Conclusion: We document expression of FLT1 in HNSCC and identify this kinase as a potential target for the modulation of radioresistance in this cancer. In a next step we will evaluate this kinase as a marker for response prediction after radiotherapy.

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Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab

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Background: The epidermal growth factor receptor directed antibody, cetuximab (Cmab), is an effective clinical therapy for patients (pts) with colorectal cancer (CRC) particularly with wild type KRAS and BRAF. Treatment in all pts is limited eventually by the development of acquired resistance but little is known about the underlying mechanism.
Materials and Methods: We established 3 Cmab resistant cell lines HCC827CR, GEOCR and A431CR through the Cmab exposure. In order to determine why these were resistant to Cmab we performed genome wide copy number analyses and analysis of ERBB family ligands. Furthermore, we obtained clinical specimens from CRC pts treated with Cmab based therapy. Specimens obtained prior to therapy and at the time of Cmab resistance were evaluated.
Results: Genome-wide copy number analysis detected the localized genomic amplification in HCC827CR, which was identified as ERBB2 and confirmed using FISH. Amplification of ERBB2 was also detected in GEOCR. ERBB2 inhibition, with trastuzumab or lapatinib, restored the Cmab sensitivity in these. In sensitive cell lines, Cmab effectively inhibited growth and ERK1/2 signaling both of which were inhibited in presence of ERBB2 amplification. In contrast, despite detecting ERBB2 activation in A431CR we did not identify ERBB2 amplification. Instead we detected increased levels of the ERBB3 ligand heregulin (HRG). The disruption of ERBB2/ERBB3 herterodimerization using pertuzumab restored Cmab sensitivity in A431CR in vitro and in vivo. CRC pts with ERBB2 amplification ($n = 13$) treated with Cmab survived significantly shorter than pts without ERBB2 amplification ($n = 220$) (Median OS 89 vs 149 days, $p = 0.0013$). We also identified evidence of ERBB2 amplification at the time of acquired resistance using either tumor biopsies or by analyzing for changes in serum HER2 extracellular domain. We further analyzed plasma HRG from CRC pts (Median, 1622 pg/ml; range 0−18,045 pg/ml). Pts who achieved response to Cmab ($n = 16$) had lower HRG concentration than pts without response ($n = 49$) (Mean, 1,050 vs 3,601 pg/ml, $p < 0.001$). In addition we identified a significant increase in plasma HRG levels obtained at the time of Cmab resistance compared to pre-treatment ($p = 0.018$).
Conclusion: We identify activation of ERBB2 signaling, either through ERBB2 amplification or HRG up-regulation, as a mechanism of both de novo and acquired Cmab resistance. These results suggest that ERBB2 inhibitors, combined with Cmab, may represent a rational therapeutic strategy in Cmab-resistant cancers.