of three doses (Q2Dx3), and paclitaxel was administered at 8 mg/kg i.p. every day for 5 days (QDx5). RTA 301 treatment caused sustained tumor regression and resulted in tumor/control (T/C) values of 5% and 16% for the high and low dose groups, respectively, while treatment with docetaxel or paclitaxel was much less active (T/C of 82% and 50%, respectively). In the second study, different doses and schedules of RTA 301 administration were compared to docetaxel and paclitaxel using the A549 NSCLC cell line. RTA 301 was administered at 5 or 10 mg/kg i.p. QDx5, or at 10 or 15 mg/kg Q2Dx3. Docetaxel was administered at 13.5 mg/kg i.v. Q2Dx3 and paclitaxel was administered at 16 mg/kg i.p. QDx5. RTA 301 treatment again out-performed docetaxel and paclitaxel, with T/C in the best performing group of 23%, compared with 51% and 59% for these other agents. The third study was performed in P-gp overexpressing NCI/ADR-RES breast tumors. RTA 301 was administered at 5 mg/kg i.p. QDx5 or 15 mg/kg i.p. Q2Dx4 and doxorubicin was administered at 2.5 mg/kg i.p. QDx5. Treatment with RTA 301 was much better tolerated than doxorubicin, allowing administration of multiple cycles. RTA 301 inhibited tumor growth to a greater extent than doxorubicin and was better tolerated in this model, suggesting that this compound may be efficacious in drug-resistant tumors. In summary, RTA 301 significantly inhibited the growth of NSCLC tumors and P-gp overexpressing breast tumors. RTA 301 exhibited greater activity and tolerability than paclitaxel, docetaxel and doxorubicin when dosed at their MTDs in these models. Based on its significant *in vivo* activity, advanced preclinical development of RTA 301 is underway.

640 POSTER

Phase I study of ispinesib (SB-715992), a kinesin spindle protein inhibitor, in combination with capecitabine in patients with advanced solid tumors

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Background: Kinesin spindle protein (KSP) is required early in mitosis for establishment of mitotic spindle bipolarity and for cell cycle progression through mitosis. Ispinesib (ISP), a KSP inhibitor, blocks assembly of a functional mitotic spindle by inhibiting spindle pole separation and leads to mitotic arrest. In a MX-1 tumor xenograft model, sub-MTD doses of both capecitabine (CAP) and ISP led to a 2.5 to 3-fold delay in tumor growth compared to CAP alone (ISP alone was inactive). This provided the impetus for the current study.
Material and Methods: Patients (pts) with advanced solid tumors, PS < 1, and < 4 prior therapies were included in this study. Escalating oral doses of CAP (750–1250 mg/m^2) were administered bid for 14 days along with escalating doses of ISP (12−18 mg/m^2) administered as a 1 hour infusion on day 1 of a 21-day cycle. Three pts were treated at each dose level, with expansion to 6 pts in the event of dose-limiting toxicity (DLT). The (OTR) was defined as the highest dose level for which $\leqslant$1/6 pts experience a DLT. Limited pharmacokinetic (PK) samples were obtained. Clinical response assessments per RECIST criteria were performed every 2 cycles.
Results: 22 pts [(12 M/10 F); median age 60.5, ECOG PS 1, median prior regimens 4], were evaluated at 5 dose levels. A median of 2 cycles were administered (range 1–11) for a total of 68 cycles. The most common toxicities (n = 15), regardless of attribution, included fatigue (5 pts), hand foot syndrome (4), diarrhea (4), pain (3), leukopenia (3), and neutropenia (3); all were Grade (Gr) 1/2 except neutropenia (Gr 4–2 pts; Gr 3–1 pt) and leukopenia (Gr 3–3 pts). DLT of prolonged (>5 days) Gr 4 neutropenia was observed at ISP doses of 15 mg/m^2 (1 pt) and 18 mg/m^2 (1 pt) with a CAP dose of 1000 mg/m^2 bid. The OTR has yet to be defined and evaluation of 18 mg/m^2 of ISP and 1250 mg/m^2 bid of CAP is ongoing. Based on preliminary PK assessment of ISP (n = 12), the concentration of ISP is not affected by the presence of CAP when compared to data from previous single agent studies of ISP. A total of 8 pts (3 breast, 1 each head & neck, bladder, tongue, colon, thyroid) had a best response of SD (duration 2.25−8.25 mo).
Conclusions: ISP has an acceptable tolerability profile at doses up to its monotherapy MTD when combined with a therapeutic dose of CAP. Determination of the OTR is ongoing. Based on the preliminary data, there is no apparent PK interaction between ISP and CAP.

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Efficacy and prediction of response to the new oral taxane DJ-927 in anthacycline pre-treated advanced breast cancer (ABC)

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Background: DJ-927 is a novel taxane, which was selected for low toxicity, oral bioavailability, and potent antitumour activity. This phase 2 study aimed to assess the efficacy of DJ-927 in anthracycline pre-treated ABC and also assess cross-resistance to other taxanes.
Methods: 34 patients with measurable disease were recruited by August 2005. One patient was not evaluable. DJ-927 was given orally at a dose of 27 or 35 mg/m^2 every 3 weeks. 8 patients were subsequently treated with single agent docetaxel. The primary end-point was response rate (assessed by RECIST criteria). Secondary end-points included: duration of response, time to tumour progression, time to treatment failure, subsequent best response to docetaxel and pharmacokinetics of DJ-927 in plasma.
Results: The median age of this cohort of 33 patients evaluable for response was 50. All had prior anthracycline: 18 received it for ABC and 15 as adjuvant or neoadjuvant therapy. Overall, the patients received 163 treatment cycles of DJ-927 (median = 4 per patient). There were 7 confirmed partial responses (21.2%); and 17 stable disease (51.5%). 2 patients withdrew consent and 7 discontinued due to toxicity. The dose of 35 mg/m^2 administered initially to 7 patients was discontinued due to 1 grade 4 haematological (neutropenia >5 days) and 1 grade 4 non-haematological toxicity (pulmonary embolism). DJ-927-related toxicity (grade 3) included: neutropenia (75%), anaemia (6%), thrombocytopenia (6%), constipation (9%), anorexia (9%), sensory neuropathy (3%), motor neuropathy (3%) and neutropenic sepsis (3%). One patient died from a non drug-related event (acute pulmonary embolism). Of those subsequently treated with single agent docetaxel (on average, 4cycles per patient), 5 (62.5%) achieved partial response and 1 (12.5%) had stable disease, suggesting significant (75%) non-cross-resistance. Currently, tumour samples of the patients are being examined by immunohistochemistry for established resistance markers to taxanes, viz. p-glycoprotein, and redox proteins (thioredoxin, thioredoxin reductase, peroxiredoxins and glutaredoxin) to derive a comparative protein profile suggesting sensitivity or resistance to DJ-927.
Conclusion: Significant antitumour activity, tolerability and non-cross resistance of DJ-927 to docetaxel was observed in this study. A molecular protein profile for identifying sensitivity to DJ-927 in comparison to other taxanes may help to personalise the choice of taxane in ABC.

642 POSTER

Pharmacological profile of SVT004703, a new oral proapoptotic compound for the treatment of cancer

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Background: We have discovered a novel structural family of substituted imidazopyrimidines (Patent no. WO 2005/014598), which exhibits high antitumorogenic efficacy both *in vitro* and *in vivo*. Members of this family have shown antiproliferative and proapoptotic activity *in vitro* through the inhibition of tubulin polymerisation. The *in vitro* and *in vivo* pharmacological profile of SVT004703, the most advanced candidate, is reported.
Material and Methods: Antiproliferative activity was assessed by the sulforhodamine B (SRB) assay in two adenocarcinoma cell lines, HCT 116 and HT-29, and the squamous cell line A-431. Apoptosis was determined by the quantification of nucleosomes of treated *versus* control cells (treated with the vehicle) through ELISA. *In vitro* tubulin polymerisation assays were performed in the presence and absence of paclitaxel, known to inhibit tubulin depolymerisation. *In vivo* efficacy was assessed in a human tumor xenograft model with A-431 cells in athymic nude mice, in which the percent change in tumor size for the treated tumors compared to control (T/C) was calculated, and also in a model of UV light-induced skin cancer in hairless Skh:HR-1 mice.
Results: Cell growth inhibition assays revealed that SVT004703, and its analogs SVT004353 and SVT004352, showed high antiproliferative activity against all the tumor cell lines tested in the submicromolar range. SVT-compounds induced apoptosis of HCT 116 cells at concentrations equal or higher than their respective GI_{50} and inhibited microtubule formation by 100% and 75% of both spontaneous or paclitaxel-induced tubulin polymerisation, respectively. Oral SVT004703 treatment of UV-irradiated hairless mice significantly inhibited tumor multiplicity. After 7 weeks of

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.

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