OPTIMAL STRATEGY WITH MULTI-TARGETED THERAPIES IN EGFR-DEPENDENT “QUADRUPLE WILD TYPE (WT) FOR KRAS, BRAF, NRAS AND PIK3CA GENES” COLORECTAL CANCER (CRC) XENOGRAFTS AFTER COMBINED TREATMENT OF IRINOTECAN PLUS CETUXIMAB

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Aim: Treatment of first line metastatic quadruple WT CRC is based on backbone chemotherapy in combination with anti-EGFR monoclonal antibodies (moAbs) such as cetuximab.

Methods: We have evaluated, in SW48 quadruple WT CRC xenografts, the effects of several kinase inhibitors, regorafenib, GDC-0941 (PIK3CA inhibitor), BAY86-9766 (MEK 1/2 inhibitor) alone or in combination with cetuximab, following the combined treatment of irinotecan and anti-EGFR moAb.

Results: SW48 CRC cell lines were injected subcutaneously into female nude mice and treated for three weeks with irinotecan plus cetuximab. The combined treatment induced a statistical significantly reduction of tumor size (p<0.001 vs control). Subsequently, mice were randomly assigned to seven treatment groups: control, cetuximab, regorafenib, GDC-0941, BAY86-9766 and their combinations with cetuximab. Mice treated for eight weeks, with regorafenib alone showed a slight reduction of tumor growth, instead the GDC-0941 or BAY86-9766 treatment caused a significant growth inhibition. When combined with cetuximab, regorafenib or BAY86-9766 significantly suppressed tumor growth as compared with single agents (p<0.007 and p<0.05 respectively). The treatment with cetuximab plus a selective MEK1/2 inhibitor caused an almost complete suppression of tumor growth, with a clinical complete response of 2 out of 8. No benefit was observed by adding cetuximab to PIK3CA inhibitor. Tumor specimens are currently collected and cell lines are generated from resistant xenograft tumors for each treatment group to investigate the possible mechanisms underlying the synergistic antitumor activity.

Conclusions: To our knowledge this is the first in vivo study that has investigated the optimal sequential treatment by using multi-targeted therapies in EGFR-dependent quadruple WT CRC tumors pre-treated with irinotecan plus cetuximab. The best antitumor effect was observed by combining the anti-EGFR monoclonal antibody, cetuximab, plus the selective small molecule MEK1/2 inhibitor BAY86-9766.

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