Background: Dasatinib is a dual Src/Bcr-Abl kinase inhibitor that maintains activity against most imatinib-resistant Bcr-Abl leukemias. Dasatinib induced complete remissions in all the preclinical models while commonly caused tumor growth delay in adult solid tumor preclinical models. The CCG Phase 1/2 Consortium has initiated a phase 1 trial of dasatinib for children with refractory solid tumors and Bcr-Abl leukemias.

Methods: The PPTP includes an in vitro panel (23 lines) as well as panels of xenografts (n=141) representing most of the common types of childhood solid tumors and childhood ALL. Dasatinib was administered orally once daily (solid tumor panels) or once daily (ALL panel) for 4 weeks (5 days on, 2 days off) at 45 μg/kg/day. Three measures of antitumor activity were used: 1) response criteria modeled after the clinical setting (i.e., partial response; complete response; CR, etc.), 2) treated to control (T/C) tumor volume at day 21; and 3) a time to event measure based on the median EFS of treated and control lines (intermediate activity required EFS T/C > 2, and high activity additionally required a net reduction in median EFS to event.

Results: Dasatinib induced significant tumor growth delay in 22% of the 27 evaluable solid tumor xenografts tested. Using the time to event measure of efficacy, dasatinib had intermediate activity against 1 (rhabdoid tumor) of 25 (4%) of the solid tumor xenografts evaluable for this activity measure. Dasatinib did not induce objective responses against any of the solid tumor xenografts, but induced a CR against the PPTP’s BcR-Abl ALL xenograft. One of 4 evaluable non-BcR-Abl ALL xenografts achieved a PR and 2 of 4 showed significant growth delay. Seven of 22 tested cell lines in the in vitro panel had EC50 < 1 μM; Kasumi-1, the most sensitive line with an EC50 of 9 nM (CHLA-266), was also sensitive to dasatinib, with EC50 values ranging from 4 nM (BT-16) to 90 nM (G401) (see dose-response curves below). MOLT-4 (T-ALL) was the only ALL line with an EC50 value < 1 μM.

Conclusions: Dasatinib was active against 7 of 22 of the PPTP in vitro panel cell lines when tested at concentrations from 0.1 nM to 1 μM. The most sensitive line was Kasumi-1 (EC50 = 9 nM), an ALL cell line that is known to have a functional Bcr-Abl fusion protein (Aubert et al., 2002). The two rhabdoid tumor cell lines in the PPTP in vitro panel had EC50 values < 1 μM (CHLA-266 = 11 nM and BT-12 = 247 nM). Because of the sensitivity of these two lines to dasatinib, additional rhabdoid tumor lines were studied. These lines were also sensitive to dasatinib, with EC50 values ranging from 4 nM (BT-16) to 90 nM (G401) (see dose-response curves above). MOLT-4 (T-ALL) was the only ALL line with an EC50 value < 1 μM.

Dasatinib demonstrated complete remission against the Bcr-Abl expressing leukemia xenograft ALL-4 (see growth curves below), and dasatinib produced intermediate activity against 2 additional ALL xenografts as assessed by the PPTP time to event measure of activity. The results for the leukemia panel were obtained with a daily dose of dasatinib and are being repeated with the twice-daily dosing schedule that was employed for the solid tumor panels.

Dasatinib induced significant differences in EFS distribution in 6 of 27 (22%) of the solid tumor xenografts (highlighted in red in the table below). Tumor regressions were not observed for dasatinib among the solid tumor xenografts evaluated.

Dasatinib demonstrated intermediate activity against the rhabdoid tumor xenograft KT-16 using the PPTP time to event measure of activity (EFS T/C) (highlighted in light blue in the table below and shown in the growth curves below).

Dasatinib demonstrated intermediate activity against the AML cell line Kasumi-1 (EC50 = 9 nM), confirming previous reports of dasatinib activity against cell lines with the gain-of-function c-KIT mutation (Asn822Lys). The AML cell line M. Kasumi-1, the most sensitive line with an EC50 of 9 nM, confirmed previous reports of dasatinib activity against cell lines with the gain-of-function c-KIT mutation (Asn822Lys). Dasatinibinduced intermediate activity against the rhabdoid tumor xenograft KT-16 using the PPTP time to event measure of activity (EFS T/C).

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