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.

Conclusions: RO5126766 showed acceptable safety profile. The most common drug-related toxicity was skin disorders. MTD was defined for QD regimen. Intermittent regimens dose escalation is ongoing. Favorable PK/PD profile associated with encouraging biological and antitumor activity were demonstrated in this heavily pre-treated population P1 study. Full safety, efficacy, PK/PD profile will be presented.

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A Phase 1 study of continuous dosing with PX-866, an irreversible, pan-isoform inhibitor of PI3 kinase

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Background: Increased signaling through the PI3 kinase pathway is relevant in multiple cancers. PX-866 is an irreversible, pan-isoform inhibitor of Class 1 PI3 kinases. In an initial phase 1 dose-escalation study evaluating an intermittent dosing schedule, PX-866 was well tolerated with diarrhea and nausea as main toxicities. PX-866 was rapidly metabolized to an active metabolite (17-OH PX-866) which demonstrated improved potency relative to parent compound in kinase and cellular assays. PX-866 was further evaluated using a continuous dosing schedule.
Methods: Patients (pts) with advanced solid tumors received PX-866 once daily on a 28 day cycle. Restaging was performed every two cycles. Archived tissue was tested for PIK3CA and KRAS mutations and PTEN deletions. Pharmacokinetics and biologic properties of PX-866 and 17-OH PX-866 were characterized. An expanded cohort of pts with pre- and post-therapy tumor biopsies was enrolled at the continuous schedule MTD of 8 mg per day.
Results: 18 pts have been treated (3 at 10 mg during dose escalation; 15 at 8 mg), with median age 62; ECOG 0/1; median prior treatments 4 (1–7), and median days on study 42 (15–217). All 10 mg pts were reduced to 8 mg after experiencing toxicity: Gr 3 diarrhea (n = 2); Gr 3 ALT/AST (n = 1). At 8 mg, Gr 1/2 adverse events (AEs) have been reported in 80% of pts, including diarrhea, nausea, and asymptomatic ALT/AST elevation. 1 pt experienced related Gr 3 diarrhea. 2 pts have required dose reduction to 6 mg for Gr 1/2 AEs. Best response has been SD in 6 (60%) and PD in 4 (40%) of 10 evaluable pts. 3 pts (pancreatic islet cell, colorectal, and prostate cancer) have received $\geqslant$4 cycles. 7 pts have not yet been assessed for response. Time-of-flight mass spectrometry from treated pts confirmed 17-OH PX-866 as the principle metabolite. PK results show parent compound below limit of quantification whereas 17-OH PX-866 shows an AUC_{INF} of 3967 hr*pg/ml and a terminal half-life of 6 hr in patients dosed at 8 mg. Paired tumor biopsies have been obtained in 5 pts to date.
Conclusions: PX-866 has been well tolerated at 8 mg per day and associated with better disease control in heavily pretreated pts than intermittent dosing. Predictive biomarkers are being explored. 17-OH PX-866 demonstrates increased potency relative to parent compound. Final safety, efficacy, PK and PD results will be presented. The safety profile and disease control rate support phase 2 development.

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A first-in-human Phase 1 study of anti-CD105 antibody therapy with TRC105 in patients with advanced solid tumors

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Background: CD105, also known as endoglin, is an endothelial cell membrane protein that is essential for angiogenesis. CD105 is not present on established mature vessels but is highly expressed on proliferating vessels in solid tumors, and tumor vessel CD105 expression is up-regulated by hypoxia and anti-VEGF therapy. TRC105 is a chimeric IgG1 anti-CD105 monoclonal antibody that inhibits angiogenesis and tumor growth via endothelial cell growth inhibition, ADCC, and apoptosis.
Methods: Safety and PK were evaluated in pts with advanced solid tumors treated with TRC105 i.v. every 2 weeks. The TRC105 dose was escalated in cohorts of 3–6 pts from 0.01 to 1 mg/kg using TRC105 produced in NS0 cells, and then from 0.3 to 15 mg/kg using TRC105 with increased ADCC activity produced in a high-expressing CHO cell line.
Results: 42 ECOG PS 0–1 pts were treated including 21 with NS0-produced TRC105 and 21 with CHO-produced TRC105. Two dose limiting toxicities (DLT) were reported in pts who received NS0-produced TRC105: one pt experienced Grade 4 gastric ulcer bleeding at 0.1 mg/kg on Day 5 which resolved spontaneously, and one pt experienced a Grade 3 infusion reaction at 1 mg/kg on Day 1 (without premedication). Infusion reactions were also noted in the initial two pts dosed at 0.3 mg/kg using TRC105 produced in CHO cells, including one Grade 3 DLT. The protocol was amended to increase the initial infusion time from 1 to 4 hours and mandate premedication, and dose escalation proceeded to 15 mg/kg. Serum TRC105 concentrations expected to saturate CD105 binding sites (>0.2 ug/mL) were maintained for seven days at 10 mg/kg. Neither HAMA nor HACA was detected in patients receiving CHO-produced TRC105. One pt with castrate-refractory prostate cancer remains on study after 29 months of TRC105 with a complete PSA response and bone scan normalization. In addition, 6-month stable disease was seen in a pt with ovarian cancer (CA125 decrease of 16%). Best response also included stable disease >2 months (n = 13) and progression (n = 22).
Conclusion: TRC105 is tolerated at doses with evidence of clinical activity. Additional monotherapy and combination studies are planned.

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A multi-center Phase 1, dose-escalation trial to determine the safety and pharmacokinetics/pharmacodynamics of BAY 86-9766 (RDEA119), a MEK inhibitor, in advanced cancer patients

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Background: BAY 86-9766 (RDEA119) is a potent, non-ATP competitive, highly selective inhibitor of MEK1/2. A phase I dose-escalation trial with BAY 86-9766 was conducted to determine the maximum tolerated dose (MTD), pharmacokinetics (PK) and pharmacodynamics (PD) in patients with advanced metastatic or locally recurrent solid tumors, who have acceptable organ function, ECOG performance status of 0–1 and a life expectancy of at least 3 months.
Materials and Methods: Forty-nine patients were enrolled and received doses ranging from 2–160 mg once daily (QD) or 50–80 mg twice daily (BID). Tumor types included 15 colorectal, 5 prostate, 5 NSCLC, 4 melanoma, 3 adrenal, 2 pancreatic, 2 breast and 13 other. Patients were given a single oral dose on Day 1 to determine PK, were off drug for 7 days, and then began a 28-day course of treatment. At least 3 patients were treated at each dose level prior to dose escalation. Safety was assessed by adverse events (AEs), clinical laboratory tests, vital signs, ECGs, ECHO/MUGA scans and physical exams. PD assessments included phosphorylated ERK (pERK) and cytokine levels from peripheral blood mononuclear cells (PBMCs) and pERK from hair follicles. If benefiting from treatment, patients continued dosing in subsequent 28-day courses. Response was assessed every 2 courses.
Results: The most common AEs were rash, fatigue, vomiting, nausea, diarrhoea and cough. At the 160 mg dose, 4 patients reported 6 central nervous system AEs, of which 2 were considered a dose limiting toxicity (DLT) (hallucinations, sleep walking, confusion, and vivid dreams and DLTs of presyncope and somnolence). Three patients continued at the same or reduced dose of RDEA119. Other DLTs reported at 160 mg were diarrhea and rash. The MTD was determined to be 100 mg/day. Group mean C_{max} and AUC_{0-24} values increased linearly following both single and multiple doses (QD and BID). At doses of 60 and 100 mg QD, a sustained suppression of induced pERK and cytokine response was seen. Stable disease was achieved in 7 patients (median: 6 months, range: 4–14 months). The safety, PD and response data will also be presented from the ongoing MTD expansion phase of the study with 10 patients each at 100 mg QD and 50 mg BID.
Conclusions: BAY 86-9766 was generally well tolerated at doses $\leqslant$100 mg daily with rash being the most common treatment-related adverse event. At the MTD, significant inhibition of pERK and associated cytokines was observed. Based on the results of this study, Phase 2 studies with BAY 86-9766 are being pursued.