for at least 4 cycles (1 cycle = 21 days) and 6 patients are still ongoing. A patient with gastric cancer (linitis plastica) and non-measurable disease by RECIST criteria experienced significant clinical benefit. Within 14 days of initiating therapy, drainage of ascites (0.5−1 L/day) via an indwelling peritoneal catheter ceased. CT scans after 2 cycles confirmed near complete resolution of ascites and a decrease in thickness of the gastric wall. Preliminary plasma PD analyses in all patients indicate significant modulations of HGF (decreased in 9/13) and VEGF (increased in 7/13) on Day 8 of Cycle 1.
Conclusions: Enhanced anti-tumor activity was observed when MGCD265 was combined with erlotinib in human xenograft models, including a NSCLC model resistant to EGFR inhibition. Clinical findings to date indicate that MGCD265 can be safely combined with erlotinib and preliminary signs of activity and plasma PD changes were observed. Dose escalation is ongoing.

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MGCD265, an orally active Met/VEGFR multitargeted kinase inhibitor, in combination with docetaxel: clinical and preclinical experience

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Background: MGCD265 is a novel, orally available and potent inhibitor of Met, Ron, VEGFR1/2/3 and Tie-2. The importance of Met overexpression in regulating the growth of several epithelial malignancies, including NSCLC, is increasingly recognized. Taxanes are commonly used in NSCLC and other multiple malignancies. The benefit of combining MGCD265 with docetaxel is being investigated.
Material and Methods: Anti-tumor activity of MGCD265 in combination with taxanes has been evaluated in multiple xenograft models including NSCLC models. In addition, the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and the potential clinical benefit of MGCD265+docetaxel is being evaluated in patients with advanced tumors in a phase I study (as part of a phase II NSCLC program) using the 3+3 design. MGCD265 is administered daily (doses ranging from 96 to 144 mg/m^2) and docetaxel is administered intravenously once every 3 weeks (doses ranging from 50 to 75 mg/m^2).
Results: Preclinical xenograft studies indicated that the combination of MGCD265 with docetaxel or paclitaxel achieved greater antitumor responses than treatment with either agent alone and was observed in the absence of overt toxicity. To date, in the ongoing phase I clinical trial, 15 patients have been recruited. Safety evaluations indicate that MGCD265 can be combined with full dose docetaxel. No DLTs have been observed to date. Five patients (33%) have been treated for more than 4 cycles (1 cycle = 21 days) and 6 patients are still ongoing. Among the ongoing patients are 4 patients with NSCLC. Their current treatment duration ranges from 18 to 40 weeks, all exceeding the expected TTP of ~12 weeks for 2nd line NSCLC patients treated with docetaxel. All 4 NSCLC patients exhibited tumor shrinkage including a PR in one patient. Eight patients (53%) with a diagnosis other than NSCLC discontinued due to PD after 2 cycles or less. PK data indicate no drug-drug interaction, consistent with preclinical findings. Preliminary plasma PD analyses indicate significant modulations of HGF (decreased in 7/12 patients) and VEGF (increased in 9/12) after the first cycle.
Conclusions: Preclinical xenograft data and preliminary clinical data, especially in NSCLC, indicate the potential for increased benefit in combining MGCD265 with docetaxel. In addition, plasma markers show significant modulation when these two drugs are combined. Dose escalation is ongoing.

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Phase 2 results of XL184 in a cohort of patients (pts) with advanced non-small cell lung cancer (NSCLC)

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Background: XL184 is an oral, potent inhibitor of MET, VEGFR2 and RET. Inhibition of angiogenesis with agents targeting VEGF has demonstrated clinical benefit in pts with advanced NSCLC. Expression of MET and/or its ligand HGF has been associated with poor survival. Co-targeting of the MET and VEGF signaling pathways using XL184 may therefore be a promising treatment strategy in pts with NSCLC. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with NSCLC.
Methods: NSCLC pts of all histological subtypes with advanced disease who failed up to 3 prior systemic treatments are eligible for this study. XL184 is administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response per mRECIST is assessed every 6 wks. Pts with partial or complete response (PR or CR) at week (wk) 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184. Pts with stable disease (SD) at wk 12 are randomized 1:1 to receive XL184 or placebo. Cross-over from placebo to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage.
Results: A total of 36 pts have been enrolled with a median age of 67 years (43% adenocarcinoma, 39% squamous carcinoma, 9% large cell carcinoma, and 9% other). The median number of prior systemic treatments was 2. Eleven pts were previously treated with an anti-VEGF pathway agent and 6 pts with an anti-EGFR agent. Of the 20 pts who were evaluable (minimum 12 wks follow up) to date, 2 pts achieved a PR, and 8 pts achieved SD and were randomized. The overall disease control rate was 50% at wk 12. One pt previously treated with sunitinib showed a 61% tumor decrease at wk 12. One pt previously treated with platinum-based chemotherapy and an EGFR inhibitor showed a 32% tumor decrease. Most frequently observed adverse events regardless of causality with CTCAE Grade $\geqslant$3 in the Lead-in Stage include diarrhea, fatigue, asthenia, and pain in extremity (each n = 2).
Conclusions: Preliminary results suggest that XL184 has single agent activity in pts with advanced NSCLC who failed multiple prior systemic therapies. XL184 was generally well tolerated. Updated efficacy and safety results will be presented.

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Phase 2 results of XL184 in a cohort of patients (pts) with advanced melanoma

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Background: XL184 is an oral, potent inhibitor of MET, VEGFR2 and RET. MET has been demonstrated to be overexpressed and activated in melanoma and is implicated in tumor cell proliferation and invasion. VEGF and VEGFR2 were shown to be overexpressed in melanoma with VEGFR2 being particularly elevated in metastatic specimens. Co-targeting of the MET and VEGF signaling pathways using XL184 may therefore be a promising treatment strategy. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with melanoma.
Methods: Melanoma pts of all subtypes with advanced disease who failed up to 2 prior systemic treatments are eligible for this study. XL184 is

administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response per mRECIST is assessed every 6 wks. Pts with partial or complete response (PR or CR) at week (wk) 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184. Pts with SD at wk 12 are randomized 1:1 to receive XL184 or placebo. Cross-over from placebo to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage.
Results: A total of 45 pts have been enrolled with a median age of 66 years (M/F 51%/49%). The median number of prior systemic treatments was 1. Of the 24 pts who were evaluable (minimum 12 wks follow up) to date, 1 pt achieved a PR, and 11 pts achieved SD and were randomized. The overall disease control rate was 50% at wk 12. One pt with cutaneous melanoma previously treated with single agent chemotherapy showed a 40% tumor decrease at wk 12. Most frequently observed adverse events regardless of causality with CTCAE Grade $\geqslant$3 in the Lead-in Stage include hypertension, constipation, and vomiting (each n = 2).
Conclusions: Preliminary results suggest that XL184 is active in pts with advanced melanoma who failed prior treatment. XL184 was generally well tolerated. Updated efficacy and safety results will be presented.

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Why is rapamycin effective against Kaposi sarcoma? An analysis of molecular pathways reveals epigenetic silencing of PTEN

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Background: Rapamycin (RAPA)/Sirolimus™ and its derivatives target the mTOR kinase within the PI3K/Akt/mTOR pathway. RAPA treatment has led to regression of transplant-associated Kaposi sarcoma (KS), but it is unclear why this cancer and selected others are responsive to mTOR inhibitors, whereas many others are not. KS is associated with the Kaposi sarcoma associated herpesvirus. We hypothesized that because of its viral etiology, the PI3K/Akt/mTOR pathway in KS would be activated post-translationally rather than by mutation and thus more responsive to small molecule inhibitors.
Material and Methods: The AMC conducted a pilot study of RAPA in HIV-associated KS and observed several partial responses. We used immuno-histochemistry and molecular methods to study the PI3K/Akt/mTOR pathway in sequential biopsies from patients on this trial, as well as an HIV-KS TMA, KS cell lines and tumors from KS mice treated with RAPA.
Results: RAPA inhibited mTORC1 signaling in HIV-KS patients as determined by loss of S6 phosphorylation. Akt was consistently activated and we saw no changes in phosphorylation at either the mTORC-independent S308 or mTORC2-dependent T473, i.e. there was no evidence for compensatory upregulation of mTORC2. We also sequenced PTEN in a series of KSHV-associated lymphomas and found no evidence of mutation or deletion. Rather these lymphomas, as well as the KS biopsies we investigated exhibited high levels of phospho-PTEN.
Conclusions: Rapamycin inhibits the mTORC1 pathway in HIV-KS. KS is representative of tumor types in which PTEN is epigenetically inactivated and it is perhaps these tumor types, which are most susceptible to mTOR inhibitors.

400 POSTER

Phase I study of JI-101, a novel oral tyrosine kinase inhibitor that selectively targets EphB4, VEGFR2, and PDGFRβ

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Background: Ephrin type-B receptor 4 (EphB4) and its ligand, ephrin B2, are involved in endothelial cell interaction. EphB4 is required for forming capillary networks during angiogenesis. Overexpression of EphB4 in certain tumors (head and neck, melanoma, ovarian, breast, colorectal, prostate) also supports its therapeutic targeting potential. JI-101 is highly selective for angiogenic kinase targets EphB4, VEGFR2, and PDGFRβ and has shown excellent *in vivo* antitumor activity.
Materials and Methods: A phase I study was conducted in patients with advanced solid tumors to determine safety and MTD of JI-101 and to evaluate once daily vs. twice daily dosing. Each cycle consisted of 28 days of oral dosing with a starting dose of 100 mg. A continuous reassessment method was used to guide dose escalation. 5 cohorts were studied: once daily doses of 100 mg, 200 mg, 400 mg and twice daily doses of 200 mg, 300 mg.
Results: 18 patients enrolled – once daily: 3 at 100 mg, 3 at 200 mg, 4 at 400 mg; twice daily: 6 at 200 mg, 2 at 300 mg. The 200 mg twice daily cohort was expanded for safety after 300 mg twice daily produced dose-limiting grade 3 fatigue. Other grade 3 toxicities were hypertension requiring medical management (across all doses), hand foot syndrome (2), and proteinuria (1). No significant mouth sores, rash, or diarrhea were seen. Two patients are completing early cycles but of the remaining 16 patients, 4 were on study for >6 months with 2 patients continuing at cycle 11 and 12. The MTD is 200 mg twice daily. Pharmacokinetic data is being analyzed and will be presented.
Conclusions: JI-101 was well-tolerated and produced prolonged stable disease in 25% of patients thus far. Studies planned: drug interaction study to determine pharmacokinetics of the combination of JI-101 and everolimus and pharmacodynamic study of JI-101 to determine objective response as measured by imaging studies and to assess EphB4 modulation in tumor biopsies and blood samples in patients with refractory head and neck cancers, ovarian cancers and KRAS mutant colon cancers.

401 POSTER

Evaluation of pharmacokinetics and safety of bosutinib in patients with chronic hepatic impairment and matched healthy subjects

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Background: Bosutinib (SKI-606), a dual inhibitor of Src and Abl tyrosine kinases, is being developed for the treatment of chronic myelogenous leukemia. Oral bosutinib 500 mg daily has shown clinical efficacy in patients with Philadelphia chromosome-positive chronic myelogenous leukemia (CML) (Cortes et al. Blood 112:1098, 2008). The objective of the current study was to evaluate the pharmacokinetics (PK) and safety of bosutinib in patients with chronic hepatic impairment (HI) and in matched healthy subjects.
Methods: This was an open-label, single-dose, parallel-group study conducted in patients with chronic HI (Child-Pugh classes A, B, and C with 6 patients in each class) and healthy subjects (n = 9) matched by sex, age, BMI and, if possible, smoking habit. All individuals received a single oral dose of bosutinib 200 mg immediately after a standard breakfast. Plasma from blood samples obtained through 96 hours postdose (and at the follow-up visit that occurred 192 to 264 hours postdose) were analyzed for bosutinib by liquid chromatography/tandem mass spectrometry. Bosutinib concentrations were analyzed using noncompartmental methods with WinNonlin. A 1-factor analysis of variance was used to compare PK parameters (healthy vs Child-Pugh classes A, B, C), and 90% confidence intervals (CIs) were obtained for the ratio of least squares geometric means (LSGM).
Results: 27 individuals aged 37–65 years enrolled. Following oral administration of bosutinib 200 mg, C_{max} and AUC, respectively, increased 2.42-fold and 2.25-fold in Child-Pugh class A, 1.99-fold and 2.0-fold in Child-Pugh class B, and 1.52-fold and 1.91-fold in Child-Pugh class C patients compared with values in healthy subjects. Bosutinib oral clearance decreased in HI patients compared with values in healthy subjects. Median t_{max} was decreased and $t_{1/2}$ was increased in HI patients. Bosutinib was highly plasma protein bound; the degree of binding was similar between HI patients and healthy subjects, suggesting no effect of HI on the plasma protein binding of bosutinib across varying degrees of HI (Child Pugh A, B, C). Thirteen (48.1%) individuals had $\geqslant$1 adverse event (AE), most commonly prolonged QT interval (n = 10, 37.0%), nausea (n = 3, 11.1%), and vomiting (n = 2, 7.4%). The incidence of QTc interval prolongation increased with declining liver function and was not related to plasma bosutinib concentrations. QTc observations in patients with liver disease in this uncontrolled study likely reflect well-known effects of the underlying condition. No serious AEs or AE-related discontinuations occurred.
Conclusions: Following a single oral dose of bosutinib 200 mg in patients with HI (Child–Pugh classes A, B, and C), mean bosutinib exposures increased approximately 2-fold compared with values in healthy subjects, with similar increases across Child-Pugh classes. Bosutinib showed acceptable tolerability in both HI and healthy subjects.