treatment, the number of skin tumors per animal were 22 for the control group and 10 for the drug-treated group ($p < 0.001$). In addition, SVT004703 at 500 ppm was effective against A-431 xenografts (T/C 55% after 4 weeks of treatment).
Conclusions: These results demonstrate the ability of members of this imidazopyrimidine family to inhibit tumor growth with a mechanism of action compatible to tubulin polymerisation inhibition. The pharmacological profile of SVT004703, including its marked oral antitumoral efficacy, deserves further preclinical and clinical development in a variety of pre-cancer and cancer diseases since it may offer clear advantages over existing treatments.

643 POSTER

Energy dependent uptake of paclitaxel poliglumex by human NSCLC tumor and murine macrophage-like cell lines

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Background: Paclitaxel poliglumex (PPX; XYOTAX™) is a novel chemotherapeutic agent composed of paclitaxel covalently bound to poly-L-glutamic acid via an ester bond. PPX has an apparent average molecular weight of 45,000 daltons and average 37% w/w paclitaxel loading; these properties result in improved aqueous solubility, extended plasma $t_{1/2}$ and lower volume of distribution when compared to paclitaxel. PPX preferentially accumulates in xenograft tumor and reticuloendothelial tissues of treated mice, as demonstrated by biodistribution studies using radiolabeled PPX and immunohistochemical studies using anti-PPX antibodies. The current study characterizes the *in vitro* cellular uptake of PPX.
Methods: NCI-H460 (human NSCLC) and RAW 264.7 (murine monocyte-macrophage) cell lines were grown to confluence. At t = 0 the media was supplemented with 0.01−10 μM ^{14}C-labeled PPX ± 10 μM Cytochalasin D and incubated for 4 hours. Radioactivity was then quantitated in the media and cellular compartments. Indirect immunofluorescence was performed with an anti-PPX monoclonal antibody (CT-2D5) which recognizes full length PPX; but not PPX fragments, poly-L-glutamic acid or paclitaxel. RAW cultures were co-stained with an anti-early endosomal antigen-1 antibody (EEA-1).
Results: Levels of ^{14}C-PPX increased 10- and 5-fold in the RAW and H460 cultures, respectively, over the 4 hours incubation period. Levels of ^{14}C-PPX uptake in RAW cells were significantly inhibited by Cytochalasin D ($p < 0.001$). CT-2D5 antibody staining demonstrated a punctate pattern in the internal membrane region of the cytoplasm in RAW & H460 cells; the immunostaining was intense, found in <1% of cells and dose dependent. In RAW cells, CT-2D5 and EEA-1 immunostaining co-localized.
Conclusions: These studies demonstrate that PPX is taken up into the cellular compartment of macrophages and NSCLC tumor cells by energy-dependent endocytosis in a dose and time dependant manner. After a 4 hour incubation PPX immunostaining co-localized with endosomes; over time endosomes fuse with lysosomes thus exposing PPX to lysosomal enzymes. These enzymes, principally cathepsin B, have been demonstrated to degrade PPX resulting in the formation of mono and diglutamyl paclitaxel metabolites. These metabolites spontaneously hydrolyze to release active paclitaxel. Due to an effect of gender on PPX clinical efficacy, the effect of 17-estradiol on PPX cellular uptake is currently being evaluated.

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The novel oral taxane BMS275183 has a favorable activity and toxicity profile in a twice weekly schedule; Preliminary findings from an extended phase I trial

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Background: BMS-275183 is a potent oral taxane with activity observed in NSCLC and prostate cancer in a phase I study of weekly administration. Twice weekly administration appeared to be better tolerated than the weekly regimen and induced less neuropathy, its most prominent toxicity (Broker et al., ASCO 2005, # 2040; CCR 2006; 12:1760–7). We report here the results of the extension of the phase I trial of the twice weekly schedule at the dose proposed for phase II trials.
Patients and Methods: BMS-275183 was given orally continuously twice weekly to adult patients (pts) with advanced solid tumors refractory to standard therapy. Dose limiting toxicities (DLT) were defined as grade (gr) ⩾3 non-hematologic toxicity, or gr 4 hematologic toxicity, or any toxicity grade causing a dose delay/omission during the first cycle. Plasma samples for pharmacokinetics (PK) were collected in week 1 and 3 for 72 hr after drug administration and analyzed using an LC/MS/MS assay.
Results: 17 pts were enrolled into the extended cohort of the predefined recommended dose of 100 mg/m^2, with a median number of 6 cycles (2−18 cycles). Main pt characteristics were: median age 58 years, male 65 %, median ECOG PS 1. The following DLTs were noted in 4/17 pts: gr 3 neutropenia (n = 1); gr 2 peripheral neuropathy (n = 1); febrile neutropenia and gr 3 neuropathy (n = 1); non-complicated gr 4 neutropenia (n = 1). In any cycle, 7 pts experienced gr 3 or 4 toxicities consisting of (a combination of) leucopenia (n = 3), fatigue (n = 3), diarrhea (n = 3), hematuria (n = 1) and neuropathy (n = 1). Neuropathy occurred less frequently than in the weekly treatment regimen: any grade neuropathy in 9/17 (53%) pts in this trial vs 31/48 (65%) pts in the weekly trial; and 78% of observed neuropathy did not exceed gr 1 in this trial, vs only 15% in the weekly trial. PK-analysis of day 1 revealed a median Tmax of 1 hr (Range: 0.5−3 hr), and a mean T* of 29.9 hr (SD: 12.5 hr). The geometric means were 1561 ng h/mL (CV: 95%) for the AUC_∞, and 247 ng/mL (CV: 109%) for the Cmax. Partial responses were observed in 2 taxane naïve NSCLC pts (duration 17+ and 8.5 months). Tumor shrinkage was observed in a pt with non-measurable prostate cancer pre-treated with docetaxel.
Conclusions: BMS-275183 is well tolerated and active in a twice weekly regimen, and induces less neuropathy than the weekly schedule. The PK shows high interpatient variability. Phase II studies employing the twice weekly schedule are planned.

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Effect of estrogen on outcome in two randomized phase III studies of paclitaxel poliglumex (PPX) in advanced non-small cell lung cancer (NSCLC)

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Background: Estrogen (E), through binding to E receptor β (ER-β), is important in lung development and physiology, and also NSCLC. Female NSCLC pts have better survival than stage-matched men; however, premenopausal women have inferior survival to older women suggesting a role for E in outcome with standard therapy [1,2]. E promotes growth of ER-β expressing human NSCLC xenografts (NCI-H460 and MT-201) and regulates the activity of cathepsin B, a protease highly expressed in aggressive tumors. Cathepsin B is required for the efficient release of paclitaxel (P) from PPX, a polymer-drug conjugate of P and poly-L-glutamic acid.
Methods: A trend toward improved survival with PPX for females but not males was observed in 2 phase III trials in chemo-naïve patients with advanced NSCLC and PS2 [3]; STELLAR 3 compared P/carboplatin vs PPX/carboplatin, STELLAR 4 compared PPX vs either gemcitabine or navelbine. To evaluate the effect of E on survival in women treated with PPX, survival was analyzed retrospectively by age and E2 levels.
Results: Younger women (<55 years old) with presumably higher E levels receiving standard therapy had a shorter survival than older women (160 vs 261 days). In contrast, younger women receiving PPX had similar survival compared to older women (304 and 271 days, resp.). In STELLAR 3, E2 levels were available for 86/93 women: E2 > 30 pg/ml was associated with improved survival in the PPX-arm compared to control (HR: 0.54; p = 0.039). For women with E2 levels ⩽30 pg/ml, treatment arm did not impact survival (HR: 1.20; p = 0.676). Overall survival (OS) by age in a combined analysis of STELLAR 3 and 4 is summarized in the table.

Median OS (days): PPX v control	
Age < 55 (n = 50)	
STELLAR 3:	238 v 126 (HR = 0.65;P = 0.297); 31% v 27% 1-yr survival
STELLAR 4:	NE v 199 (HR = 0.36;P = 0.06); 57% v 14% 1-yr survival
Composite:	304 v 160 (HR = 0.51;P = 0.038); 42% v 22% 1-yr survival
Age ⩾ 55 (n = 148)	
STELLAR 3:	231 v 277 (HR = 0.76;P = 0.335); 40% v 24% 1-yr survival
STELLAR 4:	301 v 211 (HR = 0.80;P = 0.394); 38% v 29% 1-yr survival
Composite:	271 v 261 (HR = 0.75;P = 0.134); 39% v 26% 1-yr survival

Conclusions: Advanced NSCLC in premenopausal women (or women on hormone replacement therapy) is associated with a poor prognosis; however, in a retrospective analysis, PPX appears to be especially active in this pt population. The modulating effect of estrogen on the activity of

PPX is prospectively evaluated in a randomized phase III trial in chemo-naïve women with advanced NSCLC.

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646 POSTER

Insights into the mechanism of microtubule stabilization by Taxol

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Background: Taxol is an important antitumor drug that stabilizes microtubules, reduces their dynamicity and promotes mitotic arrest and cell death. Although photoaffinity labeling and electron crystallography have localized the binding pocket for Taxol on β-tubulin, there is little insight into the mechanism by which the drug stabilizes microtubules.
Materials and Methods: Tubulin from the marginal band of chicken erythrocytes that contains a single α- and β-isotype, α1 and βVI, was used for all experiments. Hydrogen/deuterium exchange (HDX) in combination with liquid chromatograph-electrospray ionization mass spectrometry (LC-ESI MS) was used to study structural changes in α-, β-tubulin either in GDP-dimers, GTP-microtubules or Taxol-microtubules in solution.
Results: HDX coupled to LC-ESI MS demonstrated a marked reduction in deuterium incorporation in both α-and β-tubulin when Taxol was present. This protection by Taxol reflects decreased solvent accessibility or a more rigid conformation in both polypeptide chains. Decreased local HDX in peptic peptides was mapped on the tubulin structure and revealed both expected and new dimer-dimer interactions. The increased rigidity in Taxol-microtubules was distinct from and complementary to that due to GTP-induced polymerization. Comparing the map of deuterium incorporation between GTP-microtubules and Taxol-microtubules, allowed us to determine not only the regions involved in Taxol binding, but also the longitudinal and lateral dimer-dimer interactions specifically affected by Taxol. Our findings are consistent with Taxol inducing tubulin to adopt a straight conformation and preventing it from shifting to a curved conformation.
Conclusions: HDX coupled to LC-ESI MS can be used effectively to answer important pharmacological and biochemical questions relevant to the function of microtubules in cells and expand our knowledge of microtubule-stabilizing drugs that are important in cancer chemotherapy.

Late-breaking posters

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A phase I dose-escalation study of weekly IMC-1121B, a fully human anti-vascular endothelial growth factor receptor 2 (VEGFR2) IgG1 monoclonal antibody (Mab), in patients (pts) with advanced cancer

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Background: Anti-VEGFR2 antibodies are effective in a variety of preclinical leukemia and solid tumor models. IMC-1121B is a fully human anti-VEGFR2 IgG1 Mab.
Methods: Cohorts of 3–6 pts (ECOG PS ⩽2) with advanced cancer and no significant cardiovascular, thrombotic or bleeding disorders received escalating doses of IMC-1121B. A single initial dose with extended PK sampling was followed by 4 weekly infusions per treatment cycle starting at 2 mg/kg. 7 dose levels up to a maximum of 16 mg/kg are planned. Human anti-human antibodies (HAHA) directed against IMC-1121B were assessed at baseline and before each Week 4 dose. Tumor response was assessed every 2 cycles, and pharmacodynamic analyses were performed at baseline and post-dosing.
Results: 19 pts (13 M; 6 F), have entered the study at the first 4 dose levels: cohort 1 (2 mg/kg) n = 6, cohort 2 (4 mg/kg) n = 4, cohort 3 (6 mg/kg) n = 4, and cohort 4 (8 mg/kg) n = 5. Toxicities ⩾ grade 2 at least possibly or probably drug-related include anorexia, nausea, vomiting, back pain, groin pain, depression, fatigue, insomnia, emboli, anemia, proteinuria, hypophosphatemia, elevated transaminases and amylase. To date, there has been one confirmed partial response (melanoma), in total 5 pts have experienced stable disease for >6 months [colon (2), gastric, thyroid, melanoma]. No HAHA levels across cohorts 1–3 have been detected. Non-compartmental PK analysis reveals dose-dependent elimination and non-linear exposure, consistent with saturable clearance mechanism(s): mean $t_{1/2}$ = 63.6, 87.9, 176.8 hrs, mean C_{max} = 43.7, 80.3, 183.3 ug/mL, and AUC_{0-Inf} = 3860, 9135, 29953 hr*ug/mL, during Cycle 1 at the 2, 4, and 6 mg/kg dose levels, respectively. Target trough levels required for activity determined from preclinical xenograft studies have been achieved.
Conclusions: Weekly administration of IMC-1121B is well tolerated at doses up to 8 mg/kg/week. There is early evidence of clinical efficacy and a non-linear dose-PK relationship, and target trough levels predicted from xenograft studies have been observed. Dose escalation continues. Updated safety, PK, HAHA, and efficacy data will be presented.

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A phase I dose-escalation study of weekly IMC-A12, a fully human insulin like growth factor-I receptor (IGF-IR) IgG1 monoclonal antibody (Mab), in patients (pts) with advanced cancer

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Background: IMC-A12 is a fully human IgG_1 monoclonal antibody directed against the human insulin like growth factor-I receptor. A phase I trial evaluating the safety and maximum tolerated dose of IMC-A12 has been initiated in patients with refractory solid tumors who no longer respond to standard therapy or for whom no standard therapy is available.
Methods: 3–6 pts (ECOG PS ⩽2) with advanced cancer will be enrolled in each cohort. IMC-A12 is administered weekly for four infusions per treatment cycle starting at 3 mg/kg. Six dose levels up to a maximum of 27 mg/kg are planned. Human anti-human antibodies (HAHA) directed against IMC-A12 are assessed at baseline and before the Week 4 dose of each cycle.
Results: 9 pts (5 M; 4 F), median age 67 years (range: 44−70), have entered the study at two dose levels. Toxicities considered related to IMC-A12 are anemia (grade 1), psoriasis (grade 1), rash (grade 1), and hyperglycemia (grade 3). The hyperglycemia was considered a DLT and resulted in patient discontinuation. To date, 2 pts remain stable after >20 infusions of IMC-A12 (1 male pt with breast cancer and 1 pt with hepatocellular cancer), and two other pts (1 colon, 1 prostate) have demonstrated reductions in tumor markers. Non-compartmental PK analysis at the 3 mg/kg dose level reveals a mean $t_{1/2}$ of 111.3 hrs, mean C_{max} of 192 ug/mL, and mean AUC_{0-Inf} of 22266 hr*ug/mL. Target trough levels determined from preclinical xenograft studies have been achieved.
Conclusions: Weekly administration of IMC-A12 appears to be well tolerated. There is early evidence of clinical activity, and the PK profile is consistent with that of other Mab's. Dose escalation continues.

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Phase I trial of BB-10901 (huN901-DM1) given daily by IV infusion for three consecutive days every three weeks in patients with SCLC and other CD56-positive solid tumors

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Background: BB-10901 is an immunonconjugate created by conjugation of the cytotoxic maytansinoid drug DM1 to a humanized version of the murine monoclonal antibody N901. BB-10901 binds with high affinity to CD56, an antigen of the family of neural cell adhesion molecules. Once bound to CD56, the conjugate is internalized and releases DM1.
Methods: Subjects were enrolled with relapsed or refractory SCLC, other pulmonary tumors of neuroendocrine origin, non-pulmonary small cell carcinoma, metastatic carcinoid tumors or other CD56+ solid tumors.
Results: Thirty nine subjects were dosed with BB-10901. Subjects are dosed by IV infusion for 3 consecutive days every 3 weeks. Cohorts of 4 subjects initially were enrolled on each dose level. Subjects received BB-10901 at 4, 8, 16, 24, 36, 48, 60, and 75 mg/m^2/day. A dose limiting toxicity (DLT), severe headache, occurred in a patient treated with BB-10901 at 75 mg/m^2/day IV given over 40 minutes. Patients are being enrolled in a 75 mg/m^2/day cohort in which BB-10901 is given at 1 mg/min. Four patients have been treated without a DLT and an additional patient will be enrolled. Six patients had drug related serious adverse events (SAEs). The SAEs consist of constipation (1 patient, 16 mg/m^2/day), fatigue (1 patient, 16 mg/m^2/day), elevated amylase/pancreatitits (two episodes in a patient with evidence of metastases to the pancreas