ND, respectively; mean C_{max} and AUC_{inf} increased in a greater-than-dose-proportional manner, suggesting nonlinear IMC-A12 pharmacokinetics (C_{max} = 333, 306, 788 and 443 μg/mL; AUC_{inf}=55744, 57613, 156460 and 669562 hr*μg/mL, respectively); and mean clearance decreased (0.07–0.02 mL/hr/kg), suggesting the approach of IMC-A12 saturation. In patients receiving IMC-A12 at escalating doses of 6, 10 or 15 mg/kg on a q2w schedule, mean $t_{1/2}$ was 149 h, 139 h, and 211 h, respectively; mean C_{max} and AUC_{inf} increased in a greater-than-dose-proportional manner, suggesting nonlinear IMC-A12 pharmacokinetics (C_{max} = 554, 734, and 1193 μg/mL; AUC_{inf}=69679, 134067, and 191176 hr*μg/mL, respectively); and mean clearance was relatively constant (0.141, 0.122, and 0.078 mL/hr/kg), suggesting IMC-A12 saturation. In the weekly and q2w groups, increases in serum levels of IGF-I and IGFBP3 were observed in all dose groups suggesting that IMC-A12 was blocking IGF-IR binding to its receptor. Serum trough concentrations observed in both weekly and q2w studies exceed target concentrations associated with anti-cancer activity in preclinical models (target trough concentration 60 to 158 μg/mL), especially at the doses recommended for further evaluation.
Conclusions: At clinically tolerable doses, IMC-A12 can achieve and maintain plasma concentrations that are sufficient to inhibit ligand binding to the IGF-IR. IMC-A12 will be further evaluated in prostate, breast, and other cancers at a dose of 10 mg/kg q2w.

555 POSTER

The PARP inhibitor, ABT-888 overcomes resistance in temozolomide refractory breast and prostate xenograft tumors implanted in metastatic sites in vivo

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PARP's role in DNA damage recognition/repair makes PARP inhibition an attractive cancer therapeutic target. ABT-888 is a potent PARP inhibitor with excellent oral bioavailability that readily crosses the blood brain barrier and has entered Phase 1 clinical trials. We have shown ABT-888's robust ability to potentiate temozolomide (TMZ) in tumors from different histological types having differential TMZ sensitivity. In this study we explored the ability of ABT-888 to potentiate TMZ efficacy in the human breast carcinoma, MDA-231-LN-luc implanted brain and human prostate carcinoma, PC3M-luc both in orthotopic and intra-tibial models. Bioluminescent cells were injected into the brain striatum of female SCID mice (MDA-231-LN-luc) and into the proximal epiphysis of the tibia in male SCID mice (PC3M-luc osteolytic cells). Zoledronic acid (ZA, 0.25 mg/kg/d, bi-weekly), a biphosphonate shown to inhibit bone resorption was also used in the intra-tibial model, where the area of decreased decalcification was quantitated in x-rays. Mice were staged based on the tumor burden evaluated in vivo with bioluminescent images (BLI) and treated with monotherapy and combinations of TMZ (50 mg/kg/d, q.d.x5) +/− ABT-888 (25 mg/kg/d, b.i.d.x5) for two cycles (PC3M-luc with 22 days rest) or three cycles (MDA-231-LN-luc with 11 days rest). There were no significant health concerns observed in the prostate study, but weight loss was observed in the breast study after the 2nd and 3rd cycles. In the prostate model, all groups with ABT-888/TMZ combination showed profound efficacy compared to groups with TMZ alone (>77% tumor growth inhibition, TGI) after the 1st cycle. However, the TMZ sensitivity was lost and tumors became refractory to TMZ during a 2nd cycle of TMZ+ZA but not with ABT-888/TMZ combination (>81% TGI). While ZA significantly improved bone integrity, no reduction in tumor burden was observed in groups without the addition of ABT-888. In the breast model, ABT-888 showed significant potentiation of TMZ activity after the 1st cycle (66% increase in tumor from size-match compared to 54% regression in the TMZ+ABT-888 group). After a 2nd cycle, tumors in the TMZ group were refractory to TMZ compared to the combination group where regression was maintained until the end of study (>40 days). We show a profound potentiation of TMZ activity by ABT-888 in two metastases models. While tumors can become refractory to TMZ treatment, ABT-888 is able to sustain sensitivity at the 2nd or 3rd cycles of combination treatment. More importantly, TMZ resistance can be prevented by ABT-888 combination therapy in crossover treatments indicating that in these studies, resistance may be overcome by PARP inhibition. Altogether, these suggest that tumors refractory to TMZ do not preclude sensitivity to ABT-888 combination therapy. The underlying mechanisms are not completely understood but may involve mechanisms independent of MGMT.

556 POSTER

MetMAb significantly enhances anti-tumor activity of anti-VEGF and/or erlotinib in several animal tumor models

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Background: Crosstalk between the Met receptor tyrosine kinase (RTK) and other RTKs has been implicated in tumor cell growth and survival. For example, Met amplification leads to acquired resistance to epidermal growth factor receptor (EGFR) inhibitors in EGFR mutant NSCLC cell lines and primary tumors. We have shown that Met inhibition, via shRNA-knockdown or the anti-Met monovalent antibody, MetMAb, sensitizes EGFR wild-type NSCLC tumors to erlotinib (Tarceva®), possibly by modulation of HER3 levels. Here we further explore how Met interacts with the VEGF pathway and explore combination efficacy in xenograft tumor models.
Materials and Methods: HGF-induced human umbilical vein endothelial cell (HUVEC) sprouting assays were performed to investigate the impact of Met in endothelial cell function. To examine possible indirect effects on angiogenesis, mRNA and protein expression were analyzed in several Met-driven tumor cell lines and xenograft tumors after Met activation (HGF-treatment) or Met inactivation (shRNA or MetMAb). Anti-tumor efficacy studies were performed in multiple xenograft models, including Met amplified lines, HGF/Met autocrine lines, and paracrine models utilizing a human-HGF transgenic SCID model (hu-HGF-Tg-SCIDs). Met was targeted via shRNA against Met or treatment with MetMAb, in combination with anti-VEGF antibodies (B20−4.1).
Results: We show how Met can play both direct and indirect roles in modulating tumor angiogenesis and that combinations of MetMAb and anti-VEGF antibodies provide improved anti-tumor efficacy. First, MetMAb effectively blocked HGF induces HUVEC cell sprouting, highlighting how Met may directly modulate tumor endothelial cell organization and migration. Second, Met modulated angiogenesis in an indirect fashion by regulating tumor cell production of angiogenic factors, such as vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8). Third, targeting Met, via shRNA or MetMAb, significantly enhanced efficacy of anti-VEGF antibodies in multiple Met-driven human xenograft tumor models. Anti-VEGF had similar efficacy to MetMAb in hu-HGF-Tg-SCID mice. MetMab plus anti-VEGF treatment resulted in additive effects that surpassed MetMab plus erlotinib. In contrast, erlotinib plus anti-VEGF antibodies were equivalent to anti-VEGF alone, highlighting the importance of Met in this model. Triple combination of MetMAb, anti-VEGF, and erlotinib showed much better activity than any two agents alone, with prolonged anti-tumor activity and 9/10 partial responses and 1/10 complete response.
Conclusions: These data indicate how Met can be a direct and indirect driver of tumor angiogenesis and highlight the potential therapeutic value of combining inhibitors of Met (such as MetMab) with those for VEGF (such as bevacizumab (Avastin®)) and/or EGFR (such as erlotinib (Tarceva®)).

557 POSTER

Pre-clinical activity of the PARP inhibitor AZD2281 in homologous recombination repair deficient triple negative breast cancer

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Background: Recently, the novel PARP inhibitor AZD2281 has been shown to have clinical activity in tumours from patients with hereditary BRCA mutations (Yap et al., 2007), supporting the concept of synthetic lethality previously described in pre-clinical models (Farmer et al. 2005; McCabe et al., 2005; Evers et al., 2008). The BRCA genes, which are associated with an increased incidence of breast and ovarian cancer, play key roles in the homologous recombination (HR) repair of DNA double strand breaks. Sensitivity to PARP inhibition has also been demonstrated in cells deficient in non-BRCA components of the HR repair pathway (McCabe et al., 2006), suggesting the broader clinical potential of PARP inhibitors in tumours that are HR deficient (HRD). Triple negative (ER−, PR−, HER2−) breast cancers have been associated with HRD, however, the extent and make-up of deficiency in this tumour type is currently not well defined. We have undertaken pre-clinical studies to assess both the sensitivity of triple negative (TN) breast cancers to AZD2281 and the nature of any HRD associated with response.
Materials and Methods: In vitro sensitivity to AZD2281 in a panel of TN cancer cell lines (including a number with defined BRCA1 mutations)