Pediatric Preclinical Testing Program (PPTP) Evaluation of the VEGFR-2 Inhibitor AZD2171


# 102

Abstract

Background: AZD2171 is an oral, highly potent and selective VEGF signaling inhibitor of all VEGFR (tyrosine kinase 1-3) and effectively blocks VEGF-induced angiogenesis and neovascular survival. AZD2171 inhibits the growth of a wide range of established adult tumor xenografts in a dose-dependent manner and in clinical evaluation in adults within the dose range of 5 mg/m2 daily for 3 weeks. These measures of antitumor activity were used: 1) response criteria modeled after the clinical setting (m, partial response (PR), complete response (CR), stable disease (SD), or disease progression (PD)); 2) tumor volumes at day 1 and day 30; 3) growth of lines; (4) overall survival (OS) and median survival (MS) of xenografts; (5) growth of lines (intermediate activity required EFS T/C of 2, and high activity additionally required EFS T/C of 4 for the relevant tumor histologies). Results: AZD2171 induced significant tumor growth delay in 84% of the solid tumor xenografts tested, with growth delay observed in each of the solid tumor panels. Using a time to event measure of efficacy, AZD2171 had intermediate and high levels of activity against 10 of 12 solid tumor xenografts evaluated for this measure, respectively. Intermediate activity was observed in 4 of 5 melanoma xenografts, 3 of 10 therapy resistant melanomas, and 3 of 3 Wilms tumor (WT) xenografts, with high level activity observed in 1 of 2 evaluable medulloblastoma (MB) xenografts, and 1 of 3 WT xenografts, but had no effect on in vivo growth of any ALL xenograft. Conclusion: AZD2171 displayed broad activity against the PPTP solid tumor panel. AZD2171 induced CR against a Wilms tumor xenograft and was effective against 20/22 cell xenografts, 3 of 3 Ewing sarcoma, and 2 of 3 Wilms tumor (WT) xenografts required a net reduction in median tumor volume at the end of the experiment).

Methods for PPTP In Vivo Testing

Methodology: In vitro testing was performed using DMSCAN, a semiautomated fluorescence-based digital image microscopy system that quantifies viable cell number using fluorescence derivative (FDA) cell numbers in tissue culture multwell plates (XelisTech, et al., Methods Mol. Med., 110: 139-155, 2005). Testing was for 96 hours at concentrations from 0.1 to 1.0 µM with 8 replicates of 6 per data point. Data were analyzed using GraphPad Prism. Fitting a non-linear regression model produced an effective dose of the compound for tumor xenograft lines in all of the PPTP, and at a dose sufficient to reduce the growth of tumor xenografts in at least 4 out of 5 cases.

• Gold tumor necrosis. For each xenograft line, 10 mice bearing SC xenografts were treated with AZD2171 for 3 weeks. Tumor volumes were measured daily. Two percent tumor diameters were measured at either 3 or 6 weeks, and tumor volumes were calculated using tumor volume = (l x w x d x 1/2). Tumor volume = log (volume/500). Tumor necrosis = 7. AZD2171 demonstrated broad activity against the PPTP panel cell line with an EC50 <1 nanomolar. AZD2171 inhibits the growth of lines (intermediate activity required EFS T/C of 2, and high activity additionally required EFS T/C of 4 for the relevant tumor histologies).

Examples of AZD2171 in Vivo Activity

• AZD2171 induces significant prolongation of time to event in 27 of 32 solid tumor xenografts tested (84%).
• AZD2171 primarily induced decreased tumor growth rates without tumor regression.
• AZD2171 demonstrated broad activity against the PPTP panel cell line with an EC50 <1 nanomolar.

In Vivo Testing Results for AZD2171

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