treatment (25 mg/kg/day, Monday-Friday) resulted in a 10 day growth delay as opposed to a 4 day delay in tumors derived from the parental cells.
Conclusions: These findings suggest that ZD6474 may have particular utility in therapeutic settings involving aggressive tumors.

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Effects of AZD2171 on pharmacokinetics (PK) of carboplatin (C) and paclitaxel (P) in patients with advanced non-small cell lung cancer (NSCLC): a study of the National Cancer Institute of Canada Clinical Trials Group

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Introduction: AZD2171, a potent oral inhibitor of the tyrosine kinase activity of all VEGFR subtypes, is currently in clinical development. Effects of AZD2171 on PK of C and P were evaluated in a phase I study of AZD2171 in combination with standard doses of C and P in patients with advanced NSCLC.
Methods: C was administered at AUC = 6, and P at 200 mg/m^2 over 3 hours, q 3 weekly. AZD2171 was administered daily starting on day 2 cycle 1 at either 30 mg or 45 mg. Blood sampling for PK was performed during day 1 of cycles 1 and 2. Plasma concentrations of C and P were quantitated with high pressure liquid chromatograph (HPLC). PK analysis was conducted using non-compartmental analysis. Effects of the presence of AZD2171 and its dose on PK parameters were analyzed using 2-way ANOVA with interaction.
Results: Cycle 1 and cycle 2 data were available for 18 patients. PK parameters are summarized in the table.

Parameter	AZD1271 dose		P value
	30 mg (n = 8)	45 mg (n = 10)	
Paclitaxel CL (L/hr)			
No AZD2171	19.5±2.9	22.4±4.6	p < 0.0001 for
With AZD2171	14.3±4.3	18.2±6.0	presence of AZD2171
Carboplatin CL (L/hr)			
No AZD2171	7.0±0.9	9.9±3.5	p = 0.04 for dose effect
With AZD2171	6.4±1.3	8.8±3.9	

P clearance was significantly reduced in cycle 2. C clearance was significantly increased at the higher AZD2171 dose level. There was no correlation between pharmacokinetic parameters and toxicity such as neutropenia or GI toxicity.
Conclusions: P Clearance was reduced by approximately 20% in cycle 2, while C clearance was increased at the higher AZD2171 dose level. Further investigations are needed to determine the clinical significance of the role of AZD2171 on these observations.

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Phase I study of daily oral AZD2171, an inhibitor of the vascular endothelial growth factor receptors (VEGFR), in combination with oxaliplatin and infusional 5-FU (mFOLFOX6) in patients with advanced colorectal cancer (CRC): a study of the National Cancer Institute of Canada Clinical Trials Group

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Background: AZD2171 is a potent oral inhibitor of the tyrosine kinase activity of all VEGFR subtypes. Purposes of this study were to determine the recommended phase II dose of AZD2171 in conjunction with standard doses of mFOLFOX6, and the tolerability, safety, pharmacokinetic (PK) profile and anti-tumor activity of this combination in patients with previously untreated advanced CRC.
Methods: Patients (pts) eligibility criteria included: locally advanced or metastatic CRC; PS 0−2; no prior chemotherapy for advanced disease; adequate hematological, liver and renal functions. AZD2171 was administered daily orally starting Day 3 cycle 1 at a starting dose of 30 mg/d. Modified FOLFOX 6 consisted of oxaliplatin 85 mg/m^2 (2 hour infusion) day 1; leucovorin 400 mg/m^2 (2 hour infusion); and 5-FU bolus 400 mg/m^2 day 1 followed by continuous 5-FU infusion at 2400 mg/m^2 over 46 hours. Cycles were repeated every 14 days. Blood sampling for PK was performed during cycles 1 and 2 for oxaliplatin and 5-FU, and cycle 2 only for AZD2171. Response was assessed by RECIST every four cycles.
Results: To date, 9 patients received 16 cycles of treatment. Of the first 3 pts enrolled at the 30 mg dose level, one grade 3 diarrhea was observed in a patient who was not compliant with anti-diarrhea therapy. The cohort was cautiously expanded to enroll 6 additional pt. One DLT of grade 3 diarrhea was observed in the expanded cohort while grade 3 diarrhea was seen in a patient who was not compliant with therapy. Other common toxicities observed so far included hypertension, fatigue and nausea. Hematologic toxicity was similar to that expected with mFOLFOX6 alone. The study continues at the AZD2171 45 mg/d dose level with enhanced guidelines for early detection and treatment of diarrhea.
Conclusions: Toxicities of this combination appear manageable and predictable. Common side effects included diarrhea, fatigue and hypertension.

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Angiogenesis in human cutaneous tumors

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Background: Angiogenesis has become one of the most widely studied topics. Normal adult vasculature is generally quiescent in nature. The induction of new blood vessel growth from a pre-existing vascular bed is a characteristic of virtually all malignant tumors. The crucial regulators of the process of angiogenesis associated with tumor development and metastasis are vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs). VEGFs are a family of endothelial cell-specific cytokines that act as endothelial cell mitogens and regulate vascular permeability. The aim of this study was to analyze changes in the VEGFs and VEGFRs expression in primary cutaneous malignant melanomas in comparison with protein expression in benign melanocytic and trichogenic tumors and with microvascular density.
Material and Methods: The study included 68 malignant melanomas, 39 pigment nevi and 27 benign trichogenic tumors. Angiogenesis was evaluated using alpha-smooth muscle actin (ASMA) and expression. VEGF, VEGF-C, VEGFR-1, VEGFR-2, ASMA and nestin detection was performed on formalin-fixed, paraffin-embedded tissue sections by indirect immunohistochemistry.
Results: Malignant melanoma cells expressed VEGFs and VEGFRs cytoplasmatically in high levels. Their remarkable overexpression accompanied mainly advanced stages (Breslow III, IV, V). On the contrary, both pigment nevi and benign trichogenic tumors revealed less intensive protein staining. Protein expression correlated with microvascular density. An increased amount of capillaries stained by ASMA and nestin was found within malignant melanomas and in the adjacent dermis, where nestin expression demonstrated new blood vessels formation. Benign tumors exhibited sparse network of blood vessels.
Conclusions: Our results indicate that VEGFs and VEGFRs expression can be involved in skin vessel formation under benign and malignant conditions. The up-regulation of the analyzed factors is associated with significantly enhanced angiogenesis and can contribute to the growth and progression of malignant cells.
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Invasion knock down of human colon cancer cells by siRNA specific for S100A4, a newly identified target gene of beta-catenin/TCF signaling

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Background: It has previously been shown that high expression of S100A4 is associated with cancer metastasis. Our aim was to elucidate the impact of gain-of-function beta-catenin on the metastasis-associated gene S100A4 in human colon cancer cell lines and tumors.
Material and Methods: We analyzed cell lines heterozygous for gain-of-function and wild-type beta-catenin, and variants homozygous for gain- or loss-of-function mutation in beta-catenin, for S100A4 expression, cell migration and invasion. beta-catenin-mediated S100A4 promoter activation

was tested by reporter assays. For human colon carcinomas, S100A4 expression, beta-catenin genotype, and metachronous metastasis were correlated.
Results: We identified S100A4 as the most regulated gene by gain-of-function beta-catenin using a 10K microarray. Cell lines with mutant beta-catenin expressed up to 60-fold elevated S100A4 levels, and displayed strongly increased cell migration and invasion. Very remarkably, invasion and migration were knocked down by S100A4 siRNA and beta-catenin siRNA. S100A4 cDNA transfection increased migration and invasion. We identified a TCF binding site within the S100A4 promoter and demonstrated the direct binding of heterodimeric beta-catenin/TCF complexes to the S100A4 promoter. Reporter assays confirmed the beta-catenin-induced S100A4 promoter activity. Transfection of dominant negative TCF blocked S100A4 expression. Furthermore, S100A4 mRNA expression was increased in primary colon cancers, which later developed distant metastases, compared to tumors which did not metastasize. Colon tumors heterozygous for gain-of-function beta-catenin showed concomitant nuclear beta-catenin localization, high S100A4 expression and metastases.
Conclusions: S100A4 is a direct beta-catenin/TCF target, which induces cell migration and invasion in cell culture. S100A4 siRNA knocks down beta-catenin-mediated migration and invasion. S100A4 has potential value for prognosis of metastasis formation in colon cancer patients.

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A population pharmacokinetic model for BIBF 1120, a triple angiokinase inhibitor, in cancer patients after single and multiple oral dosing

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Background: BIBF 1120 is a triple angiokinase inhibitor targeting VEGFR, PDGFR, FGFR kinases. The objective of the population pharmacokinetic analysis was to develop a model that describes the pharmacokinetics (PK) of BIBF 1120 in cancer patients and can be used to simulate further dosing schedules.
Methods: PK Data of three Phase I clinical trials were used for analysis, in which BIBF 1120 was orally administered to cancer patients, who received doses ranging from 50 mg to 450 mg once daily (q.d.) and 150 mg to 300 mg twice daily (b.i.d.) for 28 days. 117 patients contributed 1734 plasma concentrations. The population PK model was developed using NONMEM® and S-Plus®. This software was used also for the simulations.
Results: A two-compartmental model with first order absorption and elimination rate adequately described the PK data of BIBF 1120 after single and multiple dose administration. The delayed absorption was accounted for by implementing two transit compartments in the model. Inter individual variability was identified on bioavailability (F), clearance (CL/F) and the first order absorption rate constant (ka). In addition, the random variability in bioavailability within a subject between day 1 and day 28 was described by a parameter for inter occasion variability (IOV). The within subject variability in bioavailability was in the same range as the between subjects variability. No time-dependency (e.g. due to (auto-) induction or inhibition), no study dependency and no dose-dependency of BIBF 1120 PK parameters could be identified. Two separate residual errors were estimated, one for the plasma concentrations in the full PK profile on day 1 and day 28 and one for trough plasma concentrations between day 1 and day 28.
Simulations demonstrated that the b.i.d. dosing schedule results in the expected increase in exposure to BIBF 1120 in cancer patients compared to q.d. dosing. Furthermore, simulations of further dosing regimens for the currently tested Phase II doses of BIBF 1120 (150 mg and 250 mg bid) were performed.
Conclusion: BIBF 1120 plasma concentrations in cancer patients were successfully described by a two-compartmental model with a first order absorption and elimination rate. Two transit compartments accounted for the delayed absorption. No significant study or dose differences or any time-dependency in BIBF 1120 PK parameters could be identified. The model developed serves as a tool to predict further dosing shedules.

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A phase I dose-escalation study of the safety and pharmacokinetics of a novel spectrum selective kinase inhibitor, XL820, administered orally to patients with solid tumors

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Background: XL820 is an orally available small molecule inhibitor of multiple receptor tyrosine kinases involved in tumor cell growth and angiogenesis. The primary targets of XL820 are wild type and mutationally-activated KIT, VEGFR2/KDR, and PDGFRβ. The purpose of this study is to define the maximum tolerated dose (MTD) and pharmacokinetics (PK) of XL820.
Methods: Patients (pts) with advanced solid malignancies are enrolled in successive cohorts to receive XL820 orally as a single dose on day 1 with pharmacokinetic (PK) sampling, followed on day 4 by 5 consecutive daily doses with additional PK sampling and observation until day 21. In subsequent cycles, pts receive daily dosing for 5 days every 14 days. Tumor response is assessed every 8 weeks by the RECIST.
Results: To date, a total of 17 pts (colon cancer [3], NSCLC [2], mesothelioma [2], GIST [1], testicular cancer [1], ocular melanoma [1], SCLC [1], ampullary cancer [1], thyroid cancer [1], pancreatic cancer [1], renal cancer [1], breast cancer [1], cholangiocarcinoma [1]) have been treated across 6 dose levels: 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 mg/kg. There has been 1 dose-limiting toxicity of CTCAE grade 3 AST in a pt dosed at 16.0 mg/kg, thus the maximum tolerated dose is not yet defined. Of 15 evaluable pts, 4 have had stable disease (3.5−8+ months). Preliminary PK analysis (0.5−8.0 mg/kg) indicates that systemic drug exposure (area under the plasma concentration-time curve; AUC) and peak plasma levels (Cmax) tend to increase with increasing XL820 dose, but not dose-proportionally with incremental XL820 dose increases. Cohort mean AUC and Cmax values (n = 3 subjects per cohort) were 10,167±4738 ng h/mL and 347±171 ng/mL, respectively, following day 1 dosing at 8.0 mg/kg. Following 5 consecutive daily doses, AUC values were generally <2-fold higher than following a single XL820 dose, suggesting minimal drug accumulation with repeat dosing. Terminal half-life values were approximately 20 hours, and appeared to be unaffected by dose level or duration of treatment.
Conclusions: XL820 is well tolerated up to the 8.0 mg/kg dose. Accrual to the 16 mg/kg cohort is ongoing.

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A Phase I study of sorafenib in combination with capecitabine in patients with advanced, solid tumors

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Background: This single-center, dose-escalation study investigated the safety and pharmacokinetics (PK) of the oral multi-kinase inhibitor sorafenib (Nexavar®) (SOR) in combination with capecitabine (CAP).
Materials and Methods: SOR was given twice daily (bid) on Day 8–21 in Cycle 1, and continuously thereafter. CAP was given orally bid from Day 1 in a 2 weeks on/1 week off schedule. Four cohorts were investigated: SOR 200 mg bid + CAP 2100 mg/m^2 (cohort 1); SOR 400 mg bid + CAP 2100 mg/m^2 (cohort 2); SOR 200 mg bid for the first two cycles, then 400 mg bid thereafter + CAP 2100 mg/m^2 (cohort 3); SOR 400 mg bid + CAP 1700 mg/m^2 (cohort 4). PK were investigated on Day 21 of Cycle 1 and Day 7 of Cycle 2 for SOR, and on Day 7 of Cycles 1 and 2 for CAP. Safety was determined based on the first two cycles in each cohort.
Results: Thirty-five patients were treated (cohorts 1–4; n = 13, 4, 6, and 12, respectively). Common tumors were colorectal cancer (CRC; n = 12) and renal cell carcinoma (RCC; n = 11). Median treatment duration was 133, 110, >225, and >157 days in cohorts 1–4, respectively. In cohort 1, one RCC patient had 932 days of treatment and one CRC patient had 496 days. Median duration on treatment (n = 35) for SOR was 147 days (range 2–925) and 131 days (range 9–903) for CAP. Frequent drug-related toxicities (all grades) over all cycles were hand–foot skin reaction (HFSR; 89%), diarrhea (71%), and fatigue (69%). In cohort 1, two patients had grade 3 dose-limiting toxicities (DLTs): HFSR (n = 1) and diarrhea/HFSR (n = 1). In cohort 2, all four discontinued after Cycle 1 or 2, due to grade 3 fatigue (n = 1); grade 2 HFSR and grade 3 mucositis (n = 1); grade 1 HFSR, grade 1 epigastric pain, and grade 1 nausea (n = 1); and grade 1 thrombopenia