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.

**644** POSTER

**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 $AUC_\infty$, 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.

**645** POSTER

**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