tissue (1) and sinonasal (1). Dose-limiting toxicities (DLTs) were assessed in 12 patients (2 pts at 20 mg/m^2 were excluded due to skipping of the second dose). 1 DLT (Gr 3 gamma-GTP increased for >7d) occurred at 20 mg/m^2. All patients experienced thrombocytopenia, and in 3 patients, it reached Gr 4 (1 at 15 mg/m^2 and the others at 20 mg/m^2) in cycle $\geqslant$2, and 2 pts required platelet transfusion. Generally, platelet counts recovered quickly without any special treatment, and almost grade 3 or 4 events recovered to grade 1 or less within 8 days. Pts enrolled at the 20 mg/m^2 cohort with baseline platelet counts <200K/mm^3 required dose delay or interruption during cycle 1, but those with higher baseline platelet counts did not. Other common toxicities were leukopenia, neutropenia, fatigue, and anorexia. PK was almost linear within the dose range examined with $T_{1/2}$ of 20 to 40 hr and systemic clearance of 40 to 60 L/hr. As efficacy outcome, SD was seen in 7/14 patients. The longest duration of exposure was 408d for the tongue cancer pt. Additional exploratory correlation analyses between the platelet reduction ratio on d7 as compared to baseline with LBH589 dose and PK parameters were performed. It was suggested that the platelet reduction ratio might be positively correlated with initial LBH589 dose, C_{max} and AUC.

Conclusions: By the time the 20 mg/m^2 cohort was completed in this trial, the parallel Western trial had established that a dose of 25 mg/m^2 was not tolerable. Therefore, in the interests of patient safety, the decision was made not to explore doses higher than 20 mg/m^2, and to declare 20 mg/m^2 the recommended phase II starting dose for Japanese pts. Pts with low baseline platelet counts should be closely monitored and considered for dose interruption and reduction as indicated.

393 POSTER

Phase I pharmacokinetics and pharmacodynamics of GDC-0152, a novel IAP protein antagonist, administered to patients with locally advanced or metastatic malignancies

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GDC-0152 is a small molecule that selectively antagonizes the inhibitor of apoptosis (IAP) proteins. IAP antagonists promote cell death via effects on both intrinsic and extrinsic pathways of apoptosis. Study IAP4050g is a phase Ia, open-label, multicenter, standard dose-escalation study (3 + 3 design) of GDC-0152 in patients with locally advanced or metastatic solid malignancies or non-Hodgkin's lymphoma without leukemic phase. The study has evaluated nine GDC-0152 doses, 0.049, 0.1, 0.2, 0.28, 0.39, 0.54, 0.76, 1.06 and 1.48 mg/kg, administered by 30-minute IV infusion once every 14 days. Plasma samples were collected at predetermined serial time points during the first two cycles. PK profiles have been obtained for the 36 evaluable patients enrolled in the first 9 cohorts. The plasma concentration-time data were analyzed using non-compartmental PK analysis (WinNonlin®, Pharsight Inc.,Mountain View, CA). The plasma concentrations of GDC-0152 declined tri-exponentially with a mean terminal elimination half-life of 4 hours. Exposures (AUC_∞) of 2580 ng·hr/mL (n = 3) and 3400 ng·hr/mL (n = 1) were achieved at doses of 1.06 mg/kg and 1.48 mg/kg, respectively. The between-patient variability in the key PK parameters, clearance and distribution volume was moderate (33.2% and 40.6%, respectively). In general, the exposures (AUC) increased in proportion to the dose during the studied dose range (0.049–1.48 mg/kg). Plasma samples were also collected for exploratory cytokine/chemokine protein analysis for identification of a potential pharmacodynamic biomarker. The plasma samples were analyzed by Luminex® human antigen multi-analyte profile assay (Rules Based Medicine, Austin,TX). To date, no-dose-dependent increases in plasma MCP-1, a chemokine elevated in plasma from preclinical studies with higher drug exposure, have been observed in a subset of patients through cohort 9. In summary, GDC-0152 exhibited dose-proportionality in exposure and no effect on the PD biomarker in the tested dose range.

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A phase I dose escalation and pharmacological study of the novel class I selective histone deacetylase inhibitor CHR-3996, in patients with advanced or treatment refractory solid tumours

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Background: CHR-3996 is an orally bioavailable HDACi that inhibits HDAC 1, 2 and 3 at low nanomolar concentrations, with pleiotropic activity against a range of human cancer cells *in vitro*. The efficacy of CHR-3996 has been established in xenograft (mouse) models of colorectal (HCT116, LoVo) and pancreatic (MiaPaCa) cancer.

Methods: This was a dose escalation study of once daily orally administered CHR-3996 (5–160 mg) in a standard 3 + 3 design in patients (PS $\leqslant$ 2) with histologically confirmed advanced solid tumors refractory to standard therapy. Patients were treated for 28 days (the dose finding phase) and could remain on therapy until evidence of PD or unacceptable toxicity. PK samples were taken from all patients on Day 1 and Day 28 of the first cycle. Acetylated lysine in PBMCs from all patients was measured using an ELISA, while histone acetylation in hair follicles was assessed with confocal microscopy.

Results: 29 patients (median age 56 years [range 24−77], 21M/8F) have been enrolled. Dose levels studied were 5, 10, 20, 40, 80, 160 and 120 mg (in 3, 4, 3, 7, 4, 5 and 3 patients respectively). At 160 mg DLT was observed consisting of two episodes of short lasting and uncomplicated thrombocytopenia G4. At 120 mg DLT has been observed in a single patient (inability to tolerate a complete cycle of treatment), and 3 additional patients are being enrolled at 120 mg. Observed drug related toxicities (all grades) included fatigue (44%), nausea (44%), vomiting (26%), anorexia (15%), and thrombocytopenia (11%). 22 patients continued CHR-3996 after day 28. PK parameters (Cmax and AUC0-t) showed dose proportionality across the range 5 − 160 mg. A partial response was seen at 160 mg in one patient with an acinar pancreatic carcinoma, and stable disease for $\geqslant$ 3 months (range 3−10 months) was observed in 7 other patients.

Conclusions: Once daily oral CHR-3996 was well tolerated and MTD is currently defined at 160 mg. Plasma concentrations of CHR-3996 achieved in this trial exceed the concentrations required for anti-tumor efficacy in preclinical models, in the absence of significant toxicity. Assessment of histone acetylation as a pharmacodynamic biomarker in PBMCs and hair follicles confirmed intracellular drug activity in most patients. 29 subjects have been treated to date, with one partial response and 7 stable diseases recorded, hinting at clinical activity of CHR-3996.

395 POSTER

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

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Background: MGCD265 is an oral multitargeted receptor tyrosine kinase (RTK) inhibitor that targets Met, VEGFR 1/2/3, Tie-2, and Ron. Although Met can be an oncogenic driver on its own, its functional interactions with other key RTKs such as EGFR, has become central to oncogenesis. Met and EGFR are coexpressed and functionally cooperate to amplify activating signals in cancer cells. Moreover, in NSCLC, Met gene amplification or overexpression of HGF was identified as a molecular mechanism through which tumors escape EGFR inhibition. These data provide a compelling rationale for concomitantly inhibiting Met and EGFR.

Material and Methods: The anti-tumor activity of MGCD265 in combination with erlotinib was evaluated in multiple xenograft models. In addition, a phase I study (as part of a phase II NSCLC program) using the 3 + 3 design is currently ongoing to evaluate the safety, tolerability, pharmacodynamics (PD), pharmacokinetics (PK) and potential benefit of MGCD265+erlotinib in patients with advanced tumors.

Results: Improved anti-tumor activity was observed when MGCD265 was combined with erlotinib in several human xenograft models including a NSCLC model resistant to erlotinib (EGFR T790M mutation). To date, in the ongoing clinical trial, 19 patients have been enrolled. MGCD265 daily doses ranged from 96 mg/m^2 to 144 mg/m^2 in combination with erlotinib at 100 to 150 mg daily. Safety evaluations indicate that MGCD265 can be combined with full dose of erlotinib. Nine patients (47%) were on study

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