Novel Targeted Agents in Head and Neck Squamous Cell Carcinoma

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KEYWORDS

• DNA damage response • Cell cycle regulation • PI3K/mTOR • NOTCH • c-MET • FGFR • Axl • Angiogenesis

KEY POINTS

- Based on current genome-wide sequencing and copy number data, there are only a few oncogenes in HNSCC that can be immediately exploited with novel targeted agents.
- Novel approaches targeting key pathways including DNA damage response and cell cycle regulation, PI3K/mTOR, NOTCH, transmembrane growth factor receptors (c-MET, FGFR, and Axl), and angiogenesis are discussed.
- Moving forward, concerted effort is required to identify better predictive biomarkers of clinical benefits and improve the therapeutic index of targeted agents.

INTRODUCTION

Recent genomic findings in head and neck squamous cell carcinoma (HNSCC) reveal a wide spectrum of genomic alterations.[1–5] A heterogeneous disease by nature, HNSCC encompasses a disparate collection of anatomic sites with complex tumor biology. One of the most distinguishing features of HNSCC is the human papillomavirus (HPV) status of the tumor, HPV-positive HNSCC having more favorable

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outcomes compared with HPV-negative HNSCC.[6,7] This genomic heterogeneity of HNSCC tumors creates an obstacle for the identification of an effective targeting agent likely to benefit most patients with HNSCC. The most successful implementation of the genomic alterations in recent years has been based on functionally activating gene mutations (eg, c-KIT activating mutations in gastrointestinal stromal tumor[8]) and copy number gain in oncogenes (eg, ERBB2/HER2 amplification in breast cancer[9]).

However, based on current genome-wide sequencing and copy number data, there are only a few oncogenes in HNSCC that can be immediately exploited with novel targeted agents. This article focuses on novel approaches targeting potentially critical pathways that are frequently altered in HNSCC, including DNA damage response and cell cycle regulation, PI3K/mTOR, NOTCH, transmembrane growth factor receptors (c-MET, FGFR, and Axl), and angiogenesis. The established therapeutic target inhibitors including epidermal growth factor receptor (EGFR) and immune check point proteins (eg, PD1 and PD-L1) are discussed elsewhere in this issue.

DNA DAMAGE RESPONSE AND CELL CYCLE REGULATION TARGETED AGENTS

Targeting Dysfunctional p53

The gene *TP53* (tumor protein p53, *p53*, or *Trp53*), was in 1979 the first tumor-suppressor gene to be identified, and the protein product of this gene, p53, is one of the most important molecules in biology, integrating numerous signals that control cell cycling and apoptosis.[10,11] The p53 network is normally inactive and responds to stimuli, such as cellular damage or stress, to perform its tumor-suppressing function.[12] There are many ways in which p53 protein malfunctions in human cancers, and at least six different mechanisms are cited: (1) amino-acid-changing mutation in the DNA binding domain; (2) deletion of the carboxy-terminal domain; (3) multiplication of the MDM2 gene in the genome; (4) viral infection; (5) deletion of the p14ARF gene; and (6) mislocalization of p53 to the cytoplasm, outside the nucleus.[12]

In HNSCC, the cause of p53 dysfunction differs between HPV-positive and HPV-negative tumors. The HPV-positive HNSCC lacks functional p53 because ubiquitination of p53 by an ubiquitin ligase, E6AP, and a viral oncoprotein, E6, leads to rapid degradation of p53, whereas *TP53* mutation is very rare.[1–4,13,14] However, *TP53* is the most frequently mutated gene in HPV-negative HNSCC, with an incidence of 47% to 87%.[1–4] These mutations can occur throughout the entire gene and typically involve missense mutations, which alter protein conformation or affect how p53 binds its DNA targets. It is also known that any *TP53* mutations in tumor DNA are associated with reduced survival after surgical treatment of HNSCC.[15–17]

Given the biologic importance of p53, there has been a significant effort to identify effective therapeutic approaches for HNSCC with p53 dysfunction. However, direct targeting of a tumor suppressor, such as p53, is currently not feasible because restoration of a lost protein function in the appropriate cellular regulatory context is difficult compared with the inhibition of overly active proteins, such as deregulated oncoproteins.[12,18] One of the ways to circumvent this problem is to find a synthetic lethal partner for dysfunctional p53. The synthetic lethality therapeutic approaches consist of a combination of two or more separate genes/proteins' functional loss leading to cell death, whereas functional loss of only one of the genes/proteins does not reduce cell viability.[19]

Moser and colleagues[20] applied a functional kinomic approach using a high-throughput RNA interference platform to identify new targets exploiting dependence on G2-M cell cycle regulators of *TP53*-mutant tumors for their viability (**Fig. 1**A and