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.

**92** POSTER

**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.

**93** POSTER

**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.

**94** POSTER

**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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**95** POSTER

**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