and time-dependent cell cycle arrest at G2/M, with appearance of 8N peaks (polyploidy) observed at 48 h and 72 h after drug exposure. In the MDA-MB-231 *in vivo* model, there were not fully additive effects of AS703569 with SoC agents cisplatin or taxotere. In vivo, AS703569 significantly inhibited tumor growth in 8/10 human primary BrCa models. The anti-tumor effect was not dependent on the status of Rb or p53. An impressive decrease of pHH3 was observed 6h after a single administration of AS703569 in the 3 primary xenografts tested, indicating that the drug induced a strong and rapid inhibition of AK activity. In a basal-like primary breast xenograft model showing tumor relapse after anthracycline-based chemotherapy, AS703569 administration significantly inhibited tumor recurrence.
Conclusions: In summary, this study shows for the first time that Aurora kinase inhibitor AS703569 has a strong anti-tumoral activity on a large panel of *in vitro* and *in vivo* human primary TNBC models. When combined with anthracyclines, it inhibited tumor recurrence in a basal-like breast cancer xenograft, suggesting that Aki could be used both in monotherapy and combination settings.

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A phase I trial of SCH900776, a selective inhibitor of checkpoint kinase CHK-1, in combination with Gemcitabine in advanced solid tumors

A. Daud[1], C. Soon[2], G. Springett[3], D. Mendelson[4], P. Munster[1], J. Goldman[4], J. Strosberg[3], G. Kato[4], J. Horowitz[5], L. Rosen[4]. *[1]University of California San Francisco, Department of Medicine Division of Hematology and Medical Oncology, San Francisco CA, USA; [2]University of California San Francisco, Department of Dermatology, San Francisco CA, USA; [3]H. Lee Moffitt Cancer Center & Research Institute, GI Oncology, Tampa FL, USA; [4]Premiere Oncology, Clinical Research, Scottsdale AZ, USA; [5]Merck Research Laboratories, Research, Kenilworth NJ, USA*

Background: In cells undergoing DNA synthesis, antimetabolite-induced replication arrest results in the induction of CHK1, halting the progression of cells through G1/S to allow for DNA damage repair. Inhibition of CHK1 by SCH 900776 is hypothesized to synergize with Gem to promote replication fork collapse and apoptosis, even in the setting of anti-metabolite resistance.
Methods: A dose escalation study of SCH 900776 alone and in combination with fixed doses of Gem was conducted in subjects with advanced solid tumors. Subjects were assessed for safety, tolerability, dose-limiting toxicity (DLT), and maximal administered dose (MAD). A recommended Phase 2 dose (RP2D) will be determined based on the safety profile at pharmacologically active exposures.
Results: Twenty-six subjects have been enrolled and treated with 10 (n = 3), 20 (n = 3), 40 (n = 7), 80 (n = 6), and 112 mg/m^2 (n = 7) of SCH 900776 administered alone and following Gem (800 mg/m^2) in Part A on Days 1 and 8 every 21 days. Four subjects at 80 mg/m^2 and 3 subjects at 112 mg/m^2 of SCH 900776 have been enrolled and treated with Gem (1000 mg/m^2) in Part B. No DLTs have been observed and one SAE (G3 hyperbilirubinemia) has been reported during SCH 900776 monotherapy lead-in. Three reversible DLTs have been observed for the combination; supraventricular tachycardia with pneumonia/pneumonitis at 40 mg/m^2 and atrial fibrillation and Grade 4 thrombocytopenia at 112 mg/m^2 (1 subject each) of SCH 900776. MAD is 112 mg/m^2. Clinical activity has been noted in 5 subjects: PR in melanoma and Cholangiocarcinoma, prolonged SD in spindle cell sarcoma and 2 SDs in pancreatic cancer previously treated with Gem. Mean t1/2 is 6.29–9.38 hrs. Cmax and AUC(I) increase dose-proportionally across the dose range of SCH 900776. Similar PK exposures exist between SCH 900776 monotherapy and in combination with Gem. Exposure threshold for preclinical activity ($\geqslant$0.5 μM Cmax) and PD evidence of target engagement were achieved in the first dose cohort (10 mg/m^2).
Conclusions: Pharmacologically active plasma concentrations of SCH 900776 associated with the modulation of the CHK1 mechanism have been safely achieved in combination with Gem with early evidence of clinical activity, including in tumors previously progressing on Gem.

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Pharmacological profile of the novel pan-CDK inhibitor BAY 1000394 in tumor models of human small cell lung cancer, breast and prostate cancer as monotherapy and combination treatment

G. Siemeister[1], A. Wengner[1], U. Lücking[1], P. Lienau[1], W. Steinke[1], C. Schatz[1], D. Mumberg[1], K. Ziegelbauer[1]. *[1]Bayer Schering Pharma AG, Global Drug Discovery, Berlin, Germany*

BAY 1000394 is a nanomolar pan CDK inhibitor based on an aminopyrimidine scaffold. It shows good solubility in water, high metabolic stability, low blood clearance and moderate oral bioavailability in rats. BAY 1000394 inhibits cell proliferation in vitro at low nanomolar concentration in a broad spectrum of human cancer cell lines and shows potent and dose-dependent inhibition of the growth of human cervical HeLa-MaTu xenograft tumors.
Here we present the pharmacological profile of BAY 1000394 in a series of xenograft models of human small cell lung cancer (SCLC), breast and prostate cancers. SCLC xenograft models were generated from either cultured cells (NCI-H146, NCI-H82, NCI-H209, NCI-H69) or patient explants propagated in SCID mice (LXFS 538, LXFS 650, Lu7530). With oral dosing at various dose levels and schedules (2 mg/kg QD; 2.5 mg/kg BID $\times$ 2 and 5 days off; 1.7 mg/kg BID $\times$ 3 and 4 days off), median tumor growth inhibition (TGI) was 86% (range 60−95%). In the NCI-H209 model BAY 1000394 was similarly efficacious as compared to cisplatin, whereas in all other SCLC models BAY 1000394 was more efficacious than cisplatin (median TGI 59%). In the NCI-H82 model, BAY 1000394 (at suboptimal doses and schedule of 0.75, 1.0, or 1.5 mg/kg BID x3 and 11 days off) in combination with either cisplatin (at optimal dose and schedule of 6 mg/kg once, 13 days off) or etoposide (at optimal dose and schedule of 12 mg/kg QD x3, 11 days off) or the combination of cisplatin and etoposide showed strong synergistic efficacy, achieving TGI in the range of 91% to 105%.
In the MDA-MB 231 xenograft model of human triple-negative breast cancer, BAY 1000394 showed strong synergy with taxanes in combination treatment. Combination of BAY 1000394 (1.5 mg/kg BID $\times$3 and 4 days off) with paclitaxel (18 mg/kg once and 13 days off) resulted in TGI of 122%, whereas monotherapies using the same doses and schedules achieved TGI of only 26% for paclitaxel and 39% for BAY 1000394. Similar synergistic activity was also observed for the combination of BAY 1000394 (1 mg/kg BID $\times$3 and 4 days off) and docetaxel (4 mg/kg Q2D $\times$5) in the PC3 xenograft model of human prostate cancer.
In conclusion, BAY 1000394 demonstrates significant antitumor activity in xenograft models of human SCLC, breast and prostate cancers, both as monotherapy and in combination with chemotherapy.

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A phase I dose-escalation study of BI 811283, an Aurora B inhibitor, administered day 1 and 15 every four weeks, in patients with advanced solid tumours

M. Scheulen[1], K. Mross[2], H. Richly[1], B. Nokay[1], A. Frost[2], D. Scharr[2], K.H. Lee[3], O. Saunders[3], J. Hilbert[4], O. Fietz[3]. *[1]West German Cancer Centre University of Essen, Innere Klinik (Tumorforschung), Essen, Germany; [2]Albert-Ludwigs-Universitat Freiburg, Tumour Biology Centre, Freiburg in Breisgau, Germany; [3]Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Research, Biberach an der Riss, Germany; [4]Boehringer Ingelheim Pharmaceuticals Inc., Clinical Pharmacokinetics/Pharmacodynamics, Ridgefield, USA*

Background: BI 811283 is a reversible, potent inhibitor of Aurora B kinase. It causes mitotic override, induction of polyploidy, apoptosis and senescence. In vivo studies showed broad anti-tumour activity in several mouse xenograft models.
Material and Methods: Patients with a variety of advanced/metastatic solid malignancies were randomised to two treatment schedules (4-week & 3-week) in a phase I dose-escalation study. This abstract reports the results of the 4-week schedule. BI 811283 was administered as a 24-hour continuous infusion via central venous access, on Days 1 and 15 every 4 weeks. All patients underwent pharmacokinetic sampling. Pre- and post-treatment skin biopsies were performed to measure levels of histone H3 phosphorylation by Western analysis and immunohistochemistry (IHC), as a marker of Aurora kinase inhibition.
Results: A total of 62 patients were treated at two centres: M/F = 29/33, median age: 60 (range: 23−76); ECOG PS: 0/1/2: 27/32/3. Median number of courses administered: 2 (range:1−16). Patients were treated at 12 dose levels: from 5 to140 mg (Days 1 and 15, q4w). The most common AEs included: fatigue, anorexia, nausea, alopecia, diarrhoea, neutropenia and leucopenia. Haematological toxicity was the main adverse event and was dose-limiting. Dose-limiting toxicities observed included: G4/G3 AST/ALT (n = 1), G3 thrombocytopenia (n = 1), G3 anaemia (n = 1) and G3 neutropenia (n = 3). Dose-limiting neutropenia was seen at higher dose levels. The maximum tolerated dose (MTD) was exceeded at 140 mg, therefore 125 mg was defined the MTD. The best response was stable disease in 16 of 51 patients (31%) with complete data set and who were evaluable. C_{max} and AUC exposure appeared to increase with dose in a linear fashion at all dose levels. Mean terminal -------$t_{1/2}$ ranged from 10−20 hours. The AUC and C_{max} values of total BI 811283 (bound to AGP + unbound) appeared to increase with increasing pre-dose levels of α-acid glycoprotein (AGP) in patients with high variability. IHC analysis of skin biopsies showed a reduction in histone H3 phosphorylation post-treatment particularly at higher doses, consistent with Aurora kinase inhibition. Western analysis was less conclusive.