Exploring the Relationship Between Genetic Heterogeneity and Acquired Resistance to Immune Checkpoint Inhibitors in Non-small Cell Lung Cancer: A Targeted Literature Review

HPR48

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INTRODUCTION

- Acquired resistance (AR) to immune checkpoint inhibitors (ICIs) is a significant challenge in treating non-small cell lung cancer (NSCLC), a leading cause of cancer-related deaths worldwide.[1,2]
- ICIs have transformed cancer treatment by reactivating the immune system to target tumors; however, their long-term effectiveness is often limited by resistance.
- Understanding AR mechanisms and their relationship to genetic diversity is crucial for advancing personalized oncology therapies.
- Current research on genetic, epigenetic, and tumor microenvironment factors in AR remains limited, revealing a substantial knowledge gap.
- Further investigation into these resistance mechanisms is essential to enhance treatment efficacy.[3]
- This study aimed to synthesize evidence on treatment outcomes in NSCLC patients with AR to ICIs—both with and without genetic factors—and to evaluate the need for genomic profiling.

METHODS

Reporting: The methodology and findings were structured in accordance with PRISMA guidelines to ensure transparency and reproducibility of the review process.

Study Design: A targeted literature review .

Tool: A Human-In-the-Loop AI literature review tool was utilized to enhance the efficiency and accuracy of the review process.

Keywords: The search utilized the keywords related to NSCLC, Immune Checkpoint Inhibitors and Resistance based on the following concept grid:

Table 1.
Concept Grid

Concept Category	Keywords and Phrases
Population	Non-small cell lung cancer (NSCLC), lung cancer, advanced NSCLC, lung adenocarcinoma, squamous NSCLC
Intervention	Immune checkpoint inhibitors (ICI), immunotherapy, PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors
Outcome	Acquired resistance, resistance mechanisms, treatment resistance, tumor progression, disease progression
Genetic Factors	Genetic mutations, genetic biomarkers, tumor mutational burden (TMB), PD-L1 expression, EGFR mutation, KRAS, MET, ALK
Mechanisms of Resistance	Tumor microenvironment, immune escape, T-cell exhaustion, immune evasion, adaptive immune resistance

Table 2.
Eligibility Criteria

Criteria	Inclusion	Exclusion
Population	Studies on adult patients with NSCLC	Studies on other cancers, pediatric patients, or non-NSCLC lung cancer subtypes
Intervention	Studies involving immune checkpoint inhibitors (e.g., PD-1, PD-L1, CTLA-4 inhibitors)	Studies not involving immune checkpoint inhibitors or focusing on non-ICI therapies
Outcome	Studies reporting acquired resistance mechanisms or disease progression	Studies without outcome data on resistance mechanisms or progression
Genetic Factors	Studies identifying genetic mutations or biomarkers (e.g., EGFR, KRAS, TMB) related to resistance	Studies without analysis of genetic or molecular biomarkers related to resistance
Mechanisms of Resistance	Studies discussing immune escape, T-cell exhaustion, tumor microenvironment, or immune evasion mechanisms	Studies focused solely on primary resistance (no acquired resistance data)
Study Design	Original research articles, clinical trials, cohort studies, systematic reviews	Case reports, editorials, commentaries, letters, non-peer-reviewed studies
Language	English	Non-English articles
Publication Date	Published within the last 5 years	Articles published more than 10 years ago
Full-Text Availability	Available full-text articles in databases (e.g., PubMed, Medline)	Abstracts only, inaccessible full-text articles

Data Extraction, Analysis, and Presentation:

- Data extraction was conducted by two independent reviewers to ensure accuracy and consistency.
- Disagreements or differences in opinions between reviewers were resolved by a third-party researcher.
- Extracted data elements included study identifiers, region, design, mechanisms of acquired resistance, and personalized assessment methods used to detect these mechanisms.
- This systematic approach aimed to provide a comprehensive overview of the research landscape in NSCLC and personalized assessments.
- The analyzed data was presented in the form diagrams and charts to facilitate visual understanding and comparison of the findings.

RESULTS

Figure 1.
PRISMA Flow Diagram

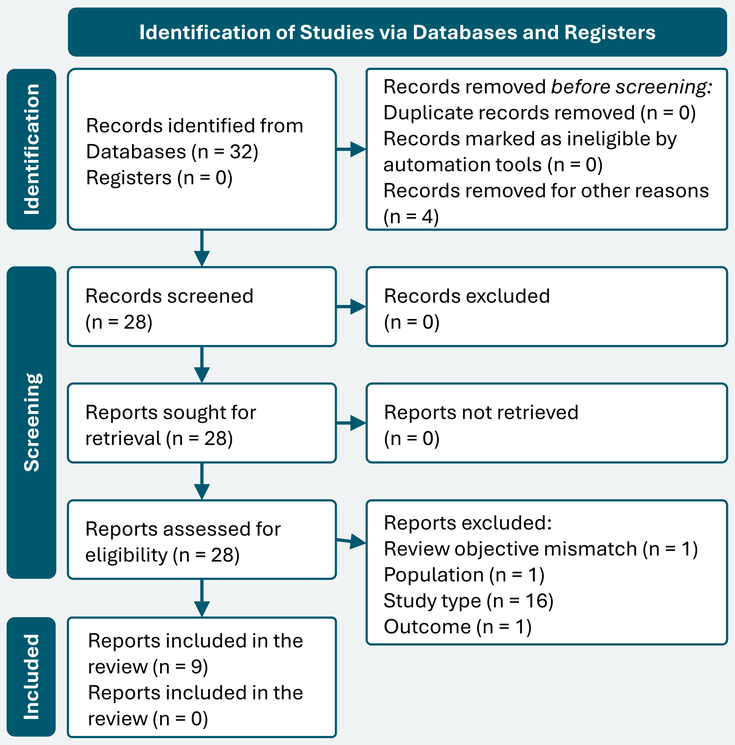
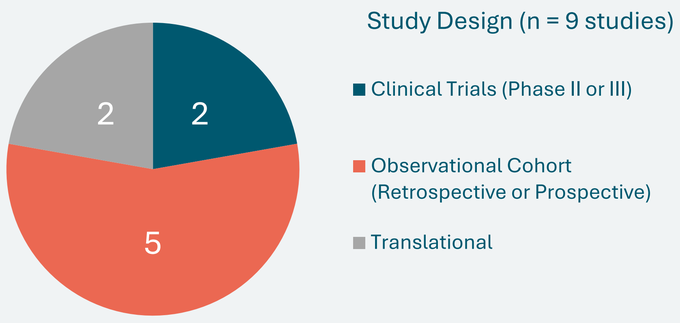


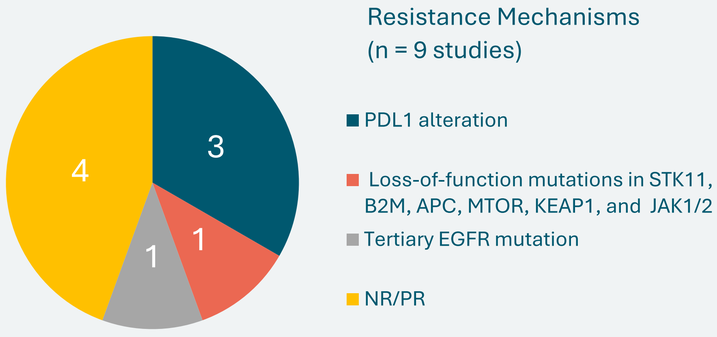
Figure 2.
Study Type



Region

- 4, 2, and 3 studies were from the United States, Europe, and UK regions.

Figure 3.
Mechanism of Acquired Resistance



Reporting Status of Personalized Assessment Methods:

- The reported personalized assessment methods in selected studies included comprehensive tumor genomic profiling, machine learning-based assessment of tumor-infiltrating lymphocytes, multiplexed immunofluorescence, HLA-I immunohistochemistry, and whole transcriptome analysis.
- 2/9 studies reported exclusive information on genetic profiling.

DISCUSSION

- Out of nine studies reviewed, only two were focused on translational oncology, indicating limited research translating findings to clinical applications.
- Four studies originated from the U.S., highlighting a need for more diverse, global research on ICI resistance in NSCLC.
- PD-L1's role as a resistance marker showed mixed results; four studies suggested it as a mechanism, while one found no association with treatment outcomes, signaling inconsistency in its predictive value.
- Reliance on PD-L1 alone may not be sufficient to understand resistance, emphasizing the need for broader molecular profiling.
- Only one study utilized multiomics data with AI/ML, showing a gap in advanced analysis approaches that could provide deeper insights into resistance.
- Multiomics and AI/ML approaches are underutilized despite their potential to integrate complex data layers, offering more precise identification of resistance mechanisms.
- Comprehensive genetic profiling can uncover a wider array of gene alterations, providing a fuller understanding of the mechanisms behind ICI resistance.
- Expanding profiling to include diverse genetic and molecular markers could improve personalized treatment strategies, especially for NSCLC patients with acquired resistance.
- There is a clear need for broader adoption of profiling and advanced data techniques to ensure a more holistic approach to understanding ICI resistance.
- Such advancements could bridge research gaps, ultimately contributing to more effective and equitable NSCLC treatment outcomes.

CONCLUSION

- Expanding beyond PD-L1 to include a range of molecular markers will improve ICI resistance management and support the development of personalized therapies through large-scale genomic studies.
- Utilizing multiomics and AI/ML in clinical practice can reveal resistance mechanisms, enabling tailored, precise treatments that advance patient-focused oncology drug development.
- Increasing global and translational research will bridge gaps, ensuring NSCLC treatments address genetic variability and lead to equitable patient outcomes.

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