

## Phospho-<sup>T356</sup>RB1 predicts survival in HPV-negative squamous cell carcinoma of the head and neck

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### Abstract

Locally advanced squamous cell carcinoma of the head and neck (SCCHN) that is not associated with human papillomavirus (HPV) has a poor prognosis in contrast to HPV-positive disease. To better understand the importance of RB1 activity in HPV-negative SCCHN, we investigated the prognostic value of inhibitory CDK4/6 phosphorylation of RB1 on threonine 356 (T<sup>356</sup>) in archival HPV-negative tumor specimens from patients who underwent surgical resection and adjuvant radiation. We benchmarked p<sup>T356</sup>RB1 to total RB1, Ki67, p<sup>T202/Y204</sup>ERK1/2, and TP53, as quantified by automatic quantitative analysis (AQUA), and correlated protein expression with tumor stage and grade. High expression of p<sup>T356</sup>RB1 but not total RB1 predicted reduced overall survival (OS; P = 0.0295), indicating the potential relevance of post-translational phosphorylation. Paired analysis of The Cancer Genome Atlas (TCGA) data for regulators of this RB1 phosphorylation identified loss or truncating mutation of negative regulator CDKN2A (p16) and elevated expression of the CDK4/6 activator CCND1 (cyclin D) as also predicting poor survival. Given that CDK4/6 inhibitors have been most effective in the context of functional RB1 and low expression or deletion of p16 in other tumor types, these data suggest such agents may merit evaluation in HPV-negative SCCHN, specifically in cases associated with high p<sup>T356</sup>RB1.

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### Keywords

Biomarkers, CDK4/6, E2F, Head and neck cancer, RB1