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.

Conclusions: MN-029 produced reductions in tumor blood flow at doses that were well tolerated. The MTD level was determined to be 180 mg/m^2.

360 POSTER

Dasatinib (BMS-354825), a novel, potent inhibitor of Bcr-Abl and Src, has a significant migration effect on human neuroblastoma and Ewing sarcoma cells

F. Timeus, N. Crescenzio, A. Fandi, A. Doria, L. Foglia, L.C. di Montezemolo. *University of Turin, Pediatric Hematology/Oncology, Turin, Italy*

Background: Dasatinib (BMS-354825) is a novel, orally available, potent inhibitor of Bcr-Abl and Src family kinases. Preclinical and clinical data have shown that dasatinib has potent activity against chronic myelogenous leukemia and acute lymphoblastic leukemia. We investigated the antiproliferative and pro-apoptotic effects of dasatinib in human neuroblastoma (NB) and Ewing sarcoma (ES) cells.
Material and Methods: The NB cells (SJ-N-KP and IMR5) and ES cells (PDE02 and 6647) were cultured in RPMI1640 with or without dasatinib (range, 10–10,000 nM). Proliferation was evaluated by cell count with trypan blu exclusion at 24, 48, and 72 hours. Apoptosis was assessed by annexin V binding (Apoptosis Detection Kits, R&D Systems), with a EPICS XL2 flow cytometer after 24-hour exposure to dasatinib. The effect of dasatinib 100 nM on cell cycle was evaluated by flow cytometry at 24, 48, and 72 hours. The effect of dasatinib 100 nM on cell migration was evaluated by the scratch test. All experiments were done in triplicate.
Results: Dasatinib exhibited a concentration-dependent antiproliferative effect on both cell types. Peak effect was observed after 24 h. PDE02 cells were the most sensitive to dasatinib (average IC_{50}, ~500 nM vs >2M. Incubation with dasatinib did not cause a significant pro-apoptotic effect. Dasatinib 100 nM caused a mean 11.3% reduction of cells in S phase and a mean 14.4% increase of cells in G0/G1 in 6647 and IMR5 cells. Dasatinib 100 nM did not show any significant effect on cell cycle in SJ-N-KP and PDE02 cells. The scratch test was evaluable only in the PDE02 cells where dasatinib 100 nM caused a 50% inhibition in cell migration.
Conclusions: Dasatinib significantly inhibited cell migration in PDE02 cells and showed some antiproliferative activity on NB and ES cells, although to a smaller extent than previously described in other cell types. Additional data will be presented.

361 POSTER

Potent antitumor activity of small molecule IAP antagonists

S. Chunduru[1], S. Condon[2], C. Benetatos[1], J. Burns[1], Y. Deng[2], M. LaPorte[2], S. Springs[1], Y. Shi[3], M. McKinlay[1,2]. *[1]TetraLogic Pharmaceuticals, Biology, Malvern, PA, USA; [2]TetraLogic Pharmaceuticals, Medicinal Chemistry, Malvern, PA, USA; [3]Princeton University, Molecular Biology, Princeton, NJ, USA*

Inhibitors of apoptosis proteins (IAPs) block the activation of downstream caspases, thus preventing apoptotic cell death in tumor cells. Mitochondrial protein Smac/DIABLO relieves this XIAP-mediated caspase-3 and -9 inhibition. The N-terminal tetrapeptide sequence of Smac, AVPI, is sufficient to release the XIAP-mediated inhibition of caspase-9. A series of drug-like dimeric peptidomimetics designed to mimic the AVPI motif was synthesized. The peptidomimetics bound with sub-nanomolar affinities to XIAP, cIAP-1, cIAP-2 and ML-IAP. High resolution co-crystal structures demonstrated the ability of the dimers to crosslink two XIAP BIR-3 domains. One representative peptidomimetic, GT13065, was cytotoxic (CC_{50} = 10 nM) to tumor cell lines as a single agent and was effective at lower concentrations when combined with sub-therapeutic concentrations of various chemotherapeutics and TRAIL. No cytotoxicity was observed in normal cells when treated with dimeric peptidomimetics alone or in combination with TRAIL (1 μg/ml) or chemotherapeutics (100 μM). The observed pharmacokinetic properties following i.v. administration to rats were encouraging: clearance rate (268 ml/hr/kg), volume of distribution (536 ml/kg) and terminal elimination half life (4.5 hours). In addition, treatment of mice-bearing human tumor xenografts with GT13065 or related compounds as single agents at doses below MTD resulted in tumor regression. Details of the studies performed with GT13065 and related compounds will be presented.

362 POSTER

A phase 2 trial of AP23573, an mTOR inhibitor, in patients (pts) with taxane-resistant androgen-independent prostate cancer (AIPC)

M.E. Gross[1], R.J. Amato[2], M. Mushtaq[2], G. Wilding[3], G. Bubley[4], C. Trudeau[5], V.M. Rivera[5], C.L. Bedrosian[5], D.B. Agus[1]. *[1]Cedars-Sinai Medical Center, Louis Warschaw Prostate Cancer Center, Los Angeles, USA; [2]The Methodist Hospital Research Institute, Genitourinary Oncology Program, Houston, USA; [3]University of Wisconsin, Comprehensive Cancer Center, Madison, USA; [4]Beth Israel Deaconess Medical Center & Dana Farber/Partners Cancer Care, Boston, USA; [5]ARIAD Pharmaceuticals, Inc., Cambridge, USA*

Background: AP23573 is a novel rapamycin analog that inhibits mTOR, a downstream effector of cellular growth, division, metabolism and angiogenesis via the PI3K/Akt and nutrient-sensing pathways. In clinical trials, AP23573 inhibited mTOR activity in target and surrogate tissues, was generally well-tolerated and active in a broad range of cancers. Molecular studies suggest the mTOR pathway is important in advanced prostate cancer. Because current treatments of taxane-resistant AIPC give poor responses, we examined the anti-tumor activity of AP23573 in this pt population.
Material and Methods: This is an open-label, single-arm trial to evaluate anti-tumor activity of AP23573. Enrolled pts had progressive taxane-resistant AIPC (growth of measurable lesions, new bone lesions, or 2 consecutive PSA increases). AP23573 (50 mg) is administered as a 30-minute i.v. infusion once weekly. PSA response is assessed at the end of each 4-week cycle, and RECIST response is performed every 2 cycles. Quality-of-life (QOL) is assessed at each cycle by the FACT-Prostate questionnaire. Correlative pharmacodynamic studies include immunohistochemistry of archival tumor samples and plasma proteomics.
Results: Enrollment is complete, with 38 patients (median age 69 years) treated. The median duration of prior taxane treatment (docetaxel and/or paclitaxel) was 5.8 months. Twenty-six (26) of 38 pts have received $\geqslant$ 4 cycles of AP23573 and 11 continue on treatment. The best response distribution for 16 of 38 patients with measurable disease was 1 partial response, 13 stable disease, and 2 progressive disease, as determined by $\geqslant$ 1 RECIST assessment. Thirty-four (34) of 38 patients were evaluable for PSA response. Twelve (12) pts had stable disease; 22 had progressive disease by PSA. Eighteen (18) patients were evaluable using the FACT-Prostate questionnaire, at 4 cycles. Fourteen (14) pts reported an improvement or stabilization of their pain compared to baseline. The most common treatment-related adverse events (> 20%) were generally mild or moderate and included mouth sores, fatigue, nausea, diarrhea, and thrombocytopenia.
Conclusions: These results suggest weekly single-agent AP23573 is well tolerated and has promising anti-tumor activity in pts with progressing taxane-resistant AIPC. Several patients have disease stabilization; with 1 partial response. Patient treatment and efficacy assessments continue.

363 POSTER

In vitro and in vivo molecular characterization of PHA-739358, an inhibitor of Aurora kinases

P. Carpinelli, R. Ceruti, A. Degrassi, D. Fancelli, L. Gianellini, A. Marsiglio, V. Croci, M. Rocchetti, G. Texido, J. Moll. *Nerviano Medical Sciences Srl., Nerviano, Italy*

Aurora kinases are involved in cell cycle progression and mitosis and their inhibition has considerable potential as a new cancer therapy. Here, we report, the preclinical profile of PHA-739358, a new potent Aurora kinases inhibitor, which is currently in clinical trials. The aim of the present study was to examine the compound with respect to its activity in different cell lines and to proof mechanism of action in vitro & in vivo. The compound induces endo-reduplications and inhibits phosphorylation of Histone H3 in several tumour cell lines, which is in agreement with the expected molecular mechanism of action. In vivo studies show significant anti-tumoral activity in different xenografts and spontaneous and transgenic animal tumor models. Tumor growth inhibition ranges from 68 to 98% when PHA-739358 was given by intravenous (IV) administration using a number of different schedules. In HL-60 xenografts, tumor regressions and cures are observed. In the transgenic TRAMP mouse model, tumor regression of >80% is seen in several animals treated with PHA-739358 as assessed by magnetic resonance imaging (MRI). Target modulation in vivo is seen in a number of different tissues (skin, bone marrow and tumor) after treatment with PHA-739358. We conclude that our novel Aurora kinases inhibitor has a promising therapeutic potential with the possibility to monitor modulation of histone H3 phosphorylation as a clinical biomarker for hitting the target in patients.