

Abstract 3588: Emergence of multiple EGFR extracellular mutations during cetuximab treatment in colorectal cancer

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Abstract

Colorectal cancer (CRC) patients who respond to the anti-EGFR antibody cetuximab often develop resistance within several months of initiating therapy. To design new lines of treatment the molecular landscape of resistant tumors must be ascertained. We investigated the role of mutations in the EGFR signalling axis on the acquisition of resistance to cetuximab in patients and cellular models.

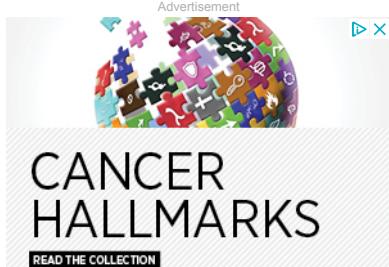
Mutational profiling was performed on both biopsies collected from 37 CRC patients who became refractory to cetuximab and on a collection of cetuximab-resistant derivatives obtained from CRC cells sensitive to EGFR blockade.

The genetic profile of tumor specimens obtained after cetuximab treatment revealed the emergence of a complex pattern of mutations in EGFR, KRAS, NRAS, BRAF and PIK3CA genes, including two novel EGFR ectodomain mutations. Mutational profiling of cetuximab resistant cells recapitulated the molecular landscape observed in clinical samples and revealed three additional EGFR ectodomain alleles.

Structural modelling showed that these mutations are located in the cetuximab-binding region, except for one mutant. Functionally, EGFR ectodomain mutations prevent binding to cetuximab but a subset is permissive for interaction with panitumumab.

In conclusion, we reported that colorectal tumors evade EGFR blockade by constitutive activation of downstream signalling effectors and through mutations affecting receptor-antibody binding. Both mechanisms of resistance may occur concomitantly. Our data have implications for designing additional lines of therapy for CRC patients who relapse upon treatment with anti-EGFR antibodies.

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