expression. Unlike mitogenic signals, the regulation of focal adhesions and induction of cell migration by ErbB was not affected by herceptin, an anti-ErbB2 used in treatment regimens for metastatic breast cancer.
Conclusion: Our results provide a mechanistic model for ErbB-induced invasion that is distinct from ErbB-induced mitogenesis. The therapeutic implications of these results will be discussed. *Supported by the Canadian Breast Cancer Alliance (CBCRA) of the National Cancer Institute of Canada and the Cancer Research Society.*

146 POSTER

E7080, a novel multi-targeted tyrosine kinase inhibitor, exhibits anti-angiogenic activity via inhibition of KIT signalling in a small cell lung cancer xenograft model

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Stem cell factor (SCF) is an important growth factor that signals through a receptor tyrosine kinase KIT for amplification/mobilization of hematopoietic progenitor cells, which differentiate into blood and/or vascular endothelial cells. Recently, it was confirmed that KIT/SCF signaling played an important role in tumor angiogenesis by mobilizing endothelial progenitor cells (ECPs) and initiating branching from pre-existing vessels. SCF expression has been reported in several tumor types such as SCLC, NSCLC, colon, breast, and renal cancer. Among them, SCF and/or KIT are expressed in up to 70% of small cell lung cancer (SCLC), in which 50% are SCF-positive alone. Because the growth of KIT-positive SCLC is stimulated by SCF, which also acts to increase angiogenesis, inhibition of this signaling pathway is a promising therapeutic approach. In this study we evaluated the efficiency of E7080 in inhibiting SCF-driven angiogenesis in a SCLC xenograft.
E7080 is an oral multi-targeted tyrosine kinase inhibitor of VEGFRs (VEGFR1–3), FGFR1 and PDGFR-beta with IC50 values of 5–50 nM in cell free kinase assay. E7080 also inhibits KIT with IC50 value of 270 nM. In tube formation assay using human umbilical vein endothelial cells, E7080 inhibited angiogenesis driven by SCF in a dose dependent manner with an IC50 value of 5.2 nM. In this model, concomitant inhibition of KIT phosphorylation was seen. E7080 also inhibited angiogenesis driven by VEGF, with an IC50 value of 5.1nM. In order to assess the efficacy of E7080 in a SCLC xenograft model, H146, a KIT-negative and SCF-positive SCLC cell line was transplanted into mice. Oral administration of E7080 inhibited tumor growth at doses from 30 to 100 mg/kg (BID, QDx21) in a dose dependent manner and produced tumor regression at 100 mg/kg. Imatinib, a KIT kinase inhibitor, also inhibited tumor growth (160 mg/kg BID, QDx21), but it did not produce tumor regression. Treatment with anti-VEGF produced a similar pattern of growth inhibition to Imatinib. Our results indicate that E7080 achieved regression as a result of anti-angiogenic activity via inhibition of both KIT and VEGFR signaling indicating that E7080 has therapeutic potential in SCLC.

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Phase I pharmacokinetic (PK) and safety study of the antiangiogenic peptide ATN-161 (Ac-PHSCN-NH2) in patients with solid tumors

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Background: ATN-161 is a five-amino acid non-competitive inhibitor of the fibronectin synergy region, which plays a critical role in mediating tumor growth, survival and metastasis through interactions with integrins. ATN-161 binds to activated integrins $\alpha5\beta1$, $\alpha v\ \beta3$, and $\alpha v\ \beta5$ on tumor cells, and newly formed blood vessels and has potent anti-tumor activity in a variety of preclinical xenograft models including prostate, breast and colon cancers, either as monotherapy or in combination with chemotherapy. The safety and PK of ATN-161 were investigated in this first in human study.
Methods: Patients with advanced solid tumors refractory to standard therapy were enrolled in sequential dose cohorts to receive 0.1, 0.25, 0.5, 1.0, 2.0, 4.0, or 8.0 mg/kg ATN-161 administered as an IV bolus injection on a thrice-weekly schedule. PK sampling was performed on Day 1 over a 7-hour period after dosing.
Results: Twenty-three patients (10 women, 13 men; median age 64 years; ECOG 0–2) were enrolled to 7 dose levels, with a median treatment duration of two months (range 0.5–10). PK data at doses up to 0.5 mg/kg showed considerable interpatient variability, in part due to undetectable plasma concentrations at late time points. At the 1.0, 2.0 and 4.0 mg/kg dose levels pharmacokinetic parameters appeared dose-independent, with mean total clearance values that ranged from 10.5 to 14.5 ml/min/kg, and terminal elimination half-lives that ranged from 210 to 268 min. At the 8 mg/kg dose level, total clearance was reduced to about 7 ml/min/kg suggestive of saturable elimination.. There were no dose-limiting toxicities or treatment-related serious adverse events. Nineteen patients were evaluable for response. There have been no objective responses. One patient with ovarian cancer had stable disease for 10 months. Two other patients, one with renal cell cancer and one with adenoid cystic cancer of the hard palate, remain on study with stable disease in their 8th and 9th cycles, respectively.
Conclusions: ATN-161 can be safely administered as a thrice-weekly infusion of at least 4.0 mg/kg and higher doses are being explored in this dose-escalating Phase I clinical trial. A recommended Phase II dose has not yet been defined.

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BAY 57-9352: an inhibitor of VEGFR-2 and PDGFR receptor tyrosine kinases that demonstrates broad anti-tumor activity as a single agent in preclinical models

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BAY 57-9352 is an orally active, small molecule inhibitor of VEGFR-2 and PDGFR tyrosine kinases in clinical development that selectively blocks key regulators of tumor angiogenesis. To explore the spectrum of *in vivo* activity of BAY 57-9352, it was tested as a single agent in a panel of human tumor xenograft models representative of breast, colon, prostate and lung cancer. Human carcinoma cells from MDA-MB-231 breast carcinoma, Colo-205 colorectal carcinoma, DU-145 prostate carcinoma and H460 non-small cell lung carcinoma cell lines were implanted subcutaneously in NCr *nu/nu* mice. Studies were run as staged models and drug was administered by oral gavage beginning at the time of staging. BAY 57-9352 inhibited the growth of each tumor type in a dose-dependent manner during the period of drug administration. Immunohistochemical analysis was used to assess the effect of BAY 57-9352 treatment in MDA-MB-231 and Colo-205 tumor models on microvascular density. Following a single administration of BAY 57-9352, the endothelial cell (EC) content of tumor xenografts, as assessed by staining for CD31 and CD34 EC markers, was reduced by 50–70% within 24 hours of the first administration of BAY 57-9352. This finding is consistent with the role of VEGF as a survival factor for EC cell survival and is furthermore consistent with the rapid onset of tumor growth suppression *in vivo* observed following drug administration. These results demonstrate the anti-angiogenic and concomitant anti-tumor activity of BAY 57-9352 in models of human breast, colon, prostate and lung cancer.

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Inhibition of vasculogenic mimicry in melanoma by the antivascular drug 5,6-dimethylxanthenone-4-acetic acid (DMXAA)

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Background: The term "vasculogenic mimicry" is used to describe the ability of some malignant tumour cells to form blood conducting vessels *de novo* without the participation of endothelial cells. Tumour cells in such structures express endothelial-like markers, suggesting a genetic reversion to an embryonic-like genotype. In human cancers, vasculogenic mimicry occurs in breast, prostate and ovarian cancer as well as melanoma, and is associated with high tumour grade, development of distant metastasis and poor overall survival. DMXAA is a low molecular weight antivascular agent that is currently in clinical trial. It acts on the tumour vascular endothelial cells in both mice and humans to induce apoptosis and other effects. We wished to determine whether DMXAA has an effect on tumour cells exhibiting vasculogenic mimicry.
Methods: An early passage human melanoma line (NZM7) was grown both *in vitro* and as a xenograft *in vivo*. Observations were made with phase contrast, confocal laser scanning and transmission electron microscopy. A human angiogenesis gene array kit was used to analyse changes of *in vitro* gene expression.
Results: NZM7 cells lines formed tubular networks when cultured on Matrigel. Addition of DMXAA prevented network formation at a concentration (30 μg/ml) that did not inhibit growth when NZM7 were cultured as monolayers on tissue culture flasks. Microarray analysis of NZM7 cells growing on Matrigel showed that DMXAA (30 μg/ml) significantly inhibited expression of 14 endothelial – and vascular-associated genes, included VE-cadherin, Ephrin B4 and MMP-2. Electron microscopic analysis of NZM7 xenografts showed that some erythrocyte-containing vessels were