



TP53 Gain-of-Function Mutations and their Role in Early Osimertinib Resistance in EGFR-Mutant Lung Adenocarcinoma

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DESCRIPTION

Lung adenocarcinoma is one of the most common forms of lung cancer and alterations in the Epidermal Growth Factor Receptor (EGFR) gene represent an important molecular driver in a subset of patients. EGFR-targeted medicines have substantially changed the management of tumours carrying activating EGFR alterations. Osimertinib, a third-generation EGFR tyrosine kinase inhibitor, is widely used because of its activity against common sensitizing EGFR alterations and the EGFR T790M resistance alteration. Despite its effectiveness, some tumours develop resistance relatively early, limiting the duration of disease control. Among the molecular factors that may contribute to this process, alterations involving TP53 have attracted considerable attention because of the central role of this gene in maintaining genomic stability and regulating cellular responses to stress. TP53 encodes the p53 protein, a major tumour-suppressor protein involved in Deoxy Ribonucleic Acid (DNA) damage responses, cell-cycle regulation, apoptosis and cellular senescence. When normal cells experience substantial genomic damage, p53 can prevent the propagation of abnormal cells by slowing cell division or promoting cell death. Mutations that disrupt this function are common in many cancers. A subset of TP53 alterations may have additional gain-of-function properties, meaning that the altered protein can acquire activities that promote tumour progression rather than simply losing normal tumour-suppressor activity.

In EGFR-mutant lung adenocarcinoma, the coexistence of TP53 alterations may influence how tumour cells respond to targeted treatment. Osimertinib suppresses signalling from activated EGFR and can substantially reduce the growth of dependent cancer cells. However, cancer is composed of genetically and biologically diverse cell populations. Cells carrying additional alterations that provide survival advantages may persist during treatment and eventually become more prominent. TP53 gain-of-function changes may contribute to this process by modifying

cellular stress responses, proliferation, DNA repair and interactions with signalling pathways that support tumour survival. Early resistance is particularly important because it differs from resistance that develops after prolonged disease control. When progression occurs soon after treatment begins, the tumour may already contain cellular populations capable of tolerating EGFR inhibition. In this setting, TP53 gain-of-function mutations could represent one component of a pre-existing biological state that makes some cancer cells less dependent on EGFR signalling. Instead of being eliminated uniformly by osimertinib, these cells may adapt to treatment-associated stress and maintain proliferative capacity.

The biological effects of TP53 mutations are highly dependent on the specific alteration. Not every TP53 mutation produces the same molecular consequences and the distinction between loss of normal p53 function and genuine gain-of-function activity is important. Certain mutant p53 proteins have been associated with changes in transcriptional regulation, cellular metabolism, invasion and interactions with other signalling proteins. These effects may create a cellular environment in which cancer cells become more adaptable when exposed to targeted therapy. Several mechanisms could connect altered p53 activity with reduced sensitivity to osimertinib. Changes in cell-cycle control may allow damaged cells to continue proliferating despite therapeutic pressure. Modified DNA damage responses may improve the ability of tumour cells to tolerate treatment-related stress. Alterations in apoptosis could also allow cells that would normally undergo programmed death to survive. In addition, mutant p53 may influence pathways involved in growth, metabolism and cellular plasticity, potentially enabling cancer cells to switch between different survival states.

The relationship between TP53 and treatment response should nevertheless be interpreted cautiously. Resistance to osimertinib is usually multifactorial. Secondary EGFR alterations, amplification of alternative receptor pathways, activation of

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downstream signalling networks, histologic transformation and other genomic or epigenomic changes can contribute to treatment failure. Consequently, the presence of a TP53 gain-of-function mutation should not automatically be interpreted as the sole explanation for early resistance. Its significance may depend on the specific EGFR alteration, the TP53 variant, tumour heterogeneity and additional molecular characteristics. Understanding this relationship could improve molecular classification of patients receiving EGFR-targeted therapy. Comprehensive genomic profiling before treatment and at progression may help identify genetic changes associated with

different resistance patterns. Longitudinal molecular assessment can also provide information about how individual tumour populations change during treatment. Such information may support the development of treatment strategies that combine EGFR inhibition with approaches directed toward alternative survival mechanisms. An EGFR alteration may initiate tumour development and remain clinically important, while additional mutations determine how effectively the tumour responds to targeted inhibition. The interaction between these molecular events can shape treatment sensitivity, disease progression and the emergence of resistant populations.