Pediatric Preclinical Testing Consortium Evaluation of the Dual SYK/FLT3 Inhibitor TAK-659 in Xenograft Models of Pediatric Acute Lymphoblastic Leukemia

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Abstract #3039

Spleen Tyrosine Kinase (SYK), a cytosolic nonreceptor tyrosine kinase, is primarily expressed in the hematopoietic lineage and is essential for B-cell receptor signaling. It is associated with malignant transformation, cancer cell proliferation, and is a prominent tyrosine-phosphorylated protein in B-lineage pediatric ALL (Zaias et al. 2016). Fms Related Receptor Tyrosine Kinase 3 (FLT3) is a Class III receptor (tyrosine kinase that regulates hematopoiesis). While uncommon in ALL, activating FLT3 mutations and internal tandem duplications are associated with poor prognosis (Shrestha and Ruiz, 2020). TAK-659 is a dual SYK/FLT3 reversible inhibitor currently undergoing clinical trials against B-cell lymphoma, acute myeloid leukemia and solid tumors. Therefore, it was of interest for the Pediatric Preclinical Testing Consortium to test TAK-659 in vivo against its patient-derived xenograft (PDX) models of pediatric ALL.

1. Introduction

While children with acute lymphoblastic leukemia (ALL) experience a 80% likelihood of cure, the outcome for certain high-risk pediatric ALL subtypes remains poor. While children with acute lymphoblastic leukemia (ALL) experience a 80% likelihood of cure, the outcome for certain high-risk pediatric ALL subtypes remains poor. While children with acute lymphoblastic leukemia (ALL) experience a 80% likelihood of cure, the outcome for certain high-risk pediatric ALL subtypes remains poor. While children with acute lymphoblastic leukemia (ALL) experience a 80% likelihood of cure, the outcome for certain high-risk pediatric ALL subtypes remains poor. While children with acute lymphoblastic leukemia (ALL) experience a 80% likelihood of cure, the outcome for certain high-risk pediatric ALL subtypes remains poor. While children with acute lymphoblastic leukemia (ALL) experience a 80% likelihood of cure, the outcome for certain high-risk pediatric ALL subtypes remains poor.

2. Study Methods

Agent administration - TAK-659 was provided by Takeda Pharmaceuticals International Inc. and was administered at 60 mg/kg by oral gavage daily for 21 days.

Study design and analysis - FLT3 and SYK mRNA expression in pediatric ALL PDXs was quantified by RNA-seq (https://pediapo.org).

TAK-659 was evaluated in vivo against a panel of 8 B-lineage PDXs including infant mixed lineage leukemia rearranged (MLL)-ALL, B-cell precursor (BCP)-ALL, and Ph-like ALL. Each PDX was heterochromically injected into 8 immune-deficient (NSG) mice per treatment group (2-5 x 105 cells/mouse; Lien et al. 2004).

Engraftment and drug responses were evaluated by enumerating the proportion of human CD45+ cells in the peripheral blood (PB) ([hiCD45+] whenever detects > 1%) at weekly intervals.

An event was defined as ≥2% huCD45+ cells in the PB, or when the mouse exhibited leukemia-related morbidity associated with high-level leukemic infiltration (≥50% huCD45+) or ≥2 of the C-diagonal markers.

Bone marrow and central regions of left and right femurs and the degree of organ infiltration (%huCD45+) were analyzed using Objective Radiation Therapy Imaging and in vivo Whole Body Imaging (VIBI) and in vivo Imaging (VoI).

The Kaplan-Meier method was used to determine event-free survival (EFS) between control (C) and treated (T) groups.

Treatment response was monitored using Objective Response Measures (ORMs) modeled after stringent clinical criteria (Houghton et al. 2007); with an EFS > 10% compared to median control EFS.

PD2 - progressive disease 2, [hiCD45+] in PB never drops below 1% and there was event before the end of the study, with an EFS < 2 median compared to median control EFS.

4. Results and Conclusions

- TAK-659 was evaluated at 60 mg/kg against a panel of 8 B-lineage PDXs selected based on the levels of FLT3 and SYK gene expression and was well tolerated.
- FLT3 and SYK gene expression were decreased in all treatment groups.
- TAK-659 significantly delayed leukemic progression in 6/8 PDXs, and significantly reduced the effect of FLT3 and SYK expression in vivo via the peripheral blood in all B-lineage PDXs.
- Only one PDX (MILL-1) achieved an objective response (partial response) with all other models exhibiting progressive disease.
- Leukemia infiltration in the blood (CP) was significantly decreased in the BCP-ALL PDXs (ALL-2, ALL-17, ALL-26), and in the left endosteal region of BM in MLL (659) by TAK-659 treatment.
- Overall, TAK-659 exhibited low to moderate single-agent in vivo activity against pediatric B-ALL PDXs representative of diverse disease subtypes.

5. References