and cisplatin (5 mg/kg i.p., once weekly) was more effective than either agent alone (T/C values of 10% versus 37% and 24%, respectively). Enhanced *in vivo* efficacy was also observed when combinations of BI 2536 (30 mg/kg i.v., once weekly) and irinotecan (12.5 mg/kg i.p., once weekly) were tested (T/C values of 8% for the combination versus 20% and 25% for BI 2536 and irinotecan, respectively). The effect of scheduling of combination regimens of BI 2536 and pemetrexed on *in vivo* activity was addressed in the Calu-6 NSCLC model where pemetrexed treatment (administered from d1 to d5 of each cycle at 150 mg/kg, i.p.) was combined with once weekly BI 2536 treatment (40 mg/kg, iv.) on d1 or d5 of each weekly cycle. A simultaneous start of the combination resulted in a T/C value of 26%. Administering BI 2536 at the end of each pemetrexed cycle resulted in similar antitumour activity (T/C value 19%). Single agents were significantly less active (T/C values of 66% and 39% for BI 2636 or pemetrexed, respectively).
Conclusion: Combining the targeted cell cycle inhibitor BI 2536 with various cytotoxic agents improved antitumour activity *in vivo* compared to single-agent treatments. These results lend support to further clinical studies of BI 2536 in combination with established chemotherapeutic drugs.

357 POSTER

A phase I safety, pharmacokinetic and pharmacodynamic study of intravenously administered PXD101 plus carboplatin or paclitaxel or both in patients with advanced solid tumors

U. Lassen[1], M. Sørensen[2], J.S. De Bono[3], R. Molife[3], L. Vidal[3], S. Settatree[3], M.V. Seiden[4], S.X. Li[5], P.B. Jensen[6]. *[1]Rigshospitalet, Department of Oncology 5073, Copenhagen, Denmark; [2]Rigshospitalet, Department of Oncology, Copenhagen, Denmark; [3]The Royal Marsden NHS Trust, Drug Development Unit, Sutton, England; [4]Massachusetts General Hospital, Division of Medical Oncology, Boston, USA; [5]CuraGen Corporation, Branford, CT, USA; [6]TopoTarget, Copenhagen, Denmark*

Background: PXD101 is a low molecular weight HDAC inhibitor of the hydroxymate class. Anti-tumour activity alone or in combination with standard chemotherapeutic agents has been demonstrated in pre-clinical models. PXD101 has been well tolerated by patients with solid and haematological malignancies in doses up to 1000 mg/m^2/d in phase I and II clinical trials. This is a Phase I study to determine the maximum tolerated dose (MTD), dose limiting toxicity (DLT), pharmacokinetics (PK) and pharmacodynamics (PD) of PXD101 administered in combination with carboplatin (C) or paclitaxel (P) or both in order to define a safe dose of the combination for a Phase II study in ovarian cancer.
Methods: Patients with histologically confirmed solid tumours, ECOG PS 0–2, $\geqslant$18 years, <3 prior chemotherapy regimens were eligible. Escalating doses of PXD101 were administered as a 30-minute IV infusion every 24 hours ($\pm$ 2 hours) for 5 days q21. C (AUC5) or P (175 mg/m^2) or both were administered 2–3 hours following PXD101 on day 3 of each cycle. Standard PK parameters were assessed for PXD101 alone, in combination with C, P or both and for C and P when administered after PXD101. Acetylation of histones H3 and H4 was performed by Western blotting of extracted histones from peripheral blood mononuclear cells (PBMC).
Results: 15 pts (median age 53 years, [range 43−66)]; 10M/5F; all ECOG PS $\leqslant$ 2) have been treated with a total of 54 cycles of PXD101 (median 2; range 1 to 6) at 4 dose levels: 1A: C and PXD101 600 mg/m^2 (5pts); 1B: P and PXD101 600 mg/m^2 (4pts); 2: C and P and PXD101 600 mg/m^2 (3pts); 3: C and P and PXD101 800 mg/m^2 (3pts). No DLT have been observed and the final dose level 4: C and P and PXD101 1000 mg/m^2 opened for inclusion in May 2006. To date, one confirmed PR in a patient with pancreatic cancer after 6 cycles and SD in 7 patients (bladder cancer 6m+, ovarian cancer 6m+, Ewing sarcoma 6m+, melanoma 5m+, cholangiocarcinoma 5m+, mesothelioma 4m+, unknown primary 2m+).
Conclusions: The novel HDAC inhibitor PXD101 is well tolerated when combined with standard dose C and P and shows activity in heavily pre-treated patients. Recruitment to a combination of C and P and full dose PXD101 at 1000 mg/m^2 continues. PK/PD and toxicity data will be presented.

358 POSTER

A phase I and pharmacokinetic (PK) study of CX-3543, a protein-rDNA quadruplex inhibitor, in patients (pts) with advanced solid tumors

A.D. Ricart[1], K.P. Papadopoulos[1], D.D. Von Hoff[2], J.K.C. Lim[3], R.F. Marschke[2]. *[1]Cancer Therapy and Research Center, Institute for Drug Development, San Antonio, USA; [2]Mayo Clinic Arizona, Scottsdale, USA; [3]Cylene Pharmaceuticals, Inc., San Diego, USA*

Background: The rate of ribosomal RNA (rRNA) biosynthesis and resultant ribosome assembly determine the proliferative state of cells, and this process is highly increased in cancer cells due to genetic alterations that deregulate the signaling pathways that control rRNA biogenesis. CX-3543 directly inhibits aberrant rRNA biogenesis in cancer cells by disrupting an essential protein-rDNA quadruplex complex that is over-expressed in cancer cells, thereby selectively triggering rapid and massive apoptotic cell death in tumor cells but not normal cells. Preclinical studies with CX-3543 demonstrated potency in suppressing xenograft tumor growth with a broad therapeutic window, and no drug resistance has been observed *in vitro* to date.
Material and Methods: CX-3543 is administered by an IV infusion each day for 5 consecutive days, repeated on a 3-week cycle, to pts with advanced cancer. This evaluation was designed to determine the maximum tolerated dose (MTD), dose limiting toxicities (DLT) and PK profile of this schedule.
Results: 21 pts were enrolled (13M/8F), median age 68 (range 44−84) and tumor types: colorectal (5), prostate (4), neuroendocrine (2), lung (2), head & neck (2), and others (6). All pts had received prior systemic therapy, with a median of 4 (range 1−7) previous regimens. CX-3543 doses in mg/m^2 (no. pts/cohort) evaluated were: 10(3), 20(4), 40(3), 80(3), and 160(8). Although nine grade 3 adverse events have been reported, none are deemed related to CX-3543. Common mild to moderate toxicities included fatigue, anorexia, nausea, and stomatitis, but there is no evidence they are related to the presence or dose level of CX-3543. There has been no significant myelotoxicity or alopecia. Two pts experienced transient mild cough and chest tightness at 160 mg/m^2 that resolved spontaneously upon completion of the infusion, and no EKG or oximetry changes occurred. The protocol was amended to extend the infusion from 1h to 2 h, which has been very well tolerated. Three pts have had stable disease $\geqslant$ 4 months (neuroendocrine, colorectal and prostate). PK parameters demonstrate linearity between dose cohorts, with a $t_{1/2}$ of approximately 10 h following the first dose. Extending the infusion to 2 h at the 160 mg/m^2 dose level decreased the C_{max} as expected, but AUC remained linear.
Conclusions: To date, CX-3543 has been well tolerated and has predictable PKs. The MTD remains to be defined and further patient enrollment is ongoing.

359 POSTER

Pharmacokinetic and pharmacodynamic effects of MN-029, a novel vascular disrupting agent (VDA), in patients (pts) with advanced solid tumors

A. Ricart[1], M. Cooney[2], J. Sarantopoulos[1], J. Brell[2], K. Locke[3], R. Gammans[3], M. Munsey[3], A. Tolcher[1], S. Remick[2]. *[1]Cancer Therapy and Research Center, Institute for Drug Development, San Antonio, USA; [2]CASE Comprehensive Cancer Center, Developmental Therapeutics Program, Cleveland, USA; [3]MediciNova, Inc., San Diego, USA*

Background: MN-029 (denibulin hydrochloride) is a novel VDA that binds reversibly to the colchicine-binding site on tubulin and inhibits microtubule assembly, resulting in disruption of the cytoskeleton of tumor endothelial cells (EC). Disruption of the tumor EC cytoskeleton ultimately leads to a temporary reduction in tumor blood flow. Changes in tumor blood flow can be used as a surrogate marker of biological activity in the clinic.
Material and Methods: MN-029 was administered IV as a 10−40 min infusion at 3-wk intervals in pts with advanced cancer. The study followed an accelerated titration design, with intrapatient dose escalation. Pharmacodynamic effects on tumor blood flow were evaluated using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).
Results: 34 pts (17M/17F) were enrolled of median age 56 (range 35−76) and the following tumor types – colorectal (7), renal (6), carcinoid (4), hepatocellular (3), ovarian (2), melanoma (2), soft tissue sarcoma (3), others (7). A total of 150 cycles of MN-029 were given, median 3/pt (range 1–26), over 10 dose levels (4, 8, 16, 24, 36, 54, 80, 120, 180 and 225 mg/m^2). Escalation proceeded until an initial dose-limiting toxicity (DLT) was observed in 1 pt in the 180 mg/m^2 cohort, consisting of a reversible episode (3 hours post-dose) of acute coronary ischemia (without sequelae and with preservation of myocardial function) probably due to coronary vasospasm. Therefore, this cohort was expanded to 6 pts, with no further DLTs observed. 2 DLTs occurred at 225 mg/m^2 (transient ischemic attack and grade 3 transaminitis), thus ending escalation. Common mild to moderate toxicities included nausea, vomiting, fatigue and diarrhea. There was no significant myelotoxicity, stomatitis or alopecia. Nine pts had stable disease after 3 cycles and five pts had prolonged ($\geqslant$ 6 months) stable disease (carcinoid [2], melanoma [2] and pancreatic [1]); the carcinoid tumor pts have had stable disease for >26 cycles and >23 cycles, respectively. Pharmacokinetic data generally indicated dose-related increases in C_{max} and AUC values, although substantial inter-patient variability was observed. Tumor blood flow reduction assessed by DCE-MRI was recorded at 120, 180 and 225 mg/m^2, but not at 80 mg/m^2.