PPX is prospectively evaluated in a randomized phase III trial in chemo-naïve women with advanced NSCLC.

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Insights into the mechanism of microtubule stabilization by Taxol

H. Xiao, P. Verdier-Pinard, N. Fernandez-Fuentes, R. Angeletti, A. Fiser, G. Orr, S. Band Horwitz. *Albert Einstein College of Medicine, Bronx, NY, USA*

Background: Taxol is an important antitumor drug that stabilizes microtubules, reduces their dynamicity and promotes mitotic arrest and cell death. Although photoaffinity labeling and electron crystallography have localized the binding pocket for Taxol on β-tubulin, there is little insight into the mechanism by which the drug stabilizes microtubules.
Materials and Methods: Tubulin from the marginal band of chicken erythrocytes that contains a single α- and β-isotype, α1 and βVI, was used for all experiments. Hydrogen/deuterium exchange (HDX) in combination with liquid chromatograph-electrospray ionization mass spectrometry (LC-ESI MS) was used to study structural changes in α-, β-tubulin either in GDP-dimers, GTP-microtubules or Taxol-microtubules in solution.
Results: HDX coupled to LC-ESI MS demonstrated a marked reduction in deuterium incorporation in both α-and β-tubulin when Taxol was present. This protection by Taxol reflects decreased solvent accessibility or a more rigid conformation in both polypeptide chains. Decreased local HDX in peptic peptides was mapped on the tubulin structure and revealed both expected and new dimer-dimer interactions. The increased rigidity in Taxol-microtubules was distinct from and complementary to that due to GTP-induced polymerization. Comparing the map of deuterium incorporation between GTP-microtubules and Taxol-microtubules, allowed us to determine not only the regions involved in Taxol binding, but also the longitudinal and lateral dimer-dimer interactions specifically affected by Taxol. Our findings are consistent with Taxol inducing tubulin to adopt a straight conformation and preventing it from shifting to a curved conformation.
Conclusions: HDX coupled to LC-ESI MS can be used effectively to answer important pharmacological and biochemical questions relevant to the function of microtubules in cells and expand our knowledge of microtubule-stabilizing drugs that are important in cancer chemotherapy.

Late-breaking posters

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A phase I dose-escalation study of weekly IMC-1121B, a fully human anti-vascular endothelial growth factor receptor 2 (VEGFR2) IgG1 monoclonal antibody (Mab), in patients (pts) with advanced cancer

R. Cohen[2], D. Camidge[1], S. Diab[1], L. Gore[1], L. Chow[1], C. O'Bryant[1], E. Temmer[2], F. Fox[3], H. Youssoufian[3], S. Eckhardt[1]. *[1]University of Colorado Cancer Center, Denver, CO, USA; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]ImClone Systems Incorporated, Branchburg, NJ, USA*

Background: Anti-VEGFR2 antibodies are effective in a variety of preclinical leukemia and solid tumor models. IMC-1121B is a fully human anti-VEGFR2 IgG1 Mab.
Methods: Cohorts of 3–6 pts (ECOG PS ⩽2) with advanced cancer and no significant cardiovascular, thrombotic or bleeding disorders received escalating doses of IMC-1121B. A single initial dose with extended PK sampling was followed by 4 weekly infusions per treatment cycle starting at 2 mg/kg. 7 dose levels up to a maximum of 16 mg/kg are planned. Human anti-human antibodies (HAHA) directed against IMC-1121B were assessed at baseline and before each Week 4 dose. Tumor response was assessed every 2 cycles, and pharmacodynamic analyses were performed at baseline and post-dosing.
Results: 19 pts (13 M; 6 F), have entered the study at the first 4 dose levels: cohort 1 (2 mg/kg) n = 6, cohort 2 (4 mg/kg) n = 4, cohort 3 (6 mg/kg) n = 4, and cohort 4 (8 mg/kg) n = 5. Toxicities ⩾ grade 2 at least possibly or probably drug-related include anorexia, nausea, vomiting, back pain, groin pain, depression, fatigue, insomnia, emboli, anemia, proteinuria, hypophosphatemia, elevated transaminases and amylase. To date, there has been one confirmed partial response (melanoma), in total 5 pts have experienced stable disease for >6 months [colon (2), gastric, thyroid, melanoma]. No HAHA levels across cohorts 1–3 have been detected. Non-compartmental PK analysis reveals dose-dependent elimination and non-linear exposure, consistent with saturable clearance mechanism(s): mean $t_{1/2}$ = 63.6, 87.9, 176.8 hrs, mean C_{max} = 43.7, 80.3, 183.3 ug/mL, and AUC_{0-Inf} = 3860, 9135, 29953 hr*ug/mL, during Cycle 1 at the 2, 4, and 6 mg/kg dose levels, respectively. Target trough levels required for activity determined from preclinical xenograft studies have been achieved.
Conclusions: Weekly administration of IMC-1121B is well tolerated at doses up to 8 mg/kg/week. There is early evidence of clinical efficacy and a non-linear dose-PK relationship, and target trough levels predicted from xenograft studies have been observed. Dose escalation continues. Updated safety, PK, HAHA, and efficacy data will be presented.

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A phase I dose-escalation study of weekly IMC-A12, a fully human insulin like growth factor-I receptor (IGF-IR) IgG1 monoclonal antibody (Mab), in patients (pts) with advanced cancer

C. Higano[1], M. Gordon[2], P. LoRusso[3], F. Fox[4], T. Katz[4], J. Roecker[4], E. Rowinsky[4], H. Youssoufian[4]. *[1]Seattle Cancer Care Alliance, Seattle, WA, USA; [2]Premiere Oncology of Arizona, Scottsdale, AZ, USA; [3]Karmanos Cancer Institute, Detroit, MI, USA; [4]ImClone Systems Incorporated, Branchburg, NJ, USA*

Background: IMC-A12 is a fully human IgG_1 monoclonal antibody directed against the human insulin like growth factor-I receptor. A phase I trial evaluating the safety and maximum tolerated dose of IMC-A12 has been initiated in patients with refractory solid tumors who no longer respond to standard therapy or for whom no standard therapy is available.
Methods: 3–6 pts (ECOG PS ⩽2) with advanced cancer will be enrolled in each cohort. IMC-A12 is administered weekly for four infusions per treatment cycle starting at 3 mg/kg. Six dose levels up to a maximum of 27 mg/kg are planned. Human anti-human antibodies (HAHA) directed against IMC-A12 are assessed at baseline and before the Week 4 dose of each cycle.
Results: 9 pts (5 M; 4 F), median age 67 years (range: 44−70), have entered the study at two dose levels. Toxicities considered related to IMC-A12 are anemia (grade 1), psoriasis (grade 1), rash (grade 1), and hyperglycemia (grade 3). The hyperglycemia was considered a DLT and resulted in patient discontinuation. To date, 2 pts remain stable after >20 infusions of IMC-A12 (1 male pt with breast cancer and 1 pt with hepatocellular cancer), and two other pts (1 colon, 1 prostate) have demonstrated reductions in tumor markers. Non-compartmental PK analysis at the 3 mg/kg dose level reveals a mean $t_{1/2}$ of 111.3 hrs, mean C_{max} of 192 ug/mL, and mean AUC_{0-Inf} of 22266 hr*ug/mL. Target trough levels determined from preclinical xenograft studies have been achieved.
Conclusions: Weekly administration of IMC-A12 appears to be well tolerated. There is early evidence of clinical activity, and the PK profile is consistent with that of other Mab's. Dose escalation continues.

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Phase I trial of BB-10901 (huN901-DM1) given daily by IV infusion for three consecutive days every three weeks in patients with SCLC and other CD56-positive solid tumors

P. Lorigan[1], P.J. Woll[2], M. O'Brien[3], F.V. Fosella[4], S. Zildjian[5], S. Welch[5], H. Xie[5], Y. Clinch[5], K. Donaldson[5], R.J. Fram[5]. *[1]The Christie Hospital, Manchester, UK; [2]Weston Park Hospital, Sheffield, UK; [3]The Royal Marsden Hospital, Sutton, UK; [4]UT M.D. Anderson Cancer Center, Houston, USA; [5]ImmunoGen, Inc., Cambridge, USA*

Background: BB-10901 is an immunonconjugate created by conjugation of the cytotoxic maytansinoid drug DM1 to a humanized version of the murine monoclonal antibody N901. BB-10901 binds with high affinity to CD56, an antigen of the family of neural cell adhesion molecules. Once bound to CD56, the conjugate is internalized and releases DM1.
Methods: Subjects were enrolled with relapsed or refractory SCLC, other pulmonary tumors of neuroendocrine origin, non-pulmonary small cell carcinoma, metastatic carcinoid tumors or other CD56+ solid tumors.
Results: Thirty nine subjects were dosed with BB-10901. Subjects are dosed by IV infusion for 3 consecutive days every 3 weeks. Cohorts of 4 subjects initially were enrolled on each dose level. Subjects received BB-10901 at 4, 8, 16, 24, 36, 48, 60, and 75 mg/m^2/day. A dose limiting toxicity (DLT), severe headache, occurred in a patient treated with BB-10901 at 75 mg/m^2/day IV given over 40 minutes. Patients are being enrolled in a 75 mg/m^2/day cohort in which BB-10901 is given at 1 mg/min. Four patients have been treated without a DLT and an additional patient will be enrolled. Six patients had drug related serious adverse events (SAEs). The SAEs consist of constipation (1 patient, 16 mg/m^2/day), fatigue (1 patient, 16 mg/m^2/day), elevated amylase/pancreatitits (two episodes in a patient with evidence of metastases to the pancreas

treated at 24 mg/m^2/day), hypotension and myocardial infarction (1 patient, 48 mg/m^2/day), 1 patient was hospitalized with grade 2 constipation, fatigue, and leg pain (75 mg/m^2/day), and 1 patient had severe headache (75 mg/m^2/day over 40 min). There were no serious hypersensitivity reactions or evidence of HAHA or HADA formation. Pharmacokinetics demonstrate that plasma clearance values are greater at lower doses (<16 mg/m^2/day) consistent with saturation of CD56+ sites such as NK cells. A patient with relapsed, metastatic CD56+ Merkel cell carcinoma had a complete response lasting at least 15 weeks and remains in clinical remission after more than one year off therapy. Eight subjects had stable disease according to RECIST criteria lasting about 21(1 subject), 18 (1 subject), 12 (2 subjects), 9 (3 subjects), and 6 weeks (1 subject).
Conclusions: The study provides evidence of safety and clinical activity of BB-10901. The MTD is not yet defined and enrollment is ongoing. The dose intensity noted with the current regimen exceeds that of a prior weekly schedule.

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A Systems approach to identifying patient responders to EGFR-targeted therapy of colorectal cancer

B. Schoeberl, B. Harms, V. Grantcharova, E. Stewart, U. Nielsen.
Merrimack Pharmaceuticals, Cambridge, MA, USA

Colorectoral cancer is the third most common cancer worldwide and the fourth most common cause of cancer mortality. Colorectoral cancer has served as a model system for the development of several therapeutic monoclonal antibodies that fulfill the promise of targeted therapies. Cetuximab and panitumumab are monoclonal antibodies that prevent ligand binding to the epidermal growth factor receptor (EGFR). Both have proven effective as single agents in colorectal cancer. Increased EGFR expression has been reported to correlate with more aggressive disease, an increase of metastases and advanced tumor stage. However, measurement of EGFR expression as a method for identifying patients most likely to respond to treatment remains controversial and the overall response rates for patients who receive cetuximab, either as a monotherapy or in combination with irinotecan, are only 10.8% and 22.9% respectively (Frieze and McCune 2006). In this work we propose a Systems approach to identify patient responders to EGFR-targeted therapies such as cetuximab and panitumumab.
We have developed a data-driven mechanistic model of the ErbB signal transduction network comprising ErbB1 (EGFR/Her1), ErbB2 (Her2), ErbB3, ErbB4 and multiple EGF-like ligands. The model was developed based on signaling data from a cancer cell line (A431) using pErbB1, pErbB2, pAKT and pERK as readouts. We show that the model can be used to predict dynamic pERK and pAKT signaling behavior and to predict responses to EGFR inhibitors in several other cell lines. Based on our simulation data we have constructed a decision tree for identifying patients most likely to respond to cetuximab based on protein expression profiles.

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A Phase 1 dose escalation study of ARQ 197, a selective inhibitor of the c-Met receptor in patients with metastatic solid tumors

L. Rosen[1], A. Garcia[1], M. Mulay[1], C. Cunningham[3], J. Nemunaitis[3], N. Senzer[3], C. Li[4], A. Dovholuk[4], S. O'Keefe[2], R. Bukowksi[2], T. Mekhail[2].
[1]Premiere Oncology, Santa Monica, CA, USA; [2]The Cleveland Clinic Foundation, Cleveland, OH, USA; [3]Mary Crowley Medical Research Center, Dallas, TX, USA; [4]ArQule, Inc, Boston, MA, USA

ARQ 197 is a first-in-class selective inhibitor of the c-Met receptor tyrosine kinase, an oncogene that has been implicated in tumor invasiveness and metastasis, cancer cell proliferation, resistance to apoptosis, chemoresistance to chemotherapy and angiogenesis. The c-Met receptor tyrosine kinase is a high-affinity receptor for hepatocyte growth factor (HGF), also known as scatter factor. c-Met and HGF are dysregulated in a broad spectrum of human cancers, thus inhibitors of c-Met such as ARQ 197 could be promising targeted agents and deserve clinical investigation.
Therefore, in early 2006, a phase 1 dose escalation study in adult patients with metastatic solid tumors who had failed prior therapy was initiated to determine the safety, tolerability and recommended phase 2 dose (RP2D), pharmacokinetics, pharmacodynamics and preliminary antitumor activity of ARQ 197. A cycle consists of the twice-daily oral administration of ARQ 197 for two weeks followed by one week without therapy. Cycles will be repeated every 3 weeks (21 days) intervals until progression of disease, unacceptable toxicity, or another discontinuation criterion is met. As of August 28, 2006 thirty patients have been enrolled with data available for 18 patients (8M/9F; median age 64.8). Thus far seven cohorts have been assessed at doses ranging from 10 to 140 mg/day (140 to 1960 mg/cycle). The dose escalation has been well tolerated and no dose limiting toxicity has been observed. Adverse events (N = 15) have been generally mild with the most common being: diarrhea (33.3%), constipation (26.7%), dry mouth (26.7%), nausea (20.0%), vomiting (20.0%), fatigue (26.7%), dizziness (20.0%), and urinary tract infection (20.0%). Grade 3 or greater events include: abdominal pain (6.7%), elevated ALP (6.7%), elevated ALT (6.7%), elevated AST (6.7%), hypokalaemia (6.7%). No drug related serious adverse events were reported and, to date, neither MTD nor RP2D has been reached. Doses through 140 mg/day of ARQ 197 exhibited favorable pharmacokinetics. Signs of clinical efficacy include a confirmed partial response (PR) in the liver in a patient with metastatic prostate adenocarcinoma treated at the 80 mg dose level. The patient remains on study after 15 weeks of therapy. Seven patients have shown stable disease (6 to 30 weeks), of which two had minor tumor regression (10.1 and 19.2%). Prolonged stable disease (more than 16 weeks) was observed in neuroendocrine, NSLC, angiomyolipoma and pancreatic cancer.
In summary, initial dose escalation of ARQ 197 has been achieved without evidence of dose limiting toxicity and there are early signs of clinical antitumor activity. Enrollment and dose escalation is continuing and updated results will be presented.