reduces total c-Met in various tumor cell lines and inhibits proliferation of tumor cells that depend on high c-Met expression. In this poster, we further explore LA480 mechanism of action. Our data demonstrate that LA480 can block HGF-induced p-Met, p-Akt and p-Erk in multiple tumor cell lines. In ligand independent MKN45 cells (a model of cancer cells with high c-Met amplification), LA480 treatment *in vitro* results in G1 cell cycle arrest, but not apoptosis. In mouse xenograft studies, LA480 significantly inhibits MKN45 tumor growth by 34% at day 15 and 91% at day 35. Consistent with cell culture data, the percentage of mitotic proliferating cells is decreased in the treated tumors by 71%. Tumors treated with LA480 are less hypoxic and have a decreased percent total apoptotic area. These findings suggest that LA480 may be a promising therapy for treatment of cancers driven by ligand-dependent and ligand-independent c-Met activation.

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Anti-IGF1R therapy with dalotuzumab is efficacious in a sub-set of KRAS mutant cetuximab refractory CRC models

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The monoclonal antibody targeting EGFR, cetuximab is currently used in the treatment of advanced colorectal cancer. Recent studies indicate that cetuximab is ineffective in the treatment of patients with colorectal cancers harboring activating mutants in KRAS or BRAF, components of the RAS-MAPK pathway. Cross-talk between EGFR and insulin like growth factor receptor (IGF1R) has been reported. MK-0646 (dalotuzumab), a monoclonal antibody targeting IGF1R is currently being developed for the treatment of various cancers. Here we have investigated activity of MK-0646 in KRAS or BRAF mutant, cetuximab refractory pre-clinical colon cancer models. A subset of cetuximab-refractory CRC cell lines (3/12) were responsive to MK-0646 treatment. Addition of cetuximab did not further potentiate MK-0646 mediated growth inhibition in KRAS/BRAF mutant CRC models. Strikingly, MK-0646-mediated inhibition of IGF1R signaling enhanced the sensitivity to irinotecan. In xenograft models that expressed high levels of IGF1R, MK-0646 significantly enhanced irinotecan-mediated growth inhibition. The combination of MK-0646 with irinotecan produced lasting tumor growth inhibition that persisted even after treatment withdrawal, indicating a durable response to this combination. In contrast, in xenograft tumors with low levels of IGF1R expression, the combination of MK-0646 and irinotecan failed to enhance irinotecan-mediated growth inhibition. In this study a molecular rationale for the combination benefit with MK-0646 and irinotecan was established. Irinotecan treatment resulted in the activation of IGF1R and PI3K signaling pathways, representing as a possible tumor survival mechanism. Combined treatment with MK-0646 and irinotecan prevented the activation of these survival signals, leading to increased anti-tumor activity. These studies suggest that MK-0646 in combination with irinotecan may have utility in the treatment of KRAS or BRAF mutant colorectal cancer patients. This hypothesis is currently being tested in the clinic. Preliminary data, from early Phase 1 clinical studies have shown activity of MK-0646 based therapy in KRAS mutant patients.

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Essential role of fibroblast growth factor receptor 2 (FGFR2) in tumorigenesis of human cancers harboring FGFR2 amplification demonstrated by a functional blocking antibody

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Fibroblast growth factors (FGFs) play important roles in regulating many fundamental biological processes including embryogenesis, tissue homeostasis, metabolism, angiogenesis, and wound healing. Dysregulated FGF signaling has been implicated in the pathogenesis of human cancers. We generated monoclonal antibodies (mAbs) against the extracellular ligand binding domain of fibroblast growth factor receptor 2 (FGFR2) to address the role of FGFR2 in tumorigenesis and to explore the potential of FGFR2 as a novel therapeutic target. Human gastric and breast cancer cell lines harboring *FGFR2* amplification predominantly express the IIIb-isoform of FGFR2. Therefore, we used an FGFR2-IIIb specific antibody, GP369, to investigate the importance of FGFR2 signaling in such cell lines *in vitro* and *in vivo*. GP369 specifically and potently suppressed ligand-induced phosphorylation of FGFR2-IIIb and downstream signaling *in vitro*. The administration of GP369 in mice significantly inhibited the growth of *FGFR2*-amplified human cancer xenografts. Our findings strongly support an essential role of FGFR2 in the initiation and/or maintenance of human cancers harboring *FGFR2* amplification. Cancer patients with activated/amplified FGFR2 signaling could potentially benefit from therapeutic intervention with FGFR2-targeting antibodies.

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Efficacy of VEGFR2 targeted mAb therapy in preclinical cancer models resistant to antiangiogenic therapy

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Several antiangiogenic agents are approved for the treatment of cancer, including the anti-VEGF mAb bevacizumab (metastatic breast and colorectal cancers) and the multi-targeted kinase inhibitor sorafenib (advanced hepatocellular carcinoma). These therapies do not confer tumor control in some patients, and the majority of tumors develop resistance. Identification of alternative treatment options that enable disease control in the setting of resistance is essential for improved patient outcomes. A monoclonal antibody targeting VEGFR2, IMC-1121B, has been associated with preliminary efficacy in TKI-refractory renal cancer and is currently being evaluated in bevacizumab and sorafenib resistant colorectal and hepatocellular cancers, respectively. We evaluated an antibody specific to murine VEGFR2, DC101, as monotherapy or in combination with chemotherapy in preclinical models of cancer resistant to sorafenib or anti-VEGF therapies.

In HuH-7 hepatocellular carcinoma xenografts, tumors that had grown on average by 100% over 8 days of sorafenib therapy (30 mg/kg, PO, daily), grew 20% over 15 days of therapy with the anti-VEGFR2 mAb DC101 (40 mg/kg, IP, 3×/week; $p < 0.0001$ versus rat IgG).

To mimic bevacizumab activity and resistance in preclinical cancer models, we developed a human antibody, S12, that specifically targets both human and mouse VEGF-A. S12 (40 mg/kg, IP, 3×/week) was combined with paclitaxel (10 mg/kg, IP, q7d) to develop refractory or non-responsive breast cancer models. In MDA-MB-231LP breast carcinoma xenografts, tumors that had grown on average by 100% over 8 days of paclitaxel + S12 therapy, grew 11% over 17 days of therapy with DC101 + 5-FU/LV (125/62 mg/kg) ($p < 0.0001$ versus saline). Antitumor benefits with the combination were significant compared to DC101 ($p = 0.0005$) or 5-FU/LV ($p = 0.0009$) alone. Similarly, DU4475 tumors that had grown on average by 100% over 17 days of paclitaxel + S12 therapy, regressed on average by 22% over 10 days of therapy with the DC101 + 5-FU/LV combination ($p < 0.0001$ versus saline), although the benefits did not reach statistical significance compared to 5-FU/LV.

These results support the conclusion that VEGFR2 targeted antibody therapy may be efficacious in breast and hepatocellular cancers that are refractory to anti-VEGF antibody based therapy or anti-VEGFR2 targeted TKIs.

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Unique molecular recognition of CD20 by the type II CD20 antibody GA101

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Background: CD20 is a specific cell surface marker found on normal and malignant B cells. Therapeutic anti-CD20 antibodies can be classified as type I and type II CD20 antibodies differing significantly in their mode of action. Rituximab is a type I CD20 antibody that has had a major impact on the treatment of malignant lymphomas. GA101 is a novel type II glycoengineered CD20 antibody. The molecular basis of the type I and type II classification of CD20 antibodies is incompletely understood.

Material and Methods: We used data from epitope mapping, point mutagenesis, co-crystallization, and protein tomography to precisely map the epitopes and characterize the molecular interactions of different anti-CD20 antibodies.

Results: The binding site of the monoclonal antibody GA101 on CD20 was found on the cyclic loop formed by the amino acids Cys167-Cys183 of human CD20. The CD20 epitope of GA101 and different type I and