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 $\leqslant$ 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, thevolociximabRP2D 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.

513 POSTER

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

N. Kersual[1], V. Garambois[1], I. Salhi[1], C. Larbouret[1], F. Bibeau[2], C. Mollevi[3], T. Chardès[1], A. Pèlegrin[1], I. Teulon[1]. [1]*Institut de Recherche en Cancérologie de Montpellier, Immunociblage et Radiobiologie en Oncologie, Montpellier, France;* [2]*Centre de Recherche et de Lutte Contre le Cancer, anatomopathology, Montpellier, France;* [3]*Centre de Recherche et de Lutte Contre le Cancer, Biostatistics, Montpellier, France*

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.

514 POSTER

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

A. Tolcher[1], J. Watermill[2], R.A. Mastico[2], R.J. Lutz[2], J. O'Keeffe[2], S. Zildjian[2], A. Phan[3], A. Mita[4], A. Qin[5]. [1]*South Texas Accelerated Research Therapeutics, Clinical Research, San Antonio, Texas, USA;* [2]*ImmunoGen Inc., Clinical Research, Waltham, USA;* [3]*MD Anderson Cancer Center, Clinical Research, Houston, USA;* [4]*Cancer Therapy & Research Center, Clinical Research, San Antonio, TX, USA;* [5]*ImmunoGen Inc, Clinical Research, Waltham, USA*

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/m^2, 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/m^2, 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 (t1/2 ~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/m^2 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/m^2 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).

515 POSTER

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

T. Junttila[1], C. Fields[1], G. Li[1], L. Crocker[1], K. Parsons[1], L. Berry[1], K. Totpal[1], G. Lewis Phillips[1], M. Sliwkowski[1]. [1]*Genentech Inc., Translational Oncology, South San Francisco, CA, USA*

Background: Trastuzumab (Herceptin®) is currently used as a treatment for patients whose breast tumors overexpress HER2/ErbB2. 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 ^{125}I-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.