synthase and incorporated into the DNA molecule, resulting in interruption of DNA synthesis. However, orally administered FTD is rapidly degraded to an inactive form by thymidine phosphorylase. TPI increases the concentration of FTD by preventing its degradation. In the U.S., 5 phase I studies were conducted at different schedules. Those studies showed divided daily dosing of TAS-102 maintained stable disease (SD) and a twice daily schedule was more feasible than a three times a day schedule. Accordingly, we conducted a phase I study with twice daily administration of TAS-102 to Japanese pts with advanced solid tumors.
Materials and Methods: Pts with advanced solid tumors, ECOG PS of 0 to 2, and adequate organ functions were eligible. TAS-102 was orally administered twice daily for days 1 to 5 and 8 to 12, repeated every four weeks. The objectives were to determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT), to assess anti-tumor activity, pharmacokinetics and pharmacodynamics.
Results: A total of 21 pts (14 males, median age 59 yrs, median prior therapy 3 regimens) were enrolled into 5 dose levels (at 30, 40, 50, 60, and 70 mg/m^2/day). Eighteen pts had colorectal cancer. Two pts experienced DLTs during cycle 1; one pt developed grade 4 neutropenia, leucopenia and thrombocytopenia at 30 mg/m^2/day, and another developed grade 4 neutropenia and leucopenia at 70 mg/m^2/day. The most common grade 3 and 4 toxicities in cycle 1 were hematological toxicities. Although the MTD was not reached, the frequency of grade 3 and 4 neutropenia tended to increase in a dose-dependent manner. Therefore, dosage was not escalated more than 70 mg/m^2/day. Although there were no objective responses, 11 pts (52%) maintained SD by RECIST. One pt with colon cancer showed partial response at one assessment. SD persisting longer than 12 wks was observed in 8 pts (38%). The pharmacokinetics in Japanese pts was comparable with the results of the U.S. study.
Conclusions: Twice daily administration of TAS-102 is well tolerated with manageable hematological toxicities in Japanese pts with advanced solid tumors. The recommended dose for phase II trial of TAS-102 administered twice daily was determined to be 70 mg/m^2/day. We are currently planning to conduct studies of TAS-102 alone and in combination with other cancer drugs.

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Phase 1 study of food effects on pharmacokinetics of brivanib alaninate in patients with advanced or metastatic solid tumors

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Background: Brivanib alaninate is the prodrug of brivanib (BMS-540215), a dual inhibitor of vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor (FGFR) signaling. In a previous pilot study (n = 5) conducted with an earlier formulation of brivanib, a high-fat meal slightly reduced C_{max} by 24% without affecting AUC. The aim of this study was to assess the effect of a high-fat meal on the PK of brivanib in patients with advanced or metastatic solid tumors.
Material and Methods: This was a phase 1, open-label, randomized, 2-treatment, 2-period, crossover study evaluating the effect of a high-fat meal or fasting on the PK of brivanib. Patients were assigned to either fasting or a high-fat meal after 10 h of fasting and received a single 800-mg oral dose of brivanib on Day 1. After a 7-day washout period, patients received a single 800-mg oral dose of brivanib on Day 8 and were allocated to the reverse meal content. PK samples were collected up to 48 h post-dose. Patients were monitored for adverse events (AEs) throughout the study. Physical examination, vital signs, and clinical laboratory tests were also assessed throughout the study.

Table: Geometric mean (CV%) of PK parameters of brivanib in fasting and high-fat meal groups

Parameter	Fasting (n = 19)	High-fat meal (n = 19)
T_{max} (h), median (range)	4.0 (1.0–9.8)	3.1 (1.0–10.0)
C_{max} (ng/mL)	2847 (40%)	2877 (46%)
AUC_{0-T} (ng·h/mL)	44,610 (32%)	39,503 (39%)
AUC_{inf} (ng·h/mL)	53,685 (36%)	48,823 (40%)
$T_{1/2}$ (h), mean (SD)	18.3 (6.4)	17.7 (5.8)

Results: A total of 29 patients were enrolled; 21 completed both parts of the study having ingested a minimum of 800 calories, while 19 were evaluable for PK. There was no effect of food on the PK of brivanib. The geometric mean PK parameters are shown in the Table. The geometric mean ratio (90% CI) of high-fat meal/fasting of C_{max} and AUC_{inf} were 1.00 (0.86 to 1.18) and 0.92 (0.82 to 1.02), respectively. The incidences of most frequently reported AEs – constipation, fatigue, hypertension, and nausea were similar in the high-fat and fasting treatment groups. Furthermore, the changes in laboratory values were similar in the 2 treatment groups.
Conclusions: The systemic exposure (C_{max} and AUC_{inf}) of brivanib, following a single oral 800 mg dose of brivanib alaninate, was unaffected by a high-fat meal compared with fasting in patients with advanced or metastatic solid tumors, confirming that brivanib can be given with or without food.

Polo kinases

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Characterization of BI 6727, a novel Polo-like kinase inhibitor with a distinct pharmacokinetic profile and efficacy in a model of taxane-resistant colon cancer

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Background: Plk1 is a key regulator of multiple steps in mitosis and an attractive target for cancer drug discovery. We have previously presented data on BI 2536, a dihydropteridinone inhibitor of Plk1 currently in Phase II clinical studies. To further explore the potential of Plk1 inhibition in oncology, we have synthesized and profiled additional derivatives and now describe BI 6727, a novel clinical candidate with distinct pharmacological and pharmacokinetic characteristics.
Material and Methods: Inhibition of Plks and other kinases was assessed in enzyme assays. The anti-proliferative activity of BI 6727 was determined using AlamarBlue assays. PK profiles were determined in mice and rats. Nude mice bearing subcutaneous xenografts derived from lung (NCI-H460) or colon cancer (HCT-116, CxB1) were treated i.v. (weekly doses, 40−50 mg/kg) or p.o. (50−70 mg/kg) using various schedules.
Results: BI 6727 is a potent and selective Plk1 inhibitor (IC50 = 0.87 nM) that blocks proliferation of multiple cancer cell lines with EC50 values in the range of 10–40 nM, inducing a distinct prometaphase arrest phenotype ("Polo-arrest") and apoptosis. The pharmacokinetic profile indicates sustained tissue exposure with a high volume of distribution and a long terminal half-life in mice (Vss = 7.6 L/kg, $t\frac{1}{2}$ = 46 h) and rats (Vss = 22 L/kg, $t\frac{1}{2}$ = 54 h). The physicochemical and pharmacokinetic properties of the compound allow in vivo testing of intravenous as well as oral (F = 40–55%) formulations. BI 6727 shows efficacy in multiple models of human cancer, including a model of taxane-resistant colorectal cancer, independent of route of administration or treatment schedule.
Conclusion: BI 6727 is a potent and selective Plk inhibitor with sustained tissue exposure that shows efficacy in multiple human cancer xenograft models using oral and intravenous dosing schedules. The compound has been advanced into clinical phase I testing.

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A phase I first-in-human study of the polo-like kinase 1-selective inhibitor, GSK461364, in patients with advanced solid tumors

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Background: Polo-like kinase 1(Plk1) plays multiple roles during mitotic progression. Plk1 over expression is present in a broad range of cancers and is associated with poor prognosis in some tumor types. GSK461364 is potent inhibitor of Plk1 (~400-fold more selective for Plk1 vs. Plk 2 or 3) and has demonstrated anti-proliferative activity against a large panel of cancer lines as well as efficacy against multiple xenograft tumor models.
Methods: Pts with advanced solid tumors, ECOG PS 0−2, and adequate organ function were included in this study. Sequential cohorts of 2−3 pts received escalating doses of GSK461364 administered as a 4-hr IV infusion on different schedules. The primary objectives of the study were to determine the MTD and PK of GSK461364. Secondary objectives included preliminary evaluation of anti-tumor activity.
Results: 12 pts (10M/2F), median age 60.5, were evaluated on two schedules at 5 dose levels [D1, 8, 15 q28: 50 mg(n = 2); 100 mg(n = 3); 150 mg(n = 3)] [D1, 2, 8, 9, 15, 16 q28: 25 mg(n = 2); 50 mg(n = 2)]. Data are available for 10 pts. A median of 2 cycles were administered for a total of 17 cycles. The most common adverse events, regardless of attribution,