting genetic mutations, highlighting the limitations of single-gene testing in guiding precise therapy.

2.3. Limitations of traditional single-driver gene stratification strategies

In conclusion, although targeted therapies such as EGFR-TKIs and KRAS G12C inhibitors have markedly improved overall survival and clinical prognosis in patients with driver gene-positive NSCLC, therapeutic efficacy still vary widely across subtypes and regimens. Co-occurring gene alterations at the KRAS G12C locus represent an emerging clinical challenge. Treatment decisions guided by conventional single-driver gene testing cannot fully capture these differences. A more refined genomic perspective is therefore needed to discover how co-mutations shape targeted therapy outcomes, which constitutes the core research question to be elaborated in the following chapter.

3. The co-mutation landscape: redefining prognostic stratification in targeted therapy

3.1. Common co-mutation types and their prognostic implications

Among patients with driver gene-positive NSCLC, those harboring the same type of gene mutation still have significant differences in prognosis with targeted treatment. As next-generation sequencing (NGS) technology has developed and become more widely used, researchers have gradually discovered that this difference may be due to other gene mutations that co-exist with the driver gene, referred to as 'driver gene co-mutations'. Among these, TP53 mutations account for the majority in EGFR-mutant NSCLC, and studies have confirmed that they are closely related to poor prognosis with EGFR-TKI treatment [5].

TP53 gene co-mutation is commently associated with a worse prognosis. Li et al. conducted a prospective cohort study that specifically focused on NSCLC patients with both EGFR and TP53 co-mutations [6]. The study evaluated whether adding chemotherapy to osimertinib could optimize outcomes in contrast to osimertinib alone. In patients with both mutations, the combination regimen obtained a greater objective response rate and longer progression-free survival, particularly in those with L858R mutations. These results illustrate that TP53 co-mutation may identify patients who require more intensive treatment. TP53 is also confirmed to be a critical biological marker for predicting the outcome of epidermal growth factor receptor-positive NSCLC.

Except TP53, other co-mutations have also been linked to prognosis of NSCLC. It is supported in a sub-group analysis of the IMpower150 III trial by West et al., found that KRAS-mutant NSCLC patients with concurrent STK11, KEAP1 or TP53 co-mutations, or high PD-L1 expression responded differently to atezolizumab plus bevacizumab and chemotherapy (ABCP) versus the ACP regimen [7]. This finding suggests that co-mutations do not have an uniform impact on prognosis.

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Clinical stratification should therefore be based on each patient's specific co-mutation profile, rather than considering "co-mutations" as a single homogeneous entity.

Overall, according to the evidence from distinct driver gene backgrounds, co-alterations like TP53 affect outcomes in NSCLC patients receiving targeted therapy strongly. For EGFR-mutated patients treated with single-agent TKIs, TP53 co-mutations predict unfavorable clinical consequence, so that combination therapy may be required. Co-mutations in STK11 and KEAP1 add further difficulty and complexity to treatment. All of the findings tell us single-gene testing alone is insufficient to accurately predict therapeutic prognosis. Comprehensive evaluation of co-mutation status via multi-gene panels is necessary to facilitate individualized treatment strategies.

3.2. Biological mechanisms by which co-mutations modulate the efficacy of targeted therapy

As demonstrated in Section 3.1, outcomes of targeted therapy in NSCLC are closely linked to TP53, STK11/KEAP1, and other co-mutated driver genes. However, to comprehend how these co-mutations influence the treatment efficacy, and whether they can instruct clinical decisions, further study is essential. This section reviews both mechanistic and clinical evidence on how co-mutations modulate targeted therapy.

p53 protein, a critical regulator encoded by the TP53 gene, is responsible for regulating DNA damage repair, cell cycle arrest and apoptosis. When TP53 is mutated, p53 protein loses its function and leads to increasing instability and tumor heterogeneity. As a result, only using a single targeted therapy, such as an EGFR-TKI, cannot fully eliminate tumors with different genetic backgrounds, which reduces treatment efficacy. This explains why TP53-mutant patients often fare worse on TKI therapy and provides a theoretical basis for combination treatment.

Clinical studies support this mechanism. In the phase III ACROSS2 trial, 126 advanced NSCLC patients carrying EGFR mutations concomitant with tumor suppressor gene mutations were enrolled. The research made a contrast between aumolertinib plus chemotherapy with aumolertinib monotherapy. The combination arm received a substantially longer median PFS than the monotherapy arm (19.78 vs 16.53 months, HR=0.58, 95% CI 0.34–0.97). The landmark PFS rates at 12, 18 and 24 months were 78.7% vs 65.3%, 67.2% vs 40.8%, and 41.0% vs 29.9%, respectively [8]. Subgroup analysis revealed that patients with concurrent TP53 mutations derived prominent PFS benefits from the combination. These findings illustrate genotype-directed treatment intensification for this specific molecular subgroup and elucidate that co-mutation profiles can guide therapeutic decisions.

3.3. Co-mutation-driven precision prognostic models

Traditional single-gene stratification commonly divides patients into eligible or ineligible for targeted therapy, overlooking the prognostic heterogeneity caused by co-mutations. Co-mutation-driven prognostic models integrate multiple genomic alterations to establish a more refined risk stratification system. Such models are typically constructed using NGS-based multi-gene profiling to identify co-mutations with independent prognostic value [9, 10]. Statistical methods such as Cox or LASSO regression then assign weights to each co-mutation gene, generating a composite prognostic score that stratifies patients into distinct risk groups.

In summary, moving from single-gene stratification to a co-mutation-driven multi-gene model is the technical foundation for precision stratification in NSCLC targeted therapy. This transition relies not only on NGS technology, but also on prognostic models that have been validated in large cohorts and shown to have clinical utility.

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4. Clinical applications of co-mutation-guided precision therapy

4.1. Optimization of therapeutic regimens

The clinical value of driver gene co-mutations is ultimately reflected in guiding treatment decisions. The ACROSS2 study provides the highest level of evidence from an evidence-based medicine perspective: in advanced NSCLC patients with EGFR mutations and tumor suppressor gene co-mutations, the median progression-free survival (19.78 vs 16.53 months, HR=0.58) was markedly extended with Aumolertinib plus chemotherapy compared with aumolertinib monotherapy [8]. Subgroup analysis demonstrated that patients with TP53 co-mutations derived particularly prominent benefits. This finding indicates that EGFR-mutated patients with TP53 or other co-mutations should be prioritized for combination therapy, whereas TKI monotherapy remains a reasonable option for those without co-mutations or with a low co-mutation burden.

4.2. Efficacy monitoring and resistance management

Co-mutation status is not the only thing worth tracking. During treatment, co-mutated clones also evolve over time. Conventional tissue biopsy is mostly a one-time procedure, making repeated sampling impractical. In contrast, liquid biopsy (ctDNA) enables noninvasive monitoring of alterations in tumor genomic variations through peripheral blood samples [9, 10]. Tracking the abundance of co-mutated clones can reveal drug resistance-related subclones early, providing clinicians with a warning signal to adjust treatment in time. This is particularly valuable after surgery, where regular ctDNA surveillance helps detect the early identification of recurrence risk.

4.3. Current challenges in clinical application

Despite their value in prognostic stratification, co-mutations still face numerous challenges in clinical translation. High-level clinical evidence is mainly limited to the specific EGFR-TP53 co-mutation pair and data on co-mutation spectra and clinical outcomes for other driver genes (ALK, ROS1 and KRAS) remain sparse, so the same precision treatment strategy cannot yet be applied to certain patient groups. We also lack clarity on prognostic differences among distinct TP53 mutation sites (e.g., missense mutations versus truncating mutations), and there is little systematic research exploring how the abundance of co-mutated clones influences treatment efficacy. Beyond the gaps in clinical evidence, NGS panels vary in detection thresholds, data analysis pipelines, and reporting standards, which limits the widespread adoption of co-mutation-based stratification. Adding to these hurdles, the cost-effectiveness of co-mutation testing requires further evaluation. Future efforts may expand the scope of therapeutic targets, establish analytical frameworks applicable to various driver genes, promote unified industry standards, facilitate the integration of co-mutation testing into routine clinical practice, and explore the application value of co-mutation information in the field of immunotherapy.

5. Conclusion

This review systematically reviews the research progress and clinical translational value of driver gene co-mutations in prognostic stratification for targeted therapy in EGFR-mutant NSCLC, and the main conclusions are as follows. First, heterogeneity in the efficacy of EGFR-TKI therapy is widespread, and conventional single-gene testing can hardly meet the clinical demand for precise stratification. Second, TP53 is the most frequently co-mutated gene in EGFR-mutant NSCLC and a

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major contributor to poor prognosis with TKI monotherapy. In addition, co-mutations in STK11 and KEAP1 are similarly linked to such heterogeneity. Third, phase III trials including ACROSS2 have verified that guiding treatment decisions based on co-mutation information is clinically feasible, in particular, patients with TP53 co-mutations gain significant benefits from TKI combined with chemotherapy. Finally, NGS multi-gene panels provide the technical foundation for comprehensive co-mutation detection, and the shift from single-gene to multi-gene testing acts as crucial technical support for precise prognostic stratification.

Nevertheless, existing evidence mainly focuses on the specific EGFR-TP53 combination. Further research is still required regarding the co-mutation spectrum of other driver genes, prognostic differences among various TP53 mutation sites, the influence of co-mutated clone abundance, and the standardization of NGS testing. With advances in genomic technology and the accumulation of more prospective clinical evidence, prognostic stratification strategies integrating co-mutation information are expected to deliver clinical benefits of precision therapy for more patients with NSCLC.

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