EXEL-2880, A SMALL-MOLECULE, ORALLY AVAILABLE TYROSINE KINASE INHIBITOR THAT TARGETS VEGFR AND THE HGF RECEPTOR, C-MET. POTENT ANTI-ANGIOGENIC AND ANTI-TUMOR EFFECTS IN VITRO AND IN VIVO

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INTRODUCTION. Vascular endothelial growth factor (VEGF) and its tyrosine kinase receptors, VEGFR1 and VEGFR2 are expressed on the surface of vascular endothelial cells and play a central role in the promotion of tumor angiogenesis1,2. Hepatocyte growth factor (HGF) and its tyrosine kinase receptor MET are overexpressed and often activated in a wide variety of tumor types, promoting tumor growth3,4. Additionally, HGF and VEGF interact synergistically to promote endothelial proliferation, tubule formation and new vessel growth in vivo5,6,7. EXEL-2880 is a new small molecule tyrosine kinase inhibitor that primarily targets the HGF and VEGF RTKs. We have evaluated the activity of EXEL-2880 in in vitro assays of tumor cell proliferation and chemotaxis, endothelial migration and tubule formation, and in vivo, using multiple tumor xenograft models (human breast cancer, human colorectal carcinoma, rat glioblastoma).

METHODS. EXEL-2880 was evaluated in in vitro kinase assays, as well as in conventional cell based assays for tumor cell proliferation, endothelial migration and endothelial tubule formation. In addition, the effects of EXEL-2880 on HGF induced MET phosphorylation (tumor cells) and on VEGF induced ERK phosphorylation (endothelial cells) were evaluated. For in vivo testing, EXEL-2880 was administered orally and effects upon in vivo target modulation as well as on the growth of a number of different xenograft cell lines determined.

RESULTS. EXEL-2880 is a potent inhibitor of MET and VEGFR2 tyrosine kinase activity, with low nM IC50 values for both kinases. In cell based assays, EXEL-2880 had broad anti-proliferative activities against a panel of tumor cell lines with IC50 values ranging from 0.15 to 3.1 µM. EXEL-2880 inhibited HGF induced responses in tumor cells (e.g. invasion, chemotaxis) with IC50 values below 50 nM. EXEL-2880 also demonstrated potent anti-angiogenic activity, inhibiting VEGF induced pERK in endothelial cells and endothelial tubule formation driven by dermal fibroblasts and xenograft cell lines with IC50 values below 50 nM. Treatment in vivo with EXEL-2880 resulted in dose-dependent and reversible inhibition of the HGF receptor (MET) in xenograft tumors and mouse liver tissue, and VEGFR2 in mouse lung tissue. Following acute administration, EXEL-2880 caused rapid disruption of the tumor vasculature and death of both tumor and endothelial cells. To determine the effect of EXEL-2880 on tumor growth in vivo, the compound was administered using both daily and intermittent oral dosing schedules. Substantial efficacy was achieved with a number of different human xenograft cell lines, and immunohistochemical analysis demonstrated profound inhibitory effects on the tumor vasculature and tumor cell death.
DISCUSSION. EXEL-2880 demonstrates potent anti-tumor and anti-angiogenic activity in preclinical models and is the first compound to enter the clinic that simultaneously targets both HGF and VEGF RTKS. A phase I clinical trial for EXEL-2880 is ongoing.

REFERENCES.