Featured Article

Magnetic Resonance Imaging Measurements of the Response of Murine and Human Tumors to the Vascular-Targeting Agent ZD6126

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ABSTRACT

Purpose: ZD6126 is a novel vascular targeting agent currently undergoing clinical evaluation. It acts by destabilizing the microtubulin of fragile and proliferating neovascular endothelial cells in tumors. The drug leads to blood vessel congestion, the selective destruction of the vasculature, and extensive necrosis in experimental tumors. The aim of the study reported here was to assess the ability of dynamic contrast enhanced magnetic resonance imaging (MRI) to measure the antivasculareffects of ZD6126 in tumors.

Experimental Design: The work was carried out in mice bearing C38 colon adenocarcinoma and in patients with advanced cancers. MRI was performed before and 6 h (human tumors) or 24 h (C38 tumors) after i.v. drug administration. Contrast agent (gadolinium diethylene triaminepentaacetaete) enhancement was characterized by the initial area under the gadolinium diethylene triaminepentaacetaete uptake time curve (IAUC). IAUC reflects blood flow, vascular permeability, and the fraction of interstitial space.

Results: The median IAUC was reduced in all C38 tumors after ZD6126 administration [by 6–48% at 50 mg/kg (n = 3), 58–91% at 100 mg/kg (n = 4), and 11–93% at 200 mg/kg (n = 6). In contrast, the administration of vehicle only led to no consistent change in median IAUC (n = 4). The ZD6126-induced changes in median IAUC appeared to be dose dependent (P = 0.045). No ZD6126-induced changes were apparent in murine muscle. Similar effects were seen in preliminary data from human tumors (11 tumors studied, 9 patients). At doses of 80 mg/m2 and higher, the median IAUC post-ZD6126 treatment was reduced in all of the tumors studied (8 tumors, 6 patients) to 36–72% from the baseline value. There was a significant trend of increasing reductions with increasing exposure (P < 0.01). No drug-induced changes in human muscle or spleen IAUC were apparent. The reproducibility of the median IAUC parameter was investigated in patients. In 19 human tumors (measured in 19 patients) inter- and intratumor coefficients of variation were 64 and 18%.

Conclusions: The contrast enhanced-MRI measured median IAUC is a useful end point for quantifying ZD6126 antivasculareffects in human tumors.

INTRODUCTION

ZD6126 is a vascular targeting agent that was developed to disrupt the tubulin cytoskeleton of tumor neovascular endothelial cells. It is a phosphate prodrug of the potent tubulin-binding agent N-acetylcyclohexin that inhibits tubulin polymerization and causes microtubule destabilization. Disrupting the fragile, proliferating neovascularization of malignant versus normal tissue confers tumor selectivity and distinguishes vascular targeting as a distinct cancer therapeutic approach from angiogenesis inhibition that is designed to prevent the formation of new blood vessels (1). N-Acetylcyclohexin disrupts rapidly the tubulin cytoskeleton and morphology of human endothelial cells in vitro (2), and the morphological effects are selective for proliferating rather than confluent endothelial cells (3). Administration of ZD6126 in vivo causes rapid effects on tumor endothelium, leading to exposure of the basal lamina and loss of endothelial cells (4). The resulting thrombosis and vessel occlusion causes extensive tumor necrosis 24 h after ZD6126 administration. These effects are seen well below the maximum-tolerated dose and are selective for tumor blood vessels in vivo with no evidence of similar effects in normal tissue endothelium (4). The drug has antitumor activity against a broad range of human xenograft and rodent models (4), including lung cancer metastases (5). A consistent observation in preclinical models is a thin rim of peripheral tumor cells surviving treatment that subsequently leads to the regrowth of a tumor. The latter finding has stimulated combination studies of ZD6126 with antiproliferative cancer therapeutic approaches that are cytotoxic to the well-oxygenated, proliferating outer rim of experimental tumors. In support of the combined modality approach, the drug significantly improves the activity of cisplatin (4, 6), paclitaxel (7), and radiation (8) in tumor models. ZD6126 is currently under-
going clinical evaluation, and preliminary studies of Phase I trials have been presented (1, 9, 10).

The clinical progress of antivascular therapy will be aided by the development and validation of methods for measuring changes in the vasculature of human tumors. Many methods are being investigated, in particular noninvasive imaging approaches such as magnetic resonance imaging (MRI), magnetic resonance angiography, magnetic resonance spectroscopy, Doppler ultrasound, and positron emission tomography (11). MRI is an attractive approach because it is widely available, it can provide whole-tumor, high-resolution pictures combining both spatial and functional information, and repeated measurements can be made (12). Although there are a number of MRI techniques that have potential in monitoring antivascular effects, contrast enhanced-MRI (DCE-MRI) is the most widely studied approach (13–15). Recommendations have now been developed for the appropriate MRI methodology for use in Phase I/II clinical trials assessing antiangiogenic and antivascular therapies (16). These recommendations state that one of two possible primary endpoints should be used which include the initial area under the contrast agent time curve (IAUC). IAUC reflects blood flow, vascular permeability, and the fraction of interstitial space.

The following study was established to assess the ability of MRI to measure the response of murine and human tumors to the vascular-targeting agent ZD6126. The hypotheses behind the studies were that the parameter IAUC could measure ZD6126 antivascular effects in tumors in a dose-dependent and reproducible fashion and that the results obtained in murine tumors could be translated into the clinic.

MATERIALS AND METHODS

Experimental Tumor Model. Studies in animals were carried out after approval by the Animal Use Committee of Wayne State University. The data were obtained using the murine C38 colon adenocarcinoma grown as s.c. tumors in the flanks of female B6D2F1 mice. ZD6126 (N-acetylcolchinol-O-phosphate) was formulated in a solution containing 20% of 5% sodium carbonate and 80% PBS at pH ~7. For the DCE-MRI experiments, ZD6126 was given as an i.v. tail vein injection at the following dose levels: 0 mg/kg (n = 4); 50 mg/kg (n = 3); 100 mg/kg (n = 4) and 200 mg/kg (n = 6). Control animals were treated with vehicle alone. For DCE-MRI experiments, animals were anesthetized (1.5% v/v halothane in oxygen) and immobilized on a bed heated by circulating temperature-controlled water. DCE-MRI was carried out immediately before and 24 h after i.v. ZD6126 administration. A comparative efficacy study was carried out of ZD6126 in C57/BL6 mice bearing C38 colon tumors. ZD6126 (100 or 200 mg/kg) was administered on day 10, when the median tumor size was 0.30 cm³ (range, 0.18–0.41 cm³). Necrosis was assessed by light microscopy. Tumor-bearing mice (three/group) were treated with ZD6126 or saline, and tumors were excised 24 h later. Tumors were fixed, processed, and scored as described previously (4). Slides were scored, subjectively and blinded, by a pathologist using the following grading system: (a) grade 1, 0–10% necrosis; (b) grade 2, >10–20%; (c) grade 3, >20–30%; (d) grade 4, >30–40%; (e) grade 5, >40–50%; (f) grade 6, >50–60%; (g) grade 7, >60–70%; (h) grade 8, >70–80%; (i) grade 9, >80–90%; and (j) grade 10; >90–100%. The mean ± SD grade for each dose group was calculated.

Patients. Studies in human tumors were carried out after ethical approval from Wayne State University Investigation Review Board and all patients gave informed consent. Preliminary data were available from 9 patients (4 male, 5 female) with liver metastases of mixed primary solid tumor origin (6 colorectal, 2 renal, 1 ovarian) who received a single i.v. dose of 56 mg/m² (n = 3), 80 mg/m² (n = 3), or 112 mg/m² (n = 3) ZD6126. MRI was performed 24–72 h before and 6 h after drug administration. The reproducibility of the method was evaluated in 19 patients with advanced solid tumors located in the liver (n = 8), bone (n = 5), soft tissue (n = 3), or pelvis (n = 3). DCE-MRI scans were performed twice separated by 2–6 days with no intervening treatment.

DCE-MRI of Murine C38 Tumors. The median tumor volume was 0.20 cm³ (range, 0.07–0.99 cm³). Images were acquired using an actively decoupled 3-cm surface coil for reception (together with a 12-cm actively decoupled birdcage volume coil for homogeneous excitation) on a Bruker Avance magnetic resonance scanner with a 4.7-T horizontal magnet. DCE-MRI data were collected continuously from five contiguous 2-mm slices through the tumor (five slices acquired every 6 s), at least one of which went through the abdomen to provide a muscle reference tissue. A spoiled gradient echo sequence was used with TE (echo time) = 1.5 ms, TR (repetition time) = 46.9 ms, and a 128 × 128 matrix (5 cm field of view). Two data sets were obtained precontrast [T₁ estimation (17) and precontrast background] and continuous images were taken before, during, and after a 0.3 mmol/kg bolus i.v. injection of the contrast agent, Gd-DTPA.

DCE-MRI of Human Tumors. MRI was performed on a 1.5-T Siemens Visionplus scanner using body coil excitation and phased array reception. Images were acquired using a spoiled gradient echo sequence (16 8-mm slices zero-filled to 32 4-mm slices, TE = 1.8 ms, TR = 3.8 ms, 128 × 256 matrix acquired zero-filled to 256 × 256 matrix with a 40-cm field of view) giving an acquisition time of 7.9 s/image set. Two data sets were obtained precontrast [T₁ estimation (17) and precontrast background] and continuous images were taken before, during, and after a 0.1 mmol/kg bolus i.v. injection of Gd-DTPA.

DCE-MRI Data Analysis. For each tumor slice, a region of interest was drawn using T₁-estimated data and/or the final enhancement over the whole tumor, excluding the surrounding normal tissue. Tumor volumes were estimated by voxel counting. Similar regions of interest were drawn over back muscle (murine human) and spleen (human), where available within the imaged field of view. The preinjection images were averaged to increase the signal to noise ratio and subtracted from the postinjection images to give enhancement images. Tumor and muscle contrast agent enhancement time courses were calculated voxelwise using the enhancement and baseline T₁ values. The change in signal (S(Gd-S0)/S0) was divided by the original signal (S0) so that the inhomogeneous sensitivity of the surface coil was divided out. The data were converted to contrast agent concentrations using the known relaxivity of Gd-DTPA: (S(Gd-S)/S0 was converted to ΔR₁ using a look-up table for the observed...
initial $R_1$, and $\Delta R_1$ was converted to contrast agent (CA) using the relationship published by Donahue et al. (18). The IAUC (i.e., first 60 s after bolus arrival) of tissue contrast was calculated on a voxel-wise basis, and the median values were obtained. The effect of increasing dose on changes in enhancement was investigated by fitting a statistical model to the log of the ratio of posttreatment to pretreatment median IAUC values with a linear term for dose. In the reproducibility study, the coefficient(s) of variation (CV) was calculated as the appropriate SD divided by the mean and expressed as a percentage. Any between tumor CV were calculated using the first scan of each tumor. There were 2 patients who had multiple tumors assessed, and for these patients, the average of the median tumor IAUC was used.

RESULTS

A single dose of ZD6126 (100 or 200 mg/kg) induced extensive tumor necrosis within 24 h in mice bearing C38 tumors. Histological examination revealed a core of central necrosis surrounded by a viable rim of tumor 24 h after ZD6126 administration. The mean ± SD tumor necrosis scores were 3.7 ± 2.1, 7.0 ± 2.6, and 9.7 ± 0.6 after 0, 100, and 200 mg/kg ZD6126, respectively. The level of necrosis after 200 mg/kg ZD6126 was significantly higher than in controls ($P = 0.009$).
Dose (mg/kg) & Tumor IAUC (mM) & Change Pre & Post & Change & Muscle IAUC (mM) & Change Pre & Post \\
0 & 0.89 & 1.56 & +74% & 0.80 & 0.92 & +15% \\
0 & 1.56 & 2.42 & +55% & 1.15 & 1.05 & −9% \\
0 & 1.78 & 3.85 & +116% & 0.75 & 1.31 & +75% \\
0 & 2.53 & 1.66 & −34% & 0.93 & 0.61 & −34% \\
50 & 1.27 & 1.19 & −6% & 1.18 & 1.26 & +6% \\
50 & 1.35 & 0.70 & −48% & 1.04 & 0.62 & −41% \\
50 & 1.89 & 1.25 & −34% & 0.95 & 1.01 & +6% \\
100 & 0.94 & 0.39 & −58% & 1.50 & 1.59 & +6% \\
100 & 2.45 & 0.34 & −86% & 1.96 & 2.30 & +18% \\
100 & 2.15 & 0.18 & −91% & 1.12 & 1.29 & +16% \\
100 & 1.63 & 0.24 & −85% & 1.34 & 1.52 & +13% \\
200 & 0.79 & 0.56 & −29% & 0.89 & 0.93 & +4% \\
200 & 0.98 & 0.87 & −11% & 0.60 & 1.10 & +83% \\
200 & 1.80 & 0.46 & −75% & 0.79 & 0.80 & +1% \\
200 & 3.08 & 0.21 & −93% & 1.41 & 0.95 & −32% \\
200 & 2.81 & 0.85 & −70% & 1.01 & 1.01 & 0% \\
200 & 2.96 & 1.87 & −37% & 0.97 & 1.73 & +79% \\

*Contrast-enhanced magnetic resonance imaging measurements of median initial area under the contrast agent time curve (IAUC) were made before (pre) and 24 h after (post) ZD6126 administration to C38-bearing animals.

DISCUSSION

Determining the clinical activity of vascular-targeting agents will be aided by the development and validation of...
MRI Measurements of ZD6126 Response

The results reported here support the use of DCE-MRI as a pharmacodynamic tool in humans. The method is similar in human and animal tumors. The between tumor CV for IAUC was 18%, which is similar to the results from a Phase I trial for CA4P (23). In contrast, there was no evidence of a dose response reduction in tumor IAUC after the administration of DMXAA to patients (24). These differences might relate to the mechanisms of action of the drugs. Both CA4P and ZD6126 are microtubule-destabilizing agents, whereas DMXAA acts by stimulating tumor and host cells to synthesize tumor necrosis factor. Tumor necrosis factor promotes the production of procoagulant factors and disrupts cytoskeletal connections, leading to increased vascular permeability.

This study used the parameter IAUC that measures Gd-DTPA inflow and also the bulk perfusion of a tumor (14). Although to date less widely used than modeled kinetic parameters, it is being used increasingly when measuring the antitumor effects of vascular-targeting agents (14, 15, 22, 24, 27). The most widely used modeled kinetic parameter is the transfer constant $K_{trans}$ that reflects Gd-DTPA delivery (perfusion), transport across the vascular endothelium (vascular permeability), and blood volume (28–30). IAUC reflects the same parameters as $K_{trans}$ and also the fraction of interstitial space. Either IAUC or $K_{trans}$ has been recommended as the primary end point for use in Phase I/II clinical trials of antivascular agents (16). The measurement of ZD6126-induced reductions in IAUC in murine and human tumors validates its use in Phase I/II clinical trials.

The IAUC parameter was reproducible in patients. The within tumor CV for IAUC were 18%, which is similar to the value of 12% for IAUC and 24% for $K_{trans}$ for repeat measurements in 16 human tumors reported elsewhere (27). It is also of note that in the Galbraith et al. (27) study a comparison was made of voxel-wise (as used here) and whole tumor analysis. The authors recommended that a voxel-wise rather than a whole tumor approach is used because it is both more reproducible and also enables the evaluation of tumor heterogeneity in parametric images (27). A within tumor CV of 17% was reported in rat GH3 prolactinomas (25), suggesting that the reproducibility of the method is similar in human and animal tumors. The between tumor CV in the human tumors studied here was higher (CV = 64%) than in animals tumors studied here (CV = 41%) or elsewhere (CV = 26%; Ref. 25). The greater between tumor...
variability in human versus animal tumors is as expected when comparing inhomogeneous human tumors with transplantable animal tumors.

In comparison with IAUC, modeled DCE-MRI kinetic parameters such as $K^{trans}$ require an arterial input function (AIF). The AIF minimizes variations between patients because of variable systemic blood supplies and the delivery of the contrast agent to a tumor. AIFs can be obtained by drawing regions of interest over major arterial blood vessels such as the carotid and vertebral arteries for head and neck imaging or the external iliac artery for imaging in the abdomen. As it is often difficult to measure an AIF in patients, a general function is shown in murine tumors that the IAUC parameter, when normalized to muscle tissue to account for differences in AIF variability and pharmacodynamic use of IAUC. We have previously shown in murine tumors that the IAUC parameter, when normalized to muscle tissue to account for differences in the systemic delivery of the contrast agent obtained in repeat scans of the same patient. In theory, allowing for differences in the systemic delivery of the contrast agent between scans should additionally improve on the reproducibility of the measurement of vascular data using an individual rather than a general AIF improves substantially the reproducibility of the measurement of vascular parameters (31). Although the IAUC parameter does not require an AIF, an AIF might be useful for the normalization of the data obtained in repeat scans of the same patient. In theory, allowing for differences in the systemic delivery of the contrast agent between scans should additionally improve on the reproducibility and pharmacodynamic use of IAUC. We have previously shown in murine tumors that the IAUC parameter, when normalized to muscle tissue to account for differences in AIF between studies, parallels estimates of $K^{trans}$ over a wide range of tissue input functions (32). Although the normalization of IAUC to muscle tissue was effective in murine models, how-

### Table 2: Human ZD6126 study data

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Tumor Type</th>
<th>Tumor size (mm)</th>
<th>Dose (mg/m²)</th>
<th>Tumor IAUC (mm)</th>
<th>Muscle IAUC (mm)</th>
<th>Spleen IAUC (mm)</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Change</td>
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<tr>
<td>2</td>
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<td>161.6</td>
<td>148.5</td>
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<td>4.98</td>
<td>4.92</td>
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<tr>
<td>3</td>
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<td>7.9</td>
<td>56</td>
<td>0.59</td>
<td>0.54</td>
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<tr>
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<td>80</td>
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<td>1.04</td>
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<td>5</td>
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<td>Ovarian carcinoma</td>
<td>23.8</td>
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<td>0.13</td>
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<tr>
<td>6</td>
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<td>20.4</td>
<td>20.5</td>
<td>80</td>
<td>1.60</td>
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<tr>
<td>7</td>
<td>F</td>
<td>Rectal carcinoma</td>
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<td>3.74</td>
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<td>3.1</td>
<td>3.8</td>
<td>80</td>
<td>1.74</td>
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<tr>
<td>9</td>
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<td>Renal cell carcinoma</td>
<td>80.8</td>
<td>80.3</td>
<td>80</td>
<td>3.15</td>
<td>1.92</td>
</tr>
</tbody>
</table>

* Contrast enhanced-magnetic resonance imaging measurements of median initial area under the contrast agent time curve (IAUC) were made before (pre) and 6 h after (post) ZD6126 administration to patients with advanced cancers. In some cases, data were not obtained because of magnetic resonance imaging unavailability or the tissue was not in the imaged field of view.

### Table 3: Human reproducibility data

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Tumor Type</th>
<th>Tumor size (mm)</th>
<th>Imaged site</th>
<th>Days</th>
<th>Tumor IAUC</th>
<th>Muscle IAUC</th>
<th>Spleen IAUC</th>
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<td></td>
<td></td>
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<td>Second</td>
<td>First</td>
<td>Second</td>
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<td>Bronchoalveolar</td>
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<td>37%</td>
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<td>0.35</td>
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<td>0.78</td>
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<tr>
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<td>Colon carcinoma</td>
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<td>51%</td>
<td>0.15</td>
<td>0.37</td>
<td>0.50</td>
<td>0.44</td>
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<td>51%</td>
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<td>0.26</td>
<td>0.87</td>
<td>0.78</td>
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<td>51%</td>
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<td>0.37</td>
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<td>51%</td>
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<td>0.44</td>
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<td>0.50</td>
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<td>0.50</td>
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* Number of days between repeat scans.

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ever, it was not used here because the low perfusion of human (Table 2) in comparison with murine (Table 1) muscle was associated with an increase in noise and variability. This is illustrated by the range of values for the percent change in IAUC between repeat scans of −41 to +83% for murine muscle (n = 17) versus −29 to +192% for human muscle (n = 8). A method has been described for the derivation of an AIF from tissue using a simple algorithm for its automatic extraction from DCE-MRI data (31). In view of the high perfusion and reproducibility of repeat scan data in human spleen (Table 2), it would of interest in the future to examine whether an AIF derived from healthy spleen tissue would be of value.

Additional improvement of the pharmacodynamic use of IAUC measurements in tumors might also be expected from using ZD6126 pharmacokinetic (i.e., drug exposure) rather than dose data. Although the complete pharmacokinetic data are not yet available for all of the patients studied here, the plasma levels of the active metabolite of ZD6126 were available for some. It is of interest to note that of the patients receiving 56 mg/m² ZD6126, patient 1 who showed a good tumor response to ZD6126 (Table 2) had plasma levels of the ZD6126 metabolite that were nearly double those of patients 2 and 3.

In conclusion the DCE-MRI measurement of IAUC is a robust and simple technique for use in humans. The approach developed in murine models has been easily translated into clinical use. IAUC can measure ZD6126 dose-dependent effects in human tumors in a reproducible manner. Therefore, a useful end point for quantifying the biological activity of ZD6126 in Phase I/II clinical trials is the measurement of IAUC using DCE-MRI.

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