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.

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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.

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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.

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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.

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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.