pneumonitis in 1/6 p at 60 mg, and two reversible G4 thrombocytopenias in 2/6 p treated at 400 mg. The MTD was established at 300 mg. Other MK-4827 related G1−2 reversible adverse events included fatigue, anorexia, nausea and myelosuppression. Dose proportional PK was observed with a mean terminal $t_{1/2}$ of 40 hours (range 37−42 hours). PD studies confirmed PARP inhibition in peripheral blood mononuclear cells at doses of ⩾80 mg. Antitumor responses were observed in both sporadic and BRCA-mutation associated (BRCA-MA) cancers. There have been 9 p with partial responses (PR) (8 confirmed, 7 ovarian, 2 breast, 8/9 BRCA-MA cancers, 8/9 with ongoing treatment), and 4 p with stable disease (SD) (2 ovarian, 2 NSCLC, 2/4 BRCA mutation carriers, 1/4 with ongoing treatment) ⩾120 days. PRs have ranged from 46–357 days and SD from 136–354 days.
Conclusions: MK-4827 was well tolerated, had linear PKs, evidence of target modulation, and promising antitumor activity. Specific cohort expansions are ongoing. Evidence of both PARP blockade and antitumor activity in both BRCA-MA and sporadic cancer has been observed.

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Dose of the molecularly targeted agents (MTA) in Phase 1 trials correlates with clinical benefit

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Introduction: The primary objective of phase 1 trials to date has been to safely select the maximum tolerated dose (MTD) of a drug or drug combination for utilization in subsequent trials. Conventional cytotoxic chemotherapy is generally more effective at the MTD. Recent single-institution data suggests that the novel MTAs may not require a MTD for efficacy. We analyzed patient (Pt)outcome results in MTA Phase 1 trials at multiple institutions throughout North America sponsored by the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (CTEP).
Methods: Data on Pts treated on monotherapy phase I trials investigating novel MTAs with a defined MTD, from 2001–2009, were collected and analyzed retrospectively. Pts were grouped into 6 cohorts depending upon the dose of best response [(complete response (CR), partial response (PR) or stable disease (SD)] as a percentage of the final identified MTD for the drug (<20%, 21−40%, 41−60%, 61−80%, 81–100%,>100%). Outcomes including response rates, overall survival and toxicity were compared. Logistic regression analysis was used to test whether there was an increase in the probability of a response as dose increased. A Cox proportional hazards model was used to determine if survival increased with increasing dose.
Results: A total of 1908 Pts treated on 53 eligible clinical trials were analyzed. Median Pt age was 61 (range: 16−93), with 59% males and 41% females and median number of prior treatments was 3 (range: 1−16). Distribution of Pts according to dose levels was as follows: <20% MTD = 93 pts, 21−40% MTD = 213 pts, 41−60% MTD = 263 pts, 61−80% MTD = 310 pts, 81–100% MTD = 508 pts and >100% MTD = 344 pts. Non-progression rates (NPR) defined as CR, PR or SD at first assessment, 3 months and 6 months was 44%, 26% and 11% respectively. The probability of both overall response (CR+PR) or NPR increases with increasing dose, p = 0.10 and p = 0.24 respectively after controlling for study influences. Overall survival also increased with increasing dose, p = 0.041.
Conclusions: Pts treated in the context of phase 1 trials with MTAs continue to derive reasonable clinical benefit. Contrary to other single institution data, our results suggest that the potential clinical benefit in terms of overall response, non-progression rate and overall survival significantly correlates with the administered dose level, with increasing benefit for patients treated at doses at or near the MTD.

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The first-in-human, first-in-class study of CUDC-101, a multi-targeted inhibitor of HDAC, EGFR, and HER2: A Phase I study in patients with advanced cancer

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Background: CUDC-101 is a synthetic small-molecule, first-in-class, multi-targeted inhibitor of both receptor tyrosine kinases (RTK), EGFR and HER2, and class I/II HDACs. Along with these direct effects, CUDC-101 also indirectly attenuates the survival signaling pathways Akt, HER3, and MET. Through this inhibition of multiple signaling networks, CUDC-101 effectively suppresses the growth of a broad range of tumor types both *in vitro* and *in vivo*,, including RTK-resistant cell lines.
Material and Methods: This phase I dose-escalation study assessed the safety and tolerability of CUDC-101 to determine the maximum tolerated dose (MTD). The pharmacokinetics (PK), pharmacodynamic (PD) biomarkers and preliminary efficacy were also investigated. Dosing was IV infusion over 1 hr on Days 1−5 of each 14 day treatment cycle. PD measurements included histone acetylation in PBMCs and EGFR, HER2 inhibition in paired skin and tumor biopsies. Tumor response was evaluated by RECIST.
Results: 25 pts (11M/14F, median age 60 [range 37−79], median prior systemic regimens: 3 [range 2−11]) with advanced solid tumors received CUDC-101 at 1of 5 dose levels (75–300 mg/m^2). Frequent tumor types included breast (24%), lung (16%), and head and neck cancers (16%). Dose-limiting-toxicities in cycles 1−2 occurred in 3 pts at 300 mg (elevated creatinine, n = 2; pericarditis, n = 1) both were transient and reversible. MTD was determined to be 275 mg/m^2. The most frequent adverse events were nausea (24%), fatigue (20%), vomiting (20%), dyspnea (20%), pyrexia (16%), and dry skin (16%), being Grade 1/2 in severity. CUDC-101 exposure increased linearly in the range of 75–300 mg/m^2, with a half life of ~2.5 hrs and AUC of 10368 hr*ng/mL at the 275 mg/m^2 dose. PD changes are currently being investigated. One confirmed partial response was achieved in a gastric cancer pt (at 275 mg/m^2) and stable disease of >3 months was seen in one pt with refractory breast cancer (150 mg/m^2). Two additional subjects (salivary gland adenocarcinoma and tongue squamous cell carcinoma) exhibited anti-tumor activity with a decrease of >20% in target lesions.
Conclusions: CUDC-101 exhibited a favorable safety and PK profile up to doses of 275 mg/m^2. Continued clinical development of CUDC-101 is supported by the early evidence of anti-tumor activity observed in this trial. An expansion phase at the MTD in specific tumor types is proposed to seek additional signals of activity and to explore alternative dosing schedules.

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First-in-human, safety, pharmacodynamic (PD) and pharmacokinetic (PK) trial of a first-in-class dual RAF/MEK inhibitor, RO5126766, in patients with advanced or metastatic solid tumour

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Background: Among the signaling pathways most frequently deregulated in human cancer is the Ras-Raf-MEK-extra-cellular signal-regulated kinase 1 and 2 (ERK1/2) pathway. RO5126766, a first-in-class dual Raf/MEK inhibitor, is being tested in a phase I (P1) study. Objectives were determination of maximum tolerated dose (MTD), dose limiting toxicities (DLTs), safety/tolerability, pharmacokinetics (PK)/pharmacodynamics (PD) and preliminary clinical activity (RECIST criteria).
Patients and Methods: Patients (pts) with advanced or metastatic solid tumors received oral RO5126766 administered on a continuous daily dosing schedule (QD) in 28 days cycles. PK and blood PD samples (PBMCs) were collected after a single dose (run-in) and cycle 1 day 15 (C1D15). Paired skin and tumor biopsies (baseline, C1D15) and sequential FDG-PET scans (baseline, C1D15, and C3D1) were taken. To increase activity window, 3 intermittent regimens, 4 days on/3 days off (4/3), 7 days on/7 days off (7/7) and once a week (QW), are currently being tested.
Results: 38 pts (25 QD, 7 4/3 and 6 7/7) in 12 cohorts (QD from 0.1 to 2.7 mg, 4/3 and 7/7 both at 2.7 and 4.0 mg) have been included. Mean age 51y, ECOG 0−1, previous chemotherapy lines median 3 (0−14). Common tumors were melanoma (15), ovarian (5) and CRC (6). Four reversible DLTs were observed on QD: grade (G) 3 blurred vision (2.7 mg), 2 G3 CK elevations (2.7 and 2.25 mg) and G3 transaminitis (1.8 mg). QD MTD was defined as 2.25 mg. QD most common related adverse events include skin (89%), GI (74%), eye (42%) and metabolic (26%) disorders. PK profiles suggest dose-linearity, a half-life ($t_{1/2}$) of 40 to 60 hrs and drug accumulation 3−7 fold in the QD regimen at steady-state. In tumor and skin biopsies modification of target related molecules (e.g. pERK, pMEK) was detected. Target inhibition close to 100% (pERK/pMEK) was observed in stimulated PBMCs. To date, of 25 evaluable pts, 1 melanoma pt has a partial response and 7 pts experienced stable disease for at least 16 wks (median, 23.5; range 16−49) associated with a reduction in SUV-max (mean, −35%; range, −81−+10; n = 6) measured by C1D15 FDG-PET.