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.

650 POSTER

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.

References

Frieze, D. A. and J. S. McCune (2006). Current status of cetuximab for the treatment of patients with solid tumors. Ann Pharmacother 40(2): 241−50.

651 POSTER

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.