MOUSE-DREAM: VEGF INHIBITION IS ACCOMPANIED BY EGFR ACTIVATION IN COLORECTAL CANCER MODELS INDEPENDENT OF KRAS STATUS PROVIDING A RATIONAL FOR COMBINATIONS OF BEVACIZUMAB AND ERLOTINIB IN THE POSITIVE GERCOR PHASE III DREAM TRIAL

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Aim: We have recently shown that EGFR- and VEGF(R)-targeted small molecules showed synergistic activity in colorectal cancer (CRC) models refractory to combinations of monoclonal antibodies independent of KRAS status. We here wished to determine the activity of bevacizumab in combination with erlotinib and to elucidate the molecular basis for the activity of the combination.

Methods: Three human CRC xenograft models, SW48 (KRAS wt, bevacizumab sensitive), HT-29 (KRAS wt, bevacizumab resistant) and SW620 (KRAS mutant, bevacizumab sensitive) were established in nude mice. Animals were treated with bevacizumab and erlotinib, alone and in combination, and the influence on tumor growth, and the presence of activated EGFR was determined. The influence of erlotinib on the viability of CRC cells and EGFR ligand expression was established under normoxia, hypoxia and hypoxia/reoxygenation.

Results: Combinations of bevacizumab and erlotinib were significantly more active than bevacizumab alone for all three xenograft models. Quantitative IHC analysis showed that bevacizumab activated EGFR in the tumor cells as well as in the tumor-associated endothelial cells which was attenuated by erlotinib. Erlotinib was more cytotoxic toward CRC cells under hypoxia and hypoxia/reoxygenation than under normoxia and was able to down-regulate the EGFR ligands TGF-alpha and amphiregulin under all experimental conditions.

Conclusions: We here show that combinations of bevacizumab and erlotinib are significantly more active than bevacizumab alone in CRC models with different KRAS status and bevacizumab sensitivity. These findings provided the rational basis for the positive GERCOR phase III DREAM trial.

Disclosure: A.K. Larsen: This research was financed in part by Roche; A. Savina: Employed by Roche; B. Chibaudel: Associated with the related DREAM clinical study sponsored by Roche; C. Tournigand: Associated with the related DREAM clinical study sponsored by Roche; T. André: Associated with the related DREAM clinical study sponsored by Roche; A. De Gramont: Associated with the related DREAM clinical study sponsored by Roche. All other authors have declared no conflicts of interest.

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