# Dynamic Contrast-Enhanced MRI (dceMRI) Evaluation of the Effects of the VEGF/PDGF Receptor Tyrosine Kinase Inhibitor AG-013736 on Tumor Vasculature in a Phase I Clinical Trial

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***Introduction:***

AG-013736 is a potent and selective inhibitor of VEGFR/PDGFR tyrosine kinases with broad preclinical activity in xenograft models (melanoma, colon, breast and lung cancer; 1). Vascular responses, assessed by dceMRI in a preclinical study, were associated with tumor growth inhibition (2). In a Phase I study, AG-013736 was administered in escalating doses to patients (pts) with solid tumors. The primary objectives were to determine maximum tolerated dose (MTD) and safety. Pharmacokinetics, clinical efficacy, and objective tumor vascular response to the drug were also assessed, and are the focus of this report.

***Methods:***

AG013736 was administered orally to 30 pts, either twice daily (BID) or once daily (QD). After the initial cohort of 6 pts where dceMRI was not required, at least 6 pts per dose level (15 mg QD; 5 mg BID fed, 5 mg BID fasted, and 20 mg BID) have been evaluated to date. Cycles were 28 days each, and dceMRI was performed at baseline (study Day –3 to Day 1), Day 2 of Cycle 1 (at $C_{max}$ following third BID dose or second QD dose), Week 4, and Week 8. All 3D dceMRI data were acquired using GE 1.5-T EchoSpeed scanners (256x128 matrix; 10 5-mm slices acquired every 11 sec; 22-36 cm FOV) before, during and after i.v. bolus injection of 0.1 mmol $kg^{-1}$ Gd-DTPA contrast agent. Tumor margins were identified in this study using Geometrically Constrained Region Growth (3) and blood regions were manually identified in the center of large vessels with no apparent flow artifact. Both blood and tumor data were fit to gamma variate curves to reduce noise. These data were fit to the Tofts (Kety) model to determine $K^{trans}$ (4) and the initial (i.e., first 90 sec) area under the curve (IAUC; 5) in the tumor divided by the blood IAUC (to account for differences in the blood input function between studies; 6). Tumor response to treatment was assessed using RECIST criteria (7).

***Results:***

AG-013736 pharmacokinetics were variable (39-96% CV), and the drug was rapidly absorbed with peak concentrations at 2-4 hours (fed state) and elimination with a 3-5 hour terminal plasma half-life. Fourteen of the 21 pts examined by dceMRI had complete image sets of adequate quality for assessing vascular response. IAUC and $K^{trans}$ measured on Day 2 were reduced from baseline by $\geq$50% in 5/14 patients, and by >30% in 11/14 patients. Two out of 5 pts with $\geq$50% decrease in $K^{trans}$ at Day 2 also demonstrated a partial clinical response (PR) after 8 weeks of treatment. Fig. 1a shows a representative slice through an adenoid cystic mass in the maxilla. The decrease in $K^{trans}$ and IAUC was most evident in the tumor periphery, which was better vascularized at baseline. This pt had a PR by week 8. Fig. 1b summarizes the average $K^{trans}$ and IAUC values derived from the index tumor in this same pt, demonstrating an objective vascular response of >50% at both Day 2 and Week 4. Figure 2 summarizes the percent change between baseline and Day 2 in mean $K^{trans}$ plotted against the drug PK AUC extrapolated from 0-24 hours in each of 14 evaluable pts, with a notable trend of increasing vascular response with increasing drug exposure.

***Discussion:***

The results demonstrate that dceMRI provides an objective measurement of the pharmacological effects of AG-013736 on tumor vasculature in humans. It is encouraging that two out of 5 pts with an objective vascular response at Day 2 also had an objective clinical response (i.e., PR). This trial has been extended to include an additional cohort dose at 2 mg BID for 2 days to better resolve the PK/PD relationship.

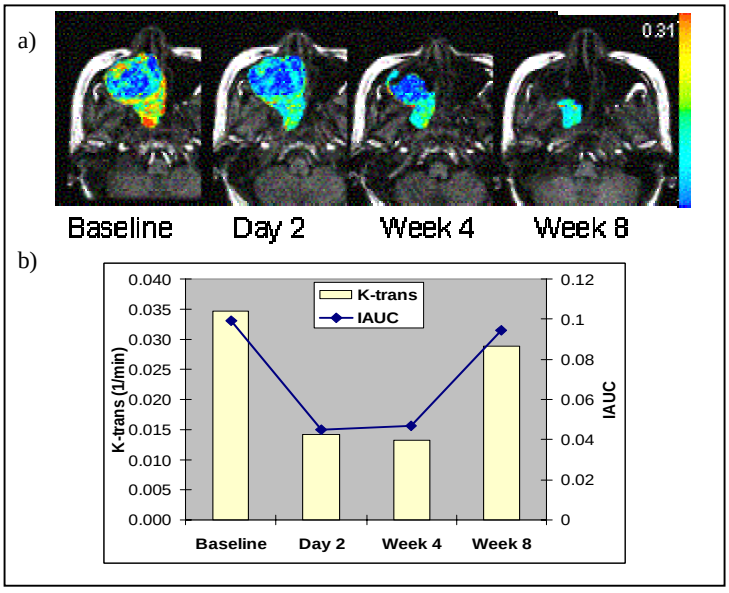


Figure 1: a) Representative slice from a pt with an adenoid cystic tumor at Day 2 , Week 4 and with a PR at Week 8. Color overlay indicates IAUC (scale at right, 0-0.31); b) Percent change in mean $K^{trans}$ and IAUC at baseline, Day2, Week 4, and Week 8.

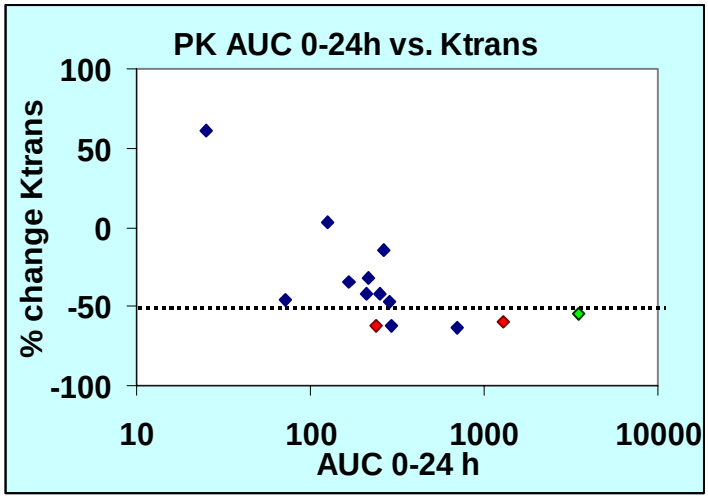


Figure 2: Percent change in mean $K^{trans}$ between baseline and Day 2 plotted against the drug PK AUC extrapolated from 0-24 hours. Red=PR's, Green=cavitated lung lesion by Week 4. Dotted horizontal line inserted to show >50% decrease in $K^{trans}$.

***References:***

[1] Hu-Lowe et al., Proc AACR #5357, 2002. [2] Wilmes et al, Proc AACR #3772, 2003. [3] E Ashton et al., JMRI, 17:300, 2003. [4] P Tofts et al., JMRI, 10:223, 1999. [5] J Mattiello and JL Evelhoch, MRM, 18:320, 1991. [6] CHK Hussain et al, Proc. 2002 ISMRM, 209. [7] Therasse P et al., J Natl Cancer Inst 2000; 92:205-216.