Pediatric Preclinical Testing Program (PPTP) stage 2 testing of the Aurora A kinase inhibitor MLN8237

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Abstract

Background: MLN8237 is a small molecule inhibitor of Aurora A kinase in adult phase 1 testing. Aurora A kinase plays a pivotal role in centrosome maturation and spindle formation during mitosis. MLN8237 demonstrated activity in preclinical models of adult cancers, and previous PPTP testing identified broad in vivo activity for MLN8237 when tested at its MTD against neuroblastoma and acute lymphoblastic leukemia (ALL) xenografts.

Methods: MLN8237 was tested against selected responsive lines from the PPTP in vivo panels at doses of 20, 10, 5, and 2.5 mg/kg administered orally twice daily 5 days a week, and again at 2 additional concentric dose models at 20, 50, and 100 mg/kg. Treatment was repeated for 6 weeks in the solid tumor xenografts and 3 weeks in the ALL xenografts, with a total treatment/observation period of 6 weeks for all xenografts. Three measures of antitumor activity were used: 1) an objective response measured model after the clinical setting; 2) a treated to control (T/C) tumor volume measure; and 3) a time to event (TTE) (increase in tumor volume) measure based on the median event-free survival (EFS) of treated and control animals for each xenograft.

Pharmacodynamic (PD) studies were performed on selected neuroblastoma lines to evaluate the effect of MLN8237 on Aurora kinase (determined by_LIF/MLN8237), with_Sp100 positive cells determined to support Aurora A rather than Aurora B kinase.

Results: Dose response testing showed 24 neuroblastoma lines were responsive to MLN8237, with an objective response at 10 mg/kg (50% of MTD), with the most sensitive neuroblastoma model (NB-1643) achieving an objective response at 5 mg/kg and with 2D ALL models showing good leukemian growth control during treatment at 5 mg/kg. Two additional neuroblastomas were not responsive to MLN8237 at a dose of 20 mg/kg. MLN8237 induced an increase in mitotic index and Sp100 positive cells following a single dose of agent that peaked at 12 hrs, returning to baseline levels within 24 hrs.

Conclusions: Dose response testing indicates MLN8237 efficacy at 50% of its MTD in a subset of responsive neuroblastomas and ALL models. PD studies are consistent with in vivo anti-neuroblastoma activity through inhibition of Aurora kinase, with broad antitumor activity across several tumor types. Clinical activity is expected in adult patients, and preclinical and pediatric clinical development of MLN8237 is proceeding under the direction of NCI/NCI/CTEP.

Abstract

Methods for PPTP In Vivo Testing

MLN8237 stage 2 testing involves dose response testing in a subset of responsive models.

- Tumor response: Each xenograft line, 10 mice bearing SC tumors initiated treatment when the tumor volume reached 100 mm^3. Two parallel tumors were maintained for each xenograft model; 1) a tumor volume measure modeled after the clinical setting; 2) a treated to control (T/C) tumor volume measure; and 3) a time to event (TTE) (increase in tumor volume) measure based on the median event-free survival (EFS) of treated and control animals for each xenograft.

- For each xenograft line 3 dose levels were tested (20, 10, 5 mg/kg) for each model. Treatment: Two parallel tumors were maintained for each xenograft model; 1) a tumor volume measure modeled after the clinical setting; 2) a treated to control (T/C) tumor volume measure; and 3) a time to event (TTE) (increase in tumor volume) measure based on the median event-free survival (EFS) of treated and control animals for each xenograft.

- 2.5 mg/kg administered orally twice daily x 5 days repeated for 6 weeks in the solid tumor xenografts and 3 weeks in the ALL xenografts, at doses of 20, 10, 5, and 2.5 mg/kg. Treatment was repeated for 6 weeks in the solid tumor xenografts and 3 weeks in the ALL xenografts, at doses of 20, 10, 5, and 2.5 mg/kg.

- Engraftment was monitored weekly by flow cytometry, and treatment was initiated when the proportion of human CD45+ cells in the peripheral blood reached 1%. The proportion of human CD45+ cells in the peripheral blood was maintained throughout the course of treatment.

- MLN8237 was provided to the Pediatric Preclinical Testing Program by Millennium Pharmaceuticals to be tested against the Duke Cancer Center xenografts through the CTA program. MLN8237 Pharmacodynamic (PD) Studies

- MLN8237 demonstrated promising anti-tumor activity at its MTD in Stage 1 testing by the PPTP, particularly for the neuroblastoma and ALL xenograft panels. Dose response testing confirmed the high level of activity for MLN8237 against ALL xenografts and selected neuroblastoma xenografts.

- Against neuroblastoma xenografts, MLN8237 induced complete responses at 50% of its MTD in the CTA program.

- Against 3 ALL xenografts studied, MLN8237 at 50% of its MTD induced CRs that were maintained during 3 weeks of treatment, and 2 of 3 models showed objective responses at 25% of the MTD.

- MLN8237 induced pharmacodynamic effects consistent with specific inhibition of Aurora A kinase with little Aurora B kinase inhibition.

- MLN8237 has entered pediatric phase 1 evaluation with plans to quickly investigate its clinical activity against neuroblastoma and ALL.

MLN8237 was provided by Millennium Pharmaceuticals and testing was supported by NCI NOC/NCI/CTEP.

MLN8237 Pharmacodynamic (PD) Studies

- MLN8237 PD effect was evaluated by determining the % mitotic cells (measured by MIF/MLN8237) and the % phospho-histone H3 positive cells following a single dose of MLN8237 (20 mg/kg). Ser10 of histone H3 is a specific Aurora B substrate.

- MLN8237 induced an ~5-fold increase in % mitotic cells that peaked at 12 hrs and returned to baseline by 24 hrs. A similar magnitude of effect and time course was observed for % phospho-histone H3 positive cells.

- MLN8237 plasma levels at 12 hrs post-dosing were ~1 pM and the % phospho-histone H3 positive cells (mitotic index, mitosis delay, respectively) that were observed (not shown). 1 pM is in the viable EC50 concentration for MLN8237 based on adult cancer preclinical modeling.

- The MLN8237-induced increase in % mitotic cells was matched by an equal increase in % phospho-Histone H3 positive cells, consistent with an Aurora A specific effect with minimal Aurora B kinase inhibition.

Conclusions

- MLN8237 demonstrated promiscuous anti-tumor activity at its MTD in Stage 1 testing by the PPTP, particularly for the neuroblastoma and ALL xenograft panels.

- Dose response testing confirmed the high level of activity for MLN8237 against ALL xenografts and selected neuroblastoma xenografts.

- Against neuroblastoma xenografts, MLN8237 induced complete responses at 50% of its MTD in 2 of 3 responsive models.

- Against 3 ALL xenografts studied, MLN8237 at 50% of its MTD induced CRs that were maintained during 3 weeks of treatment, and 2 of 3 models showed objective responses at 25% of the MTD.

- MLN8237 induced pharmacodynamic effects consistent with specific inhibition of Aurora A kinase with little Aurora B kinase inhibition.

- MLN8237 has entered pediatric phase 1 evaluation with plans to quickly investigate its clinical activity against neuroblastoma and ALL.

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