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Impact of Genomic Co-Alterations on Response to Futibatinib in Cancer Treatment

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DESCRIPTION

Futibatinib, an irreversible Fibroblast Growth Factor Receptor (FGFR) inhibitor, has emerged as a potential targeted therapy for patients with FGFR alterations, particularly in advanced solid tumors. FGFR aberrations, including fusions, rearrangements and mutations, are well-established drivers of tumorigenesis across various cancer types. Despite its efficacy, responses to futibatinib are highly variable among patients. One major factor contributing to this variability is the presence of genomic co-alterations that may affect drug sensitivity, resistance and overall therapeutic outcomes. This article describes the correlation between genomic co-alterations and the therapeutic response to futibatinib, indicating their role in predicting treatment outcomes and guiding personalized cancer therapy.

Mechanism of action of futibatinib

Futibatinib is a highly selective and irreversible inhibitor of *FGFR1-4*. It covalently binds to a specific cysteine residue in the FGFR kinase domain, thereby blocking downstream signaling pathways such as MAPK, PI3K-AKT and STAT. These pathways are critical for cell proliferation, survival and angiogenesis. Futibatinib has demonstrated significant clinical activity in cancers harboring FGFR aberrations, particularly in intrahepatic cholangiocarcinoma, urothelial carcinoma and other FGFR-driven malignancies.

However, not all patients with FGFR alterations derive equal benefit from futibatinib. Emerging evidence suggests that co-existing genomic alterations in parallel or downstream signaling pathways may modulate the drug's effectiveness.

Genomic Co-Alterations and Their Impact on Futibatinib Response Genomic co-alterations refer to additional mutations, amplifications, or deletions in cancer-related genes that occur alongside FGFR aberrations. These co-alterations can significantly influence the response to FGFR inhibitors like futibatinib.

RAS/RAF pathway alterations: Mutations in KRAS, NRAS, or BRAF can activate downstream signaling independently of FGFR, potentially bypassing the inhibitory effect of futibatinib. These mutations are often associated with primary or acquired resistance.

***PIK3CA* mutations:** Alterations in the PI3K/AKT/mTOR pathway, such as *PIK3CA* mutations, can sustain survival signals despite FGFR inhibition. Tumors with these mutations may exhibit reduced sensitivity to futibatinib.

***TP53* mutations:** Mutations in *TP53*, a critical tumor suppressor gene, are frequently associated with genomic instability and resistance to various targeted therapies, including FGFR inhibitors.

MYC amplifications: Amplification of the MYC oncogene can drive uncontrolled cell proliferation, potentially counteracting the therapeutic effects of futibatinib.

ERBB family alterations: Mutations or amplifications in ERBB2 (HER2) and ERBB3 can activate alternative growth signaling pathways, reducing dependency on FGFR signaling.

Clinical evidence linking co-alterations to futibatinib response

Clinical studies investigating the efficacy of futibatinib have provided insights into the role of genomic co-alterations in modulating therapeutic outcomes. Retrospective analyses of clinical trials have shown that patients with FGFR alterations but without significant co-alterations in pathways like RAS, PIK3CA, or ERBB tend to have better and more durable responses to futibatinib.

In contrast, patients with specific co-alterations, such as *KRAS* mutations or PIK3CA pathway activation, often exhibit reduced Progression-Free Survival (PFS) and Overall Response Rates (ORR). These findings establish the importance of comprehensive genomic profiling to identify both FGFR

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aberrations and co-existing genomic alterations before initiating futibatinib therapy.

Potential biomarkers for futibatinib response

The integration of Next-Generation Sequencing (NGS) and other molecular diagnostic tools has enabled the identification of biomarkers predictive of futibatinib response. Biomarkers such as the absence of *KRAS* and *PIK3CA* mutations, low Tumor Mutational Burden (TMB) and intact *TP53* status have been correlated with favorable responses to futibatinib.

Conversely, patients with high levels of genomic instability, characterized by multiple concurrent co-alterations, may require combination therapies to overcome essential resistance.

Therapeutic Strategies to Overcome Resistance Understanding the genomic region of tumors treated with futibatinib can inform combination treatment strategies. Potential approaches include:

- Combining futibatinib with MEK inhibitors in cases with RAS/RAF mutations.
- Targeting the PI3K/AKT pathway alongside FGFR inhibition.
- Using immune checkpoint inhibitors to address tumors with high mutational burden.

These combination therapies are currently being evaluated in clinical trials, aiming to improve outcomes for patients with FGFR-driven tumors and relevant genomic co-alterations.

Genomic co-alterations play a critical role in determining the response to futibatinib in patients with FGFR-driven tumors. Mutations in lead pathways such as RAS, PI3K, TP53 and ERBB can modulate drug sensitivity, contributing to primary or acquired resistance. Comprehensive genomic profiling is essential for identifying these co-alterations and customizing therapeutic strategies accordingly. Future research should focus on validating predictive biomarkers and describing combination therapies to optimize futibatinib efficacy in genomically complex tumors. With advancements in precision oncology, personalized approaches to targeting FGFR alterations hold the potential for improving cancer treatment outcomes.