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Targeted Therapy in Non-Small Cell Lung Cancer: Current Landscape and Future Directions.

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases worldwide and remains a leading cause of cancer-related mortality. In recent decades, advances in molecular oncology have revolutionized NSCLC treatment, shifting the paradigm from conventional chemotherapy to targeted therapy. Targeted agents are designed to specifically inhibit molecular alterations that drive tumor growth, thus improving efficacy while minimizing toxicity. Key molecular targets in NSCLC include epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, ROS1 fusions, BRAF mutations, and KRAS alterations [1, 2, 3, 4, 5].

The development of tyrosine kinase inhibitors (TKIs) against these targets has led to significant improvements in progression-free survival (PFS) and quality of life for selected patients. For example, osimertinib, an EGFR TKI, has demonstrated efficacy in both first-line settings and in cases of acquired T790M resistance. Similarly, ALK inhibitors such as alectinib and lorlatinib have shown superiority over earlier-generation drugs, offering better central nervous system (CNS) penetration and prolonged disease control.

Current Landscape

Targeted therapy in NSCLC is guided by comprehensive molecular profiling, enabling oncologists to match patients with the most appropriate agents. The most established targets include:

- **EGFR Mutations:** Found in ~15% of NSCLC patients in Western populations and up to 40% in Asian populations. Osimertinib has become the standard first-line therapy due to its improved PFS and CNS activity.
- **ALK Rearrangements:** Present in ~5% of cases, predominantly in younger, non-smoking patients. Alectinib and lorlatinib are preferred for their potent activity and CNS protection.
- **ROS1 Rearrangements:** Targeted by crizotinib and entrectinib, offering high response rates.
- **BRAF V600E Mutations:** Treated with dabrafenib plus trametinib, showing benefit in advanced disease.
- **KRAS G12C Mutations:** Recently targeted by sotorasib and adagrasib, marking a breakthrough in a previously untargetable mutation.

Despite these advances, challenges remain—most notably, acquired resistance to TKIs, tumor heterogeneity, and limited access to testing in low-resource settings. Liquid biopsies and next-generation sequencing (NGS) are increasingly used to identify resistance mechanisms and guide subsequent treatment lines.

Future Directions

Research is now focused on overcoming resistance through combination regimens, next-generation inhibitors, and novel target discovery. Bispecific antibodies, antibody-drug conjugates (ADCs), and combination strategies integrating targeted therapy

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with immunotherapy hold promise. Additionally, the use of artificial intelligence in biomarker discovery and patient selection is expected to accelerate personalized medicine in NSCLC.

Another frontier lies in earlier disease stages, where targeted therapies are being evaluated as adjuvant or neoadjuvant treatments to reduce recurrence rates. Furthermore, improved access to molecular diagnostics globally will be critical to ensuring equitable patient benefit from these therapies.

Conclusion

Targeted therapy has transformed the treatment landscape of NSCLC, offering precision medicine approaches that yield superior outcomes for biomarker-selected patients. While current agents have achieved remarkable success in specific subgroups, the inevitable development of resistance underscores the need for ongoing innovation. The integration of molecular diagnostics, novel agents, and rational combination strategies will define the next era of NSCLC management, with the ultimate goal of prolonging survival and improving quality of life for patients worldwide.

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