Table 1

Dose level	>50% Decline	>90% Decline
60 mg/day	41% (9/22)	9% (2/22)
150 mg/day	57% (13/23)	13% (3/23)
240 mg/day	50% (14/28)	29% (8/28)

Conclusions: MDV3100 is a novel AR antagonist in clinical investigation. The observed PSA responses are consistent with the inhibition of AR signaling. MDV3100 has been well-tolerated to date and appears to be a promising candidate for the treatment of CRPC. Pt recruitment and follow-up are continuing. The analyses of the associations among PSA, CTC, radiographic, and PET outcomes are ongoing and will be presented.

161 POSTER

Potent anticancer activity of panobinostat (LBH589) in models of hormone-refractory prostate cancer (HRPC): targeting the androgen receptor

W. Shao[1], J. Growney[1], G. O'Connor[1], Y. Feng[1], H. Scher[2], Y.M. Yao[1], S. Fawell[1], P. Atadja[1]. *[1]Novartis Institutes for BioMedical Research, Oncology, Cambridge, MA, USA; [2]Memorial Sloan Kettering Cancer Center, Oncology, New York, USA*

Background: Panobinostat (LBH589) is a highly potent pan-deacetylase (pan-DAC) inhibitor which has demonstrated preliminary clinical efficacy in hematologic and solid malignancies, including prostate cancer. Panobinostat inhibits the molecular chaperone heat shock protein 90, promoting degradation of client proteins such as the androgen receptor (AR) and human epidermal growth factor receptor type 2 (HER-2), which play critical roles in the growth and survival of prostate cancer. The anticancer effects of panobinostat were investigated in both *in vitro* and *in vivo* prostate cancer models, including effects on AR and HER-2 protein levels.
Materials and Methods: Cell lines of known AR status and different degrees of androgen dependence were treated with panobinostat. Effects on cell proliferation (IC_{50}) and viability (LD_{50}) were measured by MTS assay. Levels of target proteins were determined by immunoblotting. Mice bearing AR+, androgen-independent CWR22Rv1 prostate tumor xenografts were treated with panobinostat alone or in combination with docetaxel. Tumor growth inhibition and delay, and AR protein levels, were determined.
Results: Panobinostat inhibited growth of 10 prostate cancer cell lines (IC_{50} 0.9–22.4 nM) and induced potent cytotoxicity in AR+ prostate cancer cells (LD_{50} 20−81.9 nM). Interestingly, AR− cells were sensitive to the antiproliferative effect of panobinostat, but not to panobinostat-induced cell death (LD_{50} >1000 nM). Panobinostat treatment depleted AR and HER-2 in both androgen-dependent and -independent prostate cancer cells. In the hormone-refractory CWR22Rv1 tumor model, single-agent panobinostat induced prolonged tumor stasis, with concomitant depletion of AR from tumor tissues. The combination of panobinostat and standard of care agent docetaxel delayed tumor growth after cessation of treatment, and increased the time to study endpoint of 90 days or 2000 mm^3 tumor volume.
Conclusions: Panobinostat is a potent anticancer agent in both *in vivo* and *in vitro* models of prostate cancer. Panobinostat depletes AR and HER-2 in both AR+ androgen-dependent and -independent prostate cancer cells, and AR in an AR+ hormone-refractory prostate cancer xenograft model at clinically attainable levels. The combination of panobinostat with docetaxel *in vivo* results in enhanced anti-tumor effects and delay of tumor progression. These studies support the continued clinical investigation of panobinostat in HRPC.

162 POSTER

Effects of SOD2 silencing on androgen receptor function and gene regulation: implications for castration-resistant prostate cancer

N. Sharifi[1], E.M. Hurt[2], S. Thomas[3], W.L. Farrar[2]. *[1]UT Southwestern Medical Center, Hematology/Oncology, Dallas, USA; [2]National Cancer Institute, Cancer Stem Cell Section, Frederick, USA; [3]SAIC-Frederick, Basic Research Program, Frederick, USA*

Background: Advanced prostate cancer is generally first treated with androgen deprivation therapy. However, tumors become resistant to and grow despite castrate levels of testosterone. Growth and proliferation of castration-resistant prostate cancer (CRPC) is mediated by gain-of-function changes in the androgen receptor (AR) and AR reactivation. Expression of manganese superoxide dismutase (SOD2), which regulates cellular reactive oxygen species, is markedly down-regulated in CRPC when compared to hormone responsive tumors.
Materials and Methods: Here, we knocked down SOD2 expression in AR-expressing LNCaP prostate cancer cells. We performed transcription factor DNA binding assays to determine changes in AR binding that occur with SOD2 knockdown. Furthermore, we performed DNA microarray analysis to identify gene expression changes induced in prostate cancer with SOD2 knockdown.
Results: Gene expression changes induced by SOD2 knockdown results in the up-regulation of genes which are also androgen responsive and 46% of genes up-regulated two-fold by the androgen ligand R1881 are also up-regulated to the same extent with SOD2 knockdown. The induction of many of these genes with SOD2 knockdown, such as VEGFA, is reversible with the antioxidant N-acetylcysteine (NAC), suggesting that this mechanism is directly linked to reactive oxygen species. Furthermore, an array for transcription factor DNA binding activity shows that SOD2 knockdown induces DNA binding by several transcription factors, including AR. SOD2 knockdown-induced AR activation was confirmed by electrophoretic mobility shift assay (EMSA) and was readily reversible with NAC.
Conclusions: These findings show that dysregulation of SOD2 induces AR activity in a reactive oxygen species-dependent manner, and suggests that there may be a role for antioxidant therapy in CRPC.

163 POSTER

The steroid sulfatase inhibitor BN83495 inhibits E1S-stimulated growth of DMBA-induced mammary tumour in rat

Z. Koob[1], M. Hillairet de Boisferon[1], F. Bichat[1], E. Bascompta[2], A. Perez[2], B. Potter[3], M. Reed[4], T. Ali[5], G.P. Prevost[6]. *[1]Oncodesign, Pharmacology, Dijon, France; [2]Ipsen, Pharmacokinetic, Barcelone, Spain; [3]Sterix, Chemistry, Bath, United Kingdom; [4]Sterix, Biology, London, United Kingdom; [5]Ipsen, Development, Slough, United Kingdom; [6]Ipsen, Discovery & Innovation, Les Ulis, France*

Steroid sulfatase (STS) is a new target for the treatment of steroid hormone dependent diseases such as breast, prostate or endometrial cancer. In breast cancer, estrogens play a major role in the establishment of the disease and between one to two-thirds of tumours are estrogen receptor (ER) positive. Despite current hormonal treatments, improvement is still necessary to achieve better disease control and improve disease outcome. BN83495 is a non-steroidal, non estrogenic, potent, irreversible STS inhibitor that blocks both the formation of E1 from estrone sulfate and androstenediol from DHEAS. The ability of BN83495 to inhibit E1S-stimulated tumor growth in the rat was examined in a DMBA-induced mammary tumor model. Based on median tumor volume and the interquartile range at the end of the treatment period, BN83495 displayed the greatest antitumor activity compared to Tamoxifen or Fulvestrant. Addition of Fulvestrant or Tamoxifen to BN83495 did not improve the potent antitumor activity observed with BN83495 alone. Pharmacokinetic data of BN83945 and effects on estradiol levels are discussed. Altogether, these preclinical results have supported the entry of BN83945 into further clinical trials for estrogen receptor-positive breast cancer patients.

Metastasis and invasion

164 POSTER

Inhibition of CXCR-4 reduces breast cancer xenograft metastasis to multiple organs

M.M. Richert[1], D. Wong[2], W. Korz[2], D.R. Welch[1]. *[1]University of Alabama at Birmingham, Pathology Cell Biology and Pharmacology/Toxicology and Comprehensive Cancer Center and Center for Metabolic Bone Disease, Birmingham, USA; [2]Chemokine Therapeutics Corp, Drug Development, Vancouver, Canada*

Regulation of metastasis occurs in part through chemokine secretion by distant organs/tissues. The chemokine CXCL12 is constitutively expressed in tissues where metastases develop, specifically lung, liver and bone. The primary receptor for CXCL12 is CXCR4. Expression of CXCR4 on breast cancer cells causes increased bone metastasis and poor overall survival in vivo. In addition, the CXCL12/CXCR4 pathway has been associated with increased migration and invasion of tumor cells in response to hypoxia and tumor angiogenesis through recruitment of bone marrow derived cells. It was hypothesized that treatment of mice with a CXCR4 antagonist would decrease the incidence of metastasis to bone and other organs in an in vivo model. The purpose of this study was to test the efficacy of CTCE-9908, a CXCR4 antagonist, as an antimetastatic agent for breast cancer. GFP-expressing MDA-MB-231 metastatic breast cancer cells were injected into the left cardiac ventricle or the tail vein of athymic mice. Mice were treated with 25 mg/kg CTCE-9908 daily beginning either the day previous to tumor cell injection or the day of tumor cell injection. After 6 or 8 weeks (intracardiac and tail vein injections, respectively),