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Treatments using Anti-MET Antibodies for Non-Small-Cell Lung Cancer

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Introduction

Non-Small-Cell Lung Cancer (NSCLC) is the leading cause of cancer-related deaths worldwide, accounting for approximately 85% of all lung cancer cases. The complexity of NSCLC arises from its genetic heterogeneity and resistance to standard therapies, making it a challenging disease to treat. While significant advancements have been made in the development of targeted therapies for NSCLC, the need for novel treatments remains paramount due to the limited efficacy and high rate of relapse associated with existing therapies. The rationale behind targeting MET in NSCLC and the use of anti-MET antibodies as a potential therapeutic approach. We will also examine the challenges and limitations of this strategy, as well as the future prospects of anti-MET-based therapies in the treatment of NSCLC [1].

One promising area of research in the treatment of NSCLC involves targeting the MET (Mesenchymal-Epithelial Transition) receptor and its signaling pathway. The MET receptor is a tyrosine kinase receptor that plays a crucial role in cellular processes such as growth, survival, migration and angiogenesis. Aberrant activation of the MET signaling pathway, often through mutations, amplifications, or overexpression of MET, is implicated in the development and progression of various cancers, including NSCLC. Consequently, targeting MET through the use of anti-MET antibodies has emerged as a promising therapeutic strategy to overcome some of the limitations of conventional treatments [2].

Description

He MET gene encodes a receptor tyrosine kinase known as Hepatocyte Growth Factor Receptor (HGFR). The ligand for the MET receptor is Hepatocyte Growth Factor (HGF), which activates the receptor upon binding, leading to a cascade of intracellular signaling events. These events primarily involve the activation of pathways related to cell survival, proliferation, migration and invasion. Among the key signaling pathways activated by MET are the PI3K/Akt, MAPK/ERK and STAT3 pathways, which are critical for the maintenance of cellular homeostasis and tumor progression. In NSCLC, the MET signaling pathway is often dysregulated, either through overexpression of MET, amplification of the MET gene, or mutations in the MET receptor itself. These alterations can lead to uncontrolled cell proliferation, increased metastatic potential and resistance to standard therapies, including chemotherapy and targeted agents like EGFR inhibitors. For instance, MET amplification has been identified as a mechanism of resistance to EGFR Tyrosine Kinase Inhibitors (TKIs), highlighting the importance of MET as a therapeutic target in EGFR-mutant NSCLC [3].

The potential of anti-MET antibodies as a therapeutic strategy for NSCLC has led to extensive preclinical and clinical research. Several anti-MET antibodies have been developed and tested in clinical trials, either as monotherapies or in combination with other treatments, such as chemotherapy, targeted therapies, or immune checkpoint inhibitors. Crizotinib, originally developed as a MET inhibitor, is a small-molecule Tyrosine Kinase Inhibitor (TKI) that targets MET, ALK and ROS1. While it is primarily known for its activity against ALK and ROS1 rearrangements, crizotinib also demonstrates significant activity against MET-driven cancers. In NSCLC, crizotinib has been shown to be effective in patients with MET amplification or mutations, particularly in those who have developed resistance to EGFR-targeted therapies. Onartuzumab is a monoclonal antibody that specifically targets the MET receptor. In preclinical studies, onartuzumab showed promising activity in inhibiting MET signaling and reducing tumor growth. Clinical trials have tested onartuzumab in combination with other agents, such as the chemotherapy agent paclitaxel, in patients with advanced NSCLC. While initial studies showed some efficacy, the overall clinical benefit was modest and further development of onartuzumab was limited due to a lack of significant improvement in overall survival [4].

Similar to other targeted therapies, resistance to anti-MET antibodies is a major concern. Over time, tumors can acquire mutations or alternate signaling pathways that bypass MET inhibition. Additionally, tumors with MET alterations often exhibit a high degree of plasticity, allowing them to adapt to targeted treatments. This highlights the need for combination therapies to prevent or overcome resistance. While anti-MET antibodies generally have a favorable safety profile, they are not without potential side effects. Common adverse events include fatigue, nausea and infusion-related reactions. More serious but rare side effects may include liver toxicity and cardiovascular complications. The combination of anti-MET antibodies with other therapies may also increase the risk of toxicities, necessitating careful monitoring in clinical practice. While anti-MET antibodies show some promise in early clinical trials, the overall clinical efficacy has been variable. Some patients may experience transient responses, but the long-term benefit remains uncertain. This variability may be attributed to factors such as the level of MET expression, the presence of other genetic alterations and the underlying biology of the tumor [5].

Conclusion

The use of anti-MET antibodies represents a promising avenue for the treatment of NSCLC, particularly in patients with MET-driven disease or those who have developed resistance to conventional therapies. The MET receptor plays a central role in tumor growth, metastasis and resistance mechanisms, making it an attractive target for therapeutic intervention. Despite some challenges in terms of patient selection, resistance and toxicity, anti-MET antibodies have shown potential in clinical trials, especially when combined with other treatment modalities. Future research should focus on identifying reliable biomarkers to predict patient responses to anti-MET therapies, as well as exploring combination strategies that can overcome resistance and improve long-term outcomes. As our understanding of the molecular drivers of NSCLC continues to evolve, anti-MET antibody therapies may play an increasingly important role in the personalized treatment of this challenging disease. By addressing the limitations of current therapies and offering new strategies

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to target MET, anti-MET antibodies have the potential to significantly impact the treatment landscape for NSCLC, improving outcomes for patients and advancing the field of precision oncology.

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Conflict of Interest

None.

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