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. Pharmacokinetics of XL184 will be analyzed in this hepatically impaired patient population.
Results: A total of 12 pts have been enrolled with a median age of 65 years (M/F 64%/36%). The median number of prior systemic treatments was 1 with 7 pts having received sorafenib. Of the 7 pts who were evaluable (minimum 12 wks follow up) to date, 2 pts achieved a PR and 5 pts achieved SD with radiological evidence of tumor shrinkage. The overall disease control rate at wk 12 was 88%. One pt previously treated with sorafenib showed a 42% tumor decrease at wk 12. Three pts with SD had an AFP reduction of more than 50% at wk 12. The overall dose reduction rate for pts on study for at least 6 wks was 67%. Most frequently observed adverse events regardless of causality with CTCAE Grade $\geqslant$3 in the Lead-in Stage include diarrhea (n = 2), nausea, fatigue, thrombocytopenia, vomiting, anemia, blister, blood magnesium increased, dehydration, epistaxis, and hypoglycemia (each n = 1).
Conclusions: Preliminary results suggest that XL184 is active in pts with advanced HCC, including those previously treated with sorafenib. Updated efficacy and safety results will be presented.

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The novel, investigational Nedd8-activating enzyme inhibitor MLN4924 in patients with metastatic melanoma: a phase 1 study

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Background: Metastatic melanoma is associated with poor prognosis; new agents with improved efficacy are needed. The investigational agent MLN4924 is a novel small-molecule inhibitor of Nedd8-activating enzyme (NAE); NAE inhibition prevents the proteasomal degradation of proteins with roles in cell cycle progression (p27), DNA damage (Cdt-1), stress response (Nrf-2), and signal transduction (pIκBα). MLN4924 is active in preclinical models of several tumor types; in patients, pharmacodynamic responses of elevated Cdt-1 and Nrf-2 levels have been seen in post-treatment skin biopsies (Kauh *et al*, ASCO 2009). The primary objectives of this study were to determine the safety profile and maximum tolerated dose (MTD) of MLN4924 in patients with metastatic melanoma.
Materials and Methods: Patients aged $\geqslant$18 years with ECOG performance status 0−2 were treated with 1-hour intravenous infusions of MLN4924 on days 1, 4, 8, and 11 of 21-day cycles. Dose escalation, starting at 50 mg/m^2 and using 1.33-fold increments, proceeded via a Bayesian continual reassessment method based on occurrence of dose-limiting toxicities (DLTs) in cycle 1. The primary endpoint included adverse events (AEs). Secondary endpoints included antitumor activity, and the pharmacokinetics (PK) and pharmacodynamics of MLN4924.
Results: To date, 12 patients (8 male; median age 55.5 years, range 34−71; median 2 prior therapies, range 0−5) have been enrolled to 5 dose levels: 50 (n = 2), 67 (n = 2), 89 (n = 2), 118 (n = 4), and 157 mg/m^2 (n = 2). One DLT, of MLN4924-related grade 3 hypophosphatemia (118 mg/m^2 dose level), has been recorded to date; the MTD has not been reached. Patients have received a median of 2 cycles (range 0 to 7+). AEs have been mostly mild/moderate (grade 1/2); the most common include nausea (n = 6), fatigue (n = 5; 2 grade 2), myalgia (n = 4), and diarrhea, pruritus, anorexia, and muscle spasms (each n = 3; 1 grade 2 anorexia). Two grade 3 AEs have been reported of cancer-related pain and transient hypophosphatemia. Six patients have discontinued due to progressive disease (1 died). One patient with brain metastases, who had received 4 prior lines of therapy, remains in stable disease after 7 cycles (67 mg/m^2 dose level). Preliminary evidence for shrinkage/softening of subcutaneous nodules has been seen in 2 patients.
Conclusions: MLN4924 was well tolerated at the current dosing schedule, and encouraging antitumor activity has been observed. Accrual and dose escalation continues. Updated safety and efficacy data, plus PK and pharmacodynamic data, will be presented.

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Vandetanib, docetaxel and carboplatin followed by maintenance vandetanib or placebo in patients with stage IIIB, IV or recurrent non-small cell lung cancer (NSCLC): a randomized phase II study (PrE0502) by PrECOG, LLC (NCT006872970)

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Background: The goal was to determine if vandetanib, a dual inhibitor of the VEGF and EGFR pathways, could improve progression-free survival (PFS) in patients (pts) with NSCLC when given as induction therapy (tx) with docetaxel and carboplatin, followed by maintenance tx, compared to maintenance placebo.
Materials and Methods: Pts with advanced stage NSCLC were randomized to receive induction docetaxel (75 mg/m^2) + carboplatin (AUC 6) on day 1 of a 21-day cycle and daily vandetanib (100 mg/day po) for 4 cycles, followed by maintenance tx with either daily vandetanib (300 mg/day po) or placebo until progression. The study was designed to demonstrate improvement in PFS with the addition of vandetanib to a median of 6.2 mos, compared to historical control median of 4.5 mos for docetaxel + carboplatin alone. Eligible pts had measurable disease per RECIST, ECOG PS 0 or 1, and no prior cytotoxic or targeted tx for advanced disease. Pts with cardiac conditions including uncontrolled hypertension or history of QT prolongation were ineligible.
Results: 162 pts were randomized between May 2008 and December 2009, of whom 158 received tx. 87% of pts had stage IV/recurrent disease; 52% were male. Median age was 63 (range 36−82). A median of 2 cycles of induction tx were given. Sixty pts received maintenance txw/placebo (median 2 cycles). Tx was discontinued primarily for progression (38%/65% for induction and maintenance) and adverse events (AE) (28%/23%). Common AEs included fatigue, dyspnea, diarrhea, dehydration, neutropenia, neutropenic fever, and leukopenia. Death on tx were reported for 19 pts, 11 from progressive disease. Neither arm demonstrated significant improvement over the historical median PFS of 4.5 mos. Median PFS among pts randomized to maintenance vandetanib was 5.3 mos (95% CI, 3.2−6.5 mos), while median PFS among pts randomized to maintenance placebo was 4.6 mos (95% CI, 2.8−4.9 mos, stratified logrank p = 0.04).
Conclusions: Although neither arm met the primary endpoint over historical control, pts randomized to vandetanib maintenance had longer PFS compared to pts randomized to placebo maintenance.

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A phase I trial of the histone deacetylase inhibitor panobinostat (LBH589) and epirubicin in patients with solid tumor malignancies

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Background: Preclinical and clinical data suggest that pre-exposure of cancer cells to a histone deacetylase inhibitor (HDACi) potentiates topoisomerase (topo) inhibitors. The HDACi-induced histone acetylation and chromatin modulation facilitates DNA access and target recruitment for topo II inhibitors. In vitro data further suggest that effective inhibition of HDAC2 is necessary for enhanced epirubicin-induced apoptosis.
Materials/Methods: This phase I trial explores the safety, tolerability, and maximum tolerated dose (MTD) of escalating doses of panobinostat given orally on days 1, 3, and 5 followed by epirubicin administered intravenously at 75 mg/m^2 on day 5 in 21-day cycles. Histone acetylation and HDAC2 expression are evaluated in pre- and post-treatment peripheral blood mononuclear cells in all patients and in tumor cells of 12 patients treated at the MTD.
Results: The trial enrolled 20 patients [5M/15F, median age 49 years (range 24−80)] in 5 panobinostat cohorts: 20, 30, 40, 50, and 60 mg. The MTD was identified as 50 mg panobinostat. Tumor types included melanoma (n = 6), breast (n = 3), sarcoma (n = 3), ovarian (n = 2), lung (n = 2), and one each of neuroblastoma, pancreatic, testicular, and colon cancer. Dose-limiting toxicities included 1/6 patient with a grade 3 atrial fibrillation in the 50 mg cohort and 2/3 patients in the 60 mg cohort with DLT, one with grade 3 fatigue and one with grade 4 thrombocytopenia. Non-dose-limiting grade 3 and 4 toxicities include neutropenia (n = 12, 60%), thrombocytopenia (n = 4, 20%), and anemia (n = 3, 15%). One patient with small cell lung cancer has an unconfirmed partial response, one patient each (melanoma, ovarian, neuroblastoma) demonstrated stable disease for