Abstract

Pediatric Preclinical Testing Program (PPTP) Evaluation of the Multi-Targeted Kinase Inhibitor Sunitinib

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Methods for PPTP In Vivo Testing

In Vivo Test Results for Sunitinib

Gene Expression for ALL Xenografts & Cell Lines

CONCLUSIONS

Sunitinib showed growth inhibitory activity against a broad range of the PPTP solid tumor xenografts, as illustrated by intermediate activity for the ETS TCC activity measure for 4 of 5 Ewing sarcomas and 4 of 6 rhabdomyosarcomas. Low growth inhibitory activity was observed for the neuroblastoma panel. A single xenograft, KT-1 (chondrosarcoma), showed an effective response to sunitinib. Sunitinib demonstrated limited activity against the PPTP ALL xenografts, with the exception of ALL-16, which showed a partial response. Responses to sunitinib were associated with the pattern of FL1 expression for the ALL xenografts.

Sunitinib is currently in phase I trials for children with cancer using the “4 weeks on/2 weeks off” treatment schedule. The observation of return to control growth rates in the respective control groups following the corresponding phase I trials of sunitinib treatment suggests that it may be advantageous to explore continuous sunitinib treatment in pediatric solid tumor models in future clinical evaluations of sunitinib for children with cancer.

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Example of Sunitinib Dose Response Curve

Gene expression data (Affymetrix U133 Plus 2.0) for the ALL xenografts and cell lines were evaluated for expression levels of several receptor tyrosine kinase (RTK) genes, including FLT3 and PDGFR. Sunitinib activity against the ALL xenografts matched the expression pattern for FLT3 and PDGFR, suggesting broad activity for sunitinib in the ALL xenografts. Another gene, B2M, showed that had PDGFR responses (ALL-1, ALL-17, and ALL-19) also had elevated FLT3 expression. B2M was linked with an ALL gene rearrangement, had FLT3 and PDGFR expression, but not with responses to sunitinib (PD1). FLT3 and PDGFR expression in the ALL xenografts were comparable to that in the matched control group.

CONCLUSIONS