PRIMARY AND ACQUIRED RESISTANCE OF COLORECTAL CANCER CELLS TO ANTI-EGFR ANTIBODIES CAN BE OVERCOME BY THE TREATMENT WITH REGORAFENIB IN COMBINATION WITH CETUXIMAB

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Aim: Advances in the molecular understanding of colorectal cancer (CRC) have demonstrated that several signaling pathways have been implicated into the resistant mechanisms to anti-EGFR monoclonal antibodies (MoAbs) such as cetuximab, including EGFR, RAS/RAF and PI3K/AKT

Methods: We have tested, in vitro and in vivo, the effects of regorafenib, a novel oral multikinase inhibitor that targets protein kinases involved in tumor angiogenesis [VEGFR1–3 and tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2)], oncogenesis (KIT, RET and RAF) and the tumor microenvironment [platelet-derived growth factor receptor-b and fibroblast growth factor receptor (FGFR)18], in a panel of human CRC cell lines with primary or acquired resistance to cetuximab

Results: among the CRC cell lines, five with a KRAS mutation (LOVO, HCT116, HCT15, SW620, SW480) and one with a BRAF mutation (HT29) were resistant to the anti-proliferative effects of cetuximab, whereas two cell lines (GEO and SW48) were highly sensitive to cetuximab. Treatment with regorafenib determined dose-dependent growth inhibition in all cancer cell lines, including two human CRC cell lines with acquired resistance to cetuximab, that previously were generated in our laboratory (GEO-CR and SW48-CR). Combined treatment with cetuximab and regorafenib induced a synergistic anti-proliferative and apoptotic effects by blocking MAPK- and AKT-pathways in cell lines with either primary or acquired resistance to cetuximab. Nude mice were injected subcutaneously with SW48-CR cells. The combined treatment with cetuximab and regorafenib caused significant tumor growth inhibition and increased mice survival. We are currently performing an experiment on an in vivo orthotopic CRC model to validate the role of combined treatment of regorafenib plus cetuximab to overcome resistance to anti-EGFR inhibitors.

Conclusions: These results suggest that the combined treatment with cetuximab and regorafenib could be a strategy for overcoming resistance to anti-EGFR therapies in CRC patients.

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