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