Pediatric Preclinical Testing Consortium evaluation of the second-generation selective nuclear export (SINE) compound KPT-8602

3. Results

3.1. Introduction

KPT-8602 is an XPO1 inhibitor that has the potential for better tolerability, allowing more frequent dosing. The KPT-8602 has reduced CNS penetration compared to selinexor (Hing, et al., 2016), which reduces CNS-mediated constitutional adverse effects and which allows more frequent and prolonged dosing in comparison to selinexor.

KPT-8602 was selected for testing based on its potential for better tolerability, allowing more frequent dosing for a more prolonged period. While weight loss was observed, KPT-8602 was well tolerated at 12.5 mg/kg for a 5-7 day schedule, a 5 week schedule for comparison. Treatment was given thrice weekly at a dose lower (10 mg/kg).

3.2. Study Methods

3.2.1. Administration

Eligible patients were required to have advanced solid disease and be 5-14 years of age with at least 2 biopsies taken before and during treatment. If a patient failed to meet all of the criteria, treatment was stopped.

The pediatric population was analyzed by event. For solid tumor xenografts, events were defined as a 4-fold increase in tumor volume from baseline. For neuroblastoma, events were defined as the time to progression of the tumor less 30% and the time to progression of the tumor less 25% as defined in the study protocol.

3.2.2. Study Methods and Analysis

Solid tumor testing used subcutaneous xenografts. Acute lymphoblastic leukemia (ALL) testing used xenograft models. In the ALL panel, KPT-8602 efficacy testing began at 15 mg/kg but because of weight loss during the initial weeks of treatment, the dose was reduced to 12.5 mg/kg for the remaining weeks of treatment. Eight mice were used to observe the dose at 12.5 mg/kg for four weeks, the dose was reduced to 10 mg/kg for the remaining weeks of treatment.

KPT-8602 induced significant differences in event survival (DFS) distribution compared to control in 7 of the 12 xenografts (see Table 1). Only the FL-A, ALL xenograft, ALL-1 failed to show any treatment effect of KPT-8602.

KPT-8602 induced significant increases in the percentage of neuroblastoma tumors treated with KPT-8602 showed significant increases in the percentage of the minimum tumor volume (or median response evaluation (see Methods for definitions). For the ALL panel, KPT-8602 efficacy testing began at 15 mg/kg but because of weight loss during the initial weeks of treatment, the dose was reduced to 12.5 mg/kg for the remaining weeks of treatment. Eight mice were used to observe the dose at 12.5 mg/kg for four weeks, the dose was reduced to 10 mg/kg for the remaining weeks of treatment.

The PPTC tested KPT-8602 to evaluate whether a higher dose with more frequent dosing translates to greater efficacy (see table below with lines highlighted in bold).

Two of the neuroblastoma lines (CHLA-79 and COG-N-451x) showed partial responses to KPT-8602, as shown in Table 2. The median response evaluation (see Methods for definitions). For the ALL panel, KPT-8602 efficacy testing began at 15 mg/kg but because of weight loss during the initial weeks of treatment, the dose was reduced to 12.5 mg/kg for the remaining weeks of treatment. Eight mice were used to observe the dose at 12.5 mg/kg for four weeks, the dose was reduced to 10 mg/kg for the remaining weeks of treatment.

A subset of the ALL and neuroblastoma xenograft lines tested with KPT-8602 were also tested with selinexor (Attiyeh, et al., 2016), allowing a preliminary evaluation of whether the more frequent dosing of KPT-8602 translates to greater efficacy (see table below with lines highlighted in bold).

For the 7 ALL PDXs tested with both agents, 5 had a better response to KPT-8602. Of the 3 neuroblastoma PDXs tested with both agents, 2 had a better response to KPT-8602.

3.3. Results (continued)

4. Discussion and Conclusions

KPT-8602 showed impressive antitumor activity for selected neuroblastoma and ALL xenograft lines, with no obvious pattern of biologic characteristics explaining the observed activity. The PPTC will continue to test additional neuroblastoma and ALL models, for which no data are currently available. The activity for KPT-8602 against ALL xenografts confirms and expands a previous report (Vercruysse, et al., 2017) showing ALL cell lines were sensitive in vitro and that ALL xenograft lines responded to KPT-8602.

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KPT-8602 would greatly accelerate clinical development of KPT-8602 for children with cancer.

5. References


More Information

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