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POSTER

Efficacy of AMG 479, a fully human anti-IGF-1R monoclonal antibody, against xenograft models displaying genetic alterations in Ras/Raf, PI3K/PTEN and p53 pathways

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Background: AMG 479 is a fully human monoclonal antibody against the type I IGF-1 receptor (IGF-1R). AMG 479 exerts its anti-tumor activity through ligand blocking and receptor internalization and degradation. Several phase II clinical trials are currently planned to assess the efficacy of AMG 479 in cancer patients. Therefore, it has become important to identify predictive biomarkers of response/resistance that could dramatically affect the clinical development and future therapeutic use of this agent.

Methods: Human xenograft models implanted in athymic female nude mice were used to examine the relationship between common tumor genetic alterations (k-ras, b-raf, PI3K, PTEN and p53) and responsiveness to AMG 479 *in vivo*. AMG 479 was dosed intraperitoneally twice per week for the duration of the experiment. Efficacy was analyzed using repeated measures ANOVA.

Results: Models with genetic alterations resulting in increased activation of the MAPK pathway (k-ras/b-raf) were found to retain sensitivity to AMG 479. Three models: Colo-205 (b-raf), MiaPaCa (k-ras) and HCT-116 (k-ras) responded to AMG 479 therapy with significant tumor growth inhibition (TGI), ranging from 40–70%. Models with aberrant p53 function or p53 mutations also showed a high degree of sensitivity to AMG 479. The p53 mutant models BxPC-3 and SK-NP-1 were inhibited better than 70%, while the mdm2 amplified model SJSA-1 showed the best sensitivity to AMG 479 reaching upwards of 80% TGI. Models displaying PI3K activating mutations showed mixed responses. The breast carcinoma model MCF-7 was resistant to AMG 479, while the colon carcinoma model DLD-1 and HCT-116 showed significant TGI. Lastly, four PTEN null/mutated tumor models showed resistance to AMG 479. No significant TGI was observed at any dose of AMG 479 in the PC-3, 786-O, Colo-320 and Cal-51 models.

Conclusion: Together these results suggest that, when evaluated independently, only loss of PTEN function may represent a negative marker for AMG 479 efficacy *in vivo*.

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Phase I study of IMGN901 (BB-10901) in patients with CD56-positive solid tumours

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Background: IMGN901 is a conjugate of the cytotoxic maytansinoid DM1 and the monoclonal antibody huN901. IMGN901 binds with high affinity to CD56 and is designed to bind to and kill CD56-expressing cancer cells. Tumors expressing CD56 include small cell lung carcinoma (SCLC), non-pulmonary small cell carcinomas, neuroendocrine tumors, and multiple myeloma.

Methods: Patients with relapsed or refractory SCLC or other CD56+ solid tumors are eligible. IMGN901 is given by IV infusion on 3 consecutive days every 21 days. Cohorts of 4 patients are enrolled on each dose level, with evidence of dose-limiting toxicity (DLT) triggering cohort expansion.

Results: Forty-four patients have been enrolled in the study. Doses of 4–75 mg/m²/day (12–225 mg/m² per 3 week cycle) have been evaluated, and the maximum tolerated dose (MTD) of IMGN901 has not yet been established. In contrast, an earlier study evaluating IMGN901 given weekly for 4 weeks every 6 weeks found an MTD of 60 mg/m²/week (240 mg/m² per 6 week cycle). DLTs reported in the current study are grade 4 fatigue (1 patient, 16 mg/m²/day), grade 3 peripheral sensory neuropathy (1 patient, 48 mg/m²/day), and severe headache/meningitis-like symptoms (1 patient at 75 mg/m²/day over 40 minutes). The rate of infusion was reduced to 1 mg/min and additional patients received 75 mg/m²/day, with grade 2 headache reported in 2 of 6 patients treated. The impact of prophylactic measures for headache being given on the day prior and day of IMGN901 administration is now being assessed. Evidence of biological activity has been reported in the current study. A patient with relapsed metastatic Merkel cell carcinoma had a durable complete response and a patient with SCLC had an unconfirmed partial response. Fourteen patients had stable disease lasting 5–18 weeks.

Conclusions: IMGN901 has shown preliminary evidence of safety and clinical activity in this study. The impact of prophylactic measures for

headache being given on the day prior and day of administration of IMGN901 are being assessed.

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Phase I study of IMC-3G3, an IgG1 monoclonal antibody targeting platelet-derived growth factor alpha (PDGFRα) in patients with advanced solid malignancies

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Background: The type III receptor tyrosine kinase PDGFRα and its ligands are expressed by a wide array of tumors and supportive stroma, playing a critical role in tumorigenesis and tumor progression by several mechanisms including tumor-driving mutations and gene amplifications and overexpression. IMC-3G3, a recombinant human IgG1 MAb that specifically targets PDGFRα, thereby blocking all PDGF ligands, induces prominent anticancer effects *in vitro* and on human tumor xenografts *in vivo*.

Materials and Methods: This Phase 1, multicenter study of IMC-3G3 administered intravenously in patients (pts) with advanced and refractory solid malignancies is enrolling five dose-escalating cohorts of 3–6 pts each. The primary objectives are to determine the MTD and safety profile. Each pt is receiving four weekly infusions of 4, 8, or 16 mg/kg IMC-3G3 per cycle (Cohorts 1–3) or infusions of IMC-3G3 every 2 weeks at 15 or 20 mg/kg (Cohorts 4 and 5). After the first and final infusion of Cycle 1, PK samples were taken at regular intervals up to 168 and 336 hrs, respectively. Each successive cohort did not begin enrollment until safety had been established in the previous cohort.

Results: 18 pts have enrolled to date (16 male, 2 female). 12 pts achieved SD (median = 14 weeks). 10 of these pts had prostate cancer. 1 pt at 16 mg/kg is ongoing at 46 weeks. 1 pt at 4 mg/kg who experienced a PSA decrement of >50% was treated for 39 weeks until PD. No DLTs were observed at any dose level in Cycle 1. Preliminary safety data for the first 12 pts enrolled show that the most commonly reported AE has been fatigue (2 of 12 pts). There were no Grade 3/4 IMC-3G3-related events or events of fluid retention reported. Following the Cycle 1 final infusion for Cohorts 1–3, as IMC-3G3 dose was escalated from 4 to 8 to 16 mg/kg; A) the mean t_{1/2} remained relatively constant (126–174 hrs), B) mean C_{max} and AUC_{inf} increased in a greater-than-dose-proportional manner, suggesting nonlinear IMC-3G3 PK (C_{max}=139, 297, and 1470 µg/mL; AUC_{inf}=23686, 48343, and 171430 hr*µg/mL for the 4, 8, and 16 mg/kg cohorts respectively), and C) mean clearance decreased (0.196–0.108 mL/hr/kg), suggesting the approach of IMC-3G3 saturation. PK data acquisition for Cohorts 4–5 is ongoing.

Conclusions: Enrollment continues with evaluation of 20 mg/kg every 2-weeks based on supportive PK data and toxicity profiles. Preliminary safety, PK, and biological activity data support further IMC-3G3 disease-directed development.

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Interim results from a Phase 1/2 study of volociximab in combination with liposomal doxorubicin in patients with advanced epithelial ovarian or primary peritoneal carcinoma that relapsed after platinum/taxane chemotherapy

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Background: A critical survival step for proliferating vascular endothelial cells is the ligation of fibronectin in the extracellular matrix to α5β1 integrin. Volociximab, a chimeric monoclonal antibody, blocks fibronectin binding to α5β1 and induces apoptosis in proliferating endothelial cells.

Materials and Methods: Volociximab is being investigated in a Phase 1/2, multicentre, international study. The objectives of Phase 1 were to evaluate the safety and tolerability of escalating doses of volociximab (V) in combination with a fixed dose and schedule of liposomal doxorubicin (LD) to determine the recommended Phase 2 dose (RP2D). Phase 2 is an open-label, parallel, 3-arm adaptive randomization phase to compare the efficacy and safety of LD + V with LD alone. Each treatment cycle is 28 days, consisting of LD (40 mg/m² q4wk) alone or in combination with V (qwk or q2wk). Patients (pts) relapsing after prior platinum/taxane chemotherapy with advanced epithelial ovarian or primary peritoneal cancer are treated until disease progression or drug intolerance. The

primary endpoint is progression free survival (PFS). Pharmacokinetics (PK) and pharmacodynamics are also being evaluated.

Results: Phase 1 of the study has been completed. A total of 9 pts were treated: 3 pts received LD + V (7.5 mg/kg qwk) in Cohort 1 and 6 pts received LD + V (15 mg/kg qwk) in Cohort 2. The median age was 62 yrs (36–72) and all pts had an ECOG PS \leq 1. All pts experienced study-related NCI CTCAE Grade 1 or 2 AEs in Cycle 1; the most common were asthenia (5 pts), fatigue (3 pts), and nausea (3 pts). No DLTs were observed. In Cohort 1, two pts withdrew at the end of Cycle 2 due to progressive disease, while one pt is continuing in Cycle 9. In Cohort 2, 3 pts experienced hand-foot syndrome (HFS) progressing to Grade 3 in Cycles 3, 3 and 4, respectively. All recovered to Grade 2 within 14 days after treatment discontinuation. 2 pts had clinical progression, one at the end of Cycle 2 and the second at the end of Cycle 4. The third pt withdrew due to an AE at the end of Cycle 2. Ongoing PK evaluation will determine if an interaction between the LD and V study drugs could explain the onset of HFS. There have been three iterations of the adaptive randomisation based on accumulating PFS data.

Conclusions: From Phase 1, thevelociximabRP2D selected for study in phase 2 was 15 mg/kg. The incidence of HFS is being closely monitored in Phase 2, which has a planned maximum enrollment of 150 patients.

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Anti-tumor effect of an anti-human Müllerian Inhibiting Substance type II receptor antibody in a nude mouse model for granulosa cell tumors: a new targeted therapy for ovarian cancer

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Background: Ovarian cancer is responsible for the highest mortality rate among patients with gynecologic malignancies. Therefore, there is an emerging need for innovative therapies for the control of advanced ovarian cancer. Immunotherapy has emerged as a potential plausible approach for the control of ovarian cancer. The monoclonal antibody 12G4 specifically recognizes the human Müllerian Inhibiting Substance type II Receptor (MISRII). MISRII is involved in Müllerian duct regression as part of the development of the male reproductive system. As it is expressed at high levels on most human Granulosa Cell Tumors and frequently found on human ovarian cancer cells, this receptor is an ideal target for antibody-based tumor targeting and growth inhibition strategies.

Materials and Methods: We first developed a severe immunodeficient Nude xenograft mouse model of human MISRII overexpressing-COV434 Granulosa Cell Tumors. Annexin/propidium iodide stain and cell cycle analysis were performed to explore the possible mechanism by which 12G4 could exert its effect. Signaling pathways affected by 12G4 were assessed using an antibody microarray. The expression of MISRII on tissue sections from ovarian tumors was studied by immunohistochemistry.

Results: Thanks to our mouse model we could show the remarkable efficacy of 12G4 in inhibiting tumor growth *in vivo*. We also could demonstrate *in vitro* an internalization of the antibody-MISRII complex as well as a significant increase of the rate of apoptosis induced by stimulation by 12G4. A corresponding blockade of MISRII-COV434 cells in the G1 phase of the cell cycle was also observed in response to the antibody. The study by antibody microarray allowed us to identify several proteins whose expression was regulated following 12G4 treatment, especially the FAK protein, an important regulator of cell survival signaling which is overexpressed in ovarian cancer. Moreover, using 12G4 antibody in an immunocytochemical study on ovarian tumors we could confirm the expression of the MISRII target in all but one sample.

Conclusion: Taken together our results indicate that 12G4 antibody may represent a novel highly specific and potentially effective therapy for the control of Granulosa Cell Tumors and of lethal ovarian cancer.

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A novel dosing strategy based on plasma levels of CanAg in a Phase II study of IMGN242 (HUC242-DM4) in gastric cancer

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Background: IMGN242 is a conjugate of the cytotoxic maytansinoid DM4 and the monoclonal antibody huC242, which binds to CanAg. In a

Phase I study, the maximum tolerated dose of IMGN242 was determined to be 168 mg/m², with ocular changes the primary dose-limiting toxicity. A Phase II study of IMGN242 was initiated in patients with CanAg-expressing gastric cancer at a dose of 168 mg/m², and initial evidence of activity was noted. However, various ocular changes were reported among some of the first patients dosed in this study.

Methods: Information on IMGN242 pharmacokinetics (PK) and safety are from a Phase I and a Phase II study in which IMGN242 is given as a single IV infusion every three weeks to patients with CanAg-expressing tumors or gastric tumors, respectively.

Results: Forty-five patients have received IMGN242 to date between these two trials. It has been identified that the level of circulating CanAg present in the plasma of patients can impact the PK of the compound. In patients with low (<1000 U/mL) levels of CanAg in their plasma, IMGN242 was found to have a two-phase PK profile, with an initial rapid distribution phase that lasted about 48 hours, followed by a slower (11/2 ~5 days) terminal elimination phase. Among patients (n = 11) with high (>1000 U/mL) levels of CanAg in their plasma, the rate of IMGN242 clearance was 3- to 5-fold greater than in the low plasma CanAg patients. It was found that the patients who had ocular toxicities had low plasma CanAg levels, and that this correlated with higher IMGN242 exposure in these patients.

Conclusions: The data indicate a possible association among the level of plasma CanAg, IMGN242 exposure, and reports of ocular toxicities in patients. The dose of 168 mg/m² appeared to be associated with greater drug exposure and a notable incidence of ocular toxicities in patients have low plasma CanAg levels, suggesting these patients should receive a lower dose of IMGN242. Assessment of preclinical and clinical PK data indicate that, in such patients, a dose of 126 mg/m² is likely to result in a level of drug exposure that can be efficacious. Therefore, the Phase II study protocol has been amended to differentiate the IMGN242 dose administered based on the patient's plasma CanAg levels (low vs. high).

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Trastuzumab-mertansine (T-DM1) retains all the mechanisms of action (MOA) of trastuzumab and is extremely effective in combination with docetaxel

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Background: Trastuzumab (Herceptin®) is currently used as a treatment for patients whose breast tumors overexpress HER2/ErB2. Trastuzumab-DM1 (T-DM1) was designed to combine the clinical benefits of trastuzumab with a potent microtubule-disrupting drug, mertansine (DM1). Currently T-DM1 is undergoing phase II clinical trials in patients whose disease is refractory to HER2 directed therapies. The MOA for trastuzumab include inhibition of PI3K/AKT signaling pathway, inhibition of HER2 shedding and Fcγ receptor-mediated engagement of immune cells, which may result in antibody-dependent cellular cytotoxicity (ADCC). In this study we analyzed whether drug conjugation affects the MOA of trastuzumab.

Methods: DM1 was conjugated to trastuzumab through a non-reducible thioether linker (4-(N-maleimidomethyl)cyclohexane-1-carboxylate or MCC). The binding affinity to HER2 was analyzed using ¹²⁵I-trastuzumab in a competitive Scatchard analysis. The ability of T-DM1 to mediate ADCC was quantified by measuring LDH released from the BT474-M1 cells as a result of ADCC activity initiated by human effector cells. HER2 shedding was examined by detecting the soluble HER2 ectodomain from BT474-M1 conditioned growth media using an ELISA. The phosphorylation state of Ser473 of AKT1 was detected using ELISA. Drug combination effects in cultured breast cancer cells were analyzed using both the Chou & Talalay and Bliss Independence methods. A trastuzumab-insensitive, HER2-transgenic allograft model was used to assess *in vivo* efficacy.

Results: The affinity of T-DM1 (K_D 0.14 nM) for HER2 was nearly identical to trastuzumab (K_D 0.17 nM). In the ADCC assay, trastuzumab resulted in 48% maximal cytotoxicity whereas similar cytotoxicity was observed using T-DM1 (max 57%). Drug conjugation did not adversely affect trastuzumab's inhibition of HER2 shedding or down-regulation of AKT signaling. Notably, T-DM1 was active against models that were insensitive to either trastuzumab or lapatinib. The combination of T-DM1 with docetaxel showed enhanced activity both *in vitro* and *in vivo* compared to either agent alone.

Conclusions: Our results show that conjugation of DM1 to trastuzumab creates a highly efficacious drug while leaving the MOA of trastuzumab intact. T-DM1 is effective in treating trastuzumab-insensitive models and has enhanced potency in combination with docetaxel.