# Co-targeting EGFR and PI3K boosts NK cell killing to overcome cetuximab resistance in head and neck cancer

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The epidermal growth factor receptor (EGFR) is a well-established therapeutic target for head and neck squamous cell carcinoma (HNSCC). However, the efficacy of the EGFR-targeted therapy cetuximab is limited by intrinsic or acquired resistance, frequently associated with compensatory activation of the phosphatidylinositol 3 kinase (PI3K)/Akt pathway. In addition to its direct antitumor effects, cetuximab also engages natural killer (NK) cells through antibody dependent cellular cytotoxicity. Therefore, we investigated whether simultaneous EGFR inhibition (cetuximab) and PI3K blockade (buparlisib) enhances anti-tumor activity and NK cell-mediated killing to overcome cetuximab resistance in HNSCC.

Dual EGFR-PI3K inhibition consistently reduced tumor cell survival and outperformed either monotherapy across an extensive panel of HNSCC models, including both 2D cultures and 3D spheroids of HNSCC cell lines with varying cetuximab resistance phenotypes. These findings were further validated in patient derived HNSCC organoids, underscoring the clinical relevance of the observed synergy. Using co cultures of HNSCC cell lines with primary human NK cells, we evaluated the effect of combined treatment on the killing capacity of NK cells. Simultaneous EGFR and PI3K inhibition significantly enhanced NK cell-mediated tumor cell killing compared with single agents. We next evaluated the combination treatment in a NK cell-humanized FcResolv hIL15 NOG mouse model engrafted with acquired cetuximab resistant HNSCC cells. Combined targeting of EGFR and PI3K significantly prolonged survival relative to single agent therapy.

In conclusion, simultaneous EGFR and PI3K inhibition not only strengthens tumor intrinsic responses but also amplifies NK cell-mediated cytotoxicity, offering a promising strategy to overcome cetuximab resistance in HNSCC.