POSTER PRESENTATIONS - PROFFERED ABSTRACTS | AUGUST 01 2015

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

Luca Lazzari; Sabrina Arena; Beatriz Bellosillo; Giulia Siravegna; Alejandro Martínez; Israel Cañadas; Noelia Ferruz; Mariangela Russo; Sandra Misale; Iria González; Mar Iglesias; Elena Gavilan; Giorgio Corti; Sebastijan Hobor; Giovanni Crisafulli; Marta Salido; Juan Sánchez; Alba Dalmases; Joaquim Bellmunt; Gianni De Fabritiis; Ana Rovira; Federica Di Nicolantonio; Joan Albanell; Alberto Bardelli; Clara Montagut

+ Author & Article Information

Cancer Res (2015) 75 (15_Supplement): 3588.

https://doi.org/10.1158/1538-7445.AM2015-3588

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.

Citation Format: Luca Lazzari, Sabrina Arena, Beatriz Bellosillo, Giulia Siravegna, Alejandro Martínez, Israel Cañadas, Noelia Ferruz, Mariangela Russo, Sandra Misale, Iria González, Mar Iglesias, Elena Gavilan, Giorgio Corti, Sebastijan Hobor, Giovanni Crisafulli, Marta Salido, Juan Sánchez, Alba Dalmases, Joaquim Bellmunt, Gianni De Fabritiis, Ana Rovira, Federica Di Nicolantonio, Joan Albanell, Alberto Bardelli, Clara Montagut. Emergence of multiple EGFR extracellular mutations during cetuximab treatment in colorectal cancer. [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18-22; Philadelphia, PA. Philadelphia (PA): AACR; Cancer Res 2015;75(15 Suppl):Abstract nr 3588. doi:10.1158/1538-7445.AM2015-3588

View Metrics

Citing Articles Via

Google Scholar

Email Alerts

Article Activity Alert

eTOC Alert

Breaking

Changes at the Top for Dana-Farber

BRAF–MEK Inhibitor Combo OK'd in Europe for NSCLC

New Restrictions on Tobacco Sales to Start in September

View more recent articles

Latest News

With Vorasidenib, Glioma Treatment Continues Evolving

Cancer Research on The Ballot: Moonshot and the Future of Oncology Priorities

Massive Pathology Dataset Powers New AI Diagnostic Tool

View more recent articles

Research Watch

PIK3CA Mutations and Metabolic Conditions Drive Clonal Expansion in Normal Esophagus

Macrophages Scavenge Myelin to Support Glioblastoma Metabolism

Personalized Adoptive Cell Transfer Shows Promise in Metastatic Colorectal Cancer

View more recent articles

Online ISSN 1538-7445 **Print ISSN** 0008-5472