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Efficacy of EGFR and IGF-1R antibody therapy is independent of PTEN status in a selection of tumor models

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Mutational inactivation or deletion of the phosphatase and tensin homologue on chromosome10 (PTEN)/MMAC1/TEP gene in human cancer cells leads to a constitutive activation of the PI3 kinase/Akt pathway in cancer cells. This constitutive activation may underlie resistance to therapies targeting receptors such as epidermal growth factor receptor (EGFR) and insulin-like growth factor-1 receptor (IGF-1R). We have evaluated whether loss of PTEN can alter the therapeutic response towards Cetuximab and IMC-A12, monoclonal antibodies targeting EGFR and IGF1R, respectively. The present study was aimed at evaluating the in vitro and in vivo responses to Cetuximab and IMC-A12 on PTEN null cancer cells (PC3 and U87MG) transfected with a functional PTEN gene. In addition we evaluated the effects of siRNA based abrogation of PTEN expression in PTEN wild type cells (BxPC3). The presence or absence of PTEN was demonstrated by western blotting or ELISA and functional PTEN was demonstrated by pAKT western blotting. In vitro proliferation assay showed no difference in growth pattern of either phenotypes of BxPC3. PTEN transfected PC3 and U87 cells showed 10–15% less tumor growth in vivo compared to mock transfected cells. However, presence or absence of PTEN has no significant impact on the efficacy of either cetuximab or IMC-A12 on these established xenograft models. In a resistant PC3 xenograft model response towards cetuximab or IMC-A12 remained the same in either phenotypes with %T/C values of cetuximab: 60% on PC3-Mock and 63% on PC3-PTEN; IMC-A12: 73% on PC3-Mock and 69% on PC3-PTEN. Similarly response towards cetuximab and IMC-A12 on U87MG remained the same. %T/C of cetuximab: 60% and 77% on mock transfected and PTEN cells respectively; IMC-A12: 50% and 57% respectively.
While some results are pending, the existing results suggest that cetuximab and IMC-A12 efficacy are not significantly related to PTEN status in the selected models.

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A monoclonal antibody (AR36A36.11.1) with potent in vivo efficacy in multiple human cancer models targets CD59

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Complement (C) activation leads to cell lysis resulting from the formation of membrane attack complexes (MAC). MACs are blocked by CD59 a C regulatory protein that is over expressed in tumor cells such as breast, colon and prostate carcinomas to evade C lyses. Targeting CD59 with antibodies to prevent this evasion is a potentially effective therapeutic approach. AR36A36.11.1, a functional monoclonal antibody targeting CD59, discovered using Arius' FunctionFIRST™ antibody generation platform, has been studied for its potential as a cancer therapeutic.
Tissue expression and distribution of CD59 detected with AR36A36.11.1 were determined by immunohistochemistry. Cytotoxicity was determined in vitro. In vivo efficacy was tested in xenografts of human cancers. PEPSCAN technology was used to determine the epitope for AR36A36.11.1 and affinity was determined by Biacore. Cytotoxic mechanism of action was assessed using in vitro C dependent cell (CDC) lysis and antigen-dependent cell-mediated cytotoxicity (ADCC).
The epitope for AR36A36.11.1 was present in various normal human tissues and was over expressed in several cancer types. AR36A36.11.1 induced in vitro cytotoxicity in the absence of effector cells and C in prostate cancer cell lines. AR36A36.11.1 exhibited potent in vivo efficacy resulting in tumor growth inhibition of 100% ($p < 0.0023$), 86% ($p < 0.0009$), 58% ($p < 0.031$) and 48% ($p < 0.0216$) in prophylactic xenografts of breast, prostate, lung and colon cancers, respectively. In an established model of breast cancer, AR36A36.11.1 exhibited highly potent dose-dependent efficacy and extended survival of the animals. In an established prostate cancer model, AR36A36.11.1 compared favorably with Taxotere. Humanized AR36A36.11.1 has similar affinity and efficacy to its murine form. The epitope for AR36A36.11.1 resides within the CD59 MAC inhibitory site consistent with the ability of AR36A36.11.1 to enhance CDC. This antibody also enhanced ADCC.
AR36A36.11.1 has significant in vivo anti-tumor activity towards a broad range of high incidence cancers. The effectiveness of AR36A36.11.1 may be due to enhanced CDC through its CD59 blocking functions. However, the potency of the antibody is maintained at low dose levels that do not activate CDC in vitro. Therefore, C-independent pathways such as ADCC or intracellular signaling may also play a role in the efficacy of AR36A36.11.1. Antibody-mediated blockade of CD59 represents a novel approach to cancer treatment.

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Novel antibody-maytansinoid conjugates with efficacy against multidrug resistant tumors

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Chemotherapy often leads to a multidrug resistant (MDR) phenotype characterized by resistance of tumor cells to a broad spectrum of anticancer drugs. One of the best studied mediators of MDR is P-glycoprotein (Pgp), also known as MDR1 or ABCB1. Pgp blocks the uptake of drugs by cells from extracellular space, and pumps various neutral or positively charged compounds out of the cells. Maytansine and its derivatives are substrates of Pgp. In this study, we used antibodies to deliver our proprietary maytansine derivatives, DM1 and DM4, inside Pgp-positive cells. These maytansinoids were conjugated to an EpCAM-binding antibody, B38.1, via either a SPDB disulfide linker, a SMCC non-reducible thioether linker, or a PEG4-containing non-reducible linker. After the conjugates bound to and entered EpCAM-expressing cells, the disulfide-linked conjugate was metabolized to neutral maytansinoid derivatives (DM4 and S-methyl-DM4), the thioether-linked conjugate to a charged product (Lysine-SMCC-DM1), and the PEG4-linked conjugate to a polar, charged compound (Lysine-PEG4-DM1). The cytotoxic potencies of these conjugates in vitro were tested toward three cell lines, the human colon carcinoma COLO 205 (EpCAM+/Pgp−), a COLO 205 clone (COLO205-MDR (EpCAM+/Pgp+) engineered to overexpress Pgp, and the naturally evolved MDR human colon carcinoma HCT15 (EpCAM+/Pgp+). The three conjugates had similar potencies toward COLO 205 cells, but differed in their activities toward COLO205-MDR and HCT15 cells. The PEG4-linked conjugate demonstrated the greatest potency, while the disulfide-linked conjugate was the least active one. The activity of the disulfide- and SMCC-linked conjugates toward COLO205-MDR and HCT15 cells was enhanced in the presence of the Pgp inhibitor cyclosporin A, suggesting that Pgp is the likely cause for the different activities of the conjugates. The activity of these conjugates against these cell lines in vivo were evaluated in subcutaneous xenograft models in SCID mice. The B38.1-PEG4-DM1 conjugate showed greater anti-tumor activity against HCT15 and COLO205-MDR tumors than either the B38.1-SMCC-DM1, or B38.1-SPDB-DM4 conjugates. The advantage of the PEG4 linker was also demonstrated with maytansinoid conjugates of an anti-CanAg antibody, huC242. Thus, antibody-maytansinoid conjugates bearing the novel PEG linker represent a promising approach for the treatment of multidrug resistant tumors.

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A phase 2, single-arm study of volociximab (an anti-a5β1 integrin antibody) monotherapy in patients with platinum-resistant advanced epithelial ovarian cancer or primary peritoneal cancer

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Background: A critical survival step for proliferating vascular endothelial cells is the ligation of fibronectin in the extracellular matrix to $\alpha5\beta1$ integrin. Volociximab, a chimeric monoclonal antibody, blocks fibronectin binding to $\alpha5\beta1$ and induces apoptosis in proliferating endothelial cells.
Materials and Methods: Volociximab was studied in a phase 2, single-arm, multicenter, 2-stage study in platinum-resistant epithelial ovarian or primary peritoneal cancer patients (pts) who had measurable disease with progression after topotecan or pegylated liposomal doxorubicin. Volociximab was administered at 15 mg/kg IV weekly until progression of disease