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.

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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.

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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