The menin inhibitor VTP-5049 enhances the in vivo efficacy of established drugs against preclinical models of aggressive infant MLLR acute lymphoblastic leukemia

Richard Lock, Kathryn Event, Sophia Kwon-Taylor, Kirth Saita, Timothy DeJesus, Eric J Saxby, Emily J Ozone, Carol R Bell, Jennifer A Tuckey, Gerard M McKenne and Malcolm A Smith*

*Children's Cancer Institute, Lung Cancer Research Centre, Centre of Signal Transduction Research (CSR), Centre for Childhood Cancer Research, LHNP, Sydney, NSW, Australia, The Jackson Laboratory, Bar Harbor, ME, USA, Children's Hospital Boston, MA, USA, Children's Hospital Los Angeles, CA, USA, The National Cancer Institute, Bethesda, MD, USA, Novosibirsk Clinical Research Centre, Novosibirsk, Russia.

Background

MLL-rearranged acute lymphoblastic leukemia (MLL-R ALL/AML)

- Over 70% of infants with ALL present with rearrangements of the mixed lineage leukemia gene (MLL-R ALL/AML), which is associated with hematological malignancies.
- MLL-R ALL/AML is a fusion protein which deregulates transcriptional elongation. This leads to dysregulated gene expression, including CDC25B gains (Figure 1).
- Dysregulation of the fusion protein is unrelated to the presence of chimeras (Figure 1).
- MLL-R ALL/AML is a fusion protein which deregulates transcriptional elongation. This leads to dysregulated gene expression, including CDC25B gains (Figure 1).

Methods

- Single agent EFS analysis was conducted at 150 mg/kg, 240 days, per group.
- Two single agent and combination treatment groups were evaluated at 150 mg/kg and 300 mg/kg, respectively.
- Three different mouse lines were used: 9- to 12-week-old normal C57BL/6 mice, 9- to 12-week-old immunodeficient Rag1-deficient mice, and 9- to 12-week-old severe combined immunodeficient mice.
- Treatment window: 28 days.
- Evaluation criteria: event-free survival (EFS) and percentage of human vs. murine CD45 in the peripheral blood (PB), which was measured by percentage of human vs. murine CD45 in the peripheral blood.
- Study design analysis:
  - All agents used in vivo against a human xenograft model MLL-R ALL.
  - Patients derived xenografts (PDXs) were previously established from patients and xenografted into syngeneic mice.
  - Agents used in vitro against a human xenograft model MLL-R AML.
  - Patients derived xenografts (PDXs) were previously established from patients and xenografted into syngeneic mice.

Results

- VTP-5049/VXL elicits therapeutic enhancement, with near complete clearance of leukemic infiltration in both PDXs. In contrast, VTP-5049/gilteritinib did not elicit therapeutic enhancement in either PDX and was not significantly more efficacious than gilteritinib alone (Figure 2A).
- VTP-5049/VXL elicits therapeutic enhancement, with near complete clearance of leukemic infiltration in both PDXs. In contrast, VTP-5049/gilteritinib did not elicit therapeutic enhancement in either PDX and was not significantly more efficacious than gilteritinib alone (Figure 2A).
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Discussion & Conclusions

- VTP-5049/VXL elicits therapeutic enhancement in two aggressive orthotopic infant MLLR ALL PDXs, as well as in a more sensitive subset of MLLR ALL PDXs.
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References


Figure 1. Summary of the menin inhibition pathway. Figure 2. VTP-5049/VXL elicits therapeutic enhancement in two infant MLLR ALL PDXs, as well as in a more sensitive subset of MLLR ALL PDXs. Figure 3. In vivo efficacy of single agent VTP-5049. Figure 4. In vivo efficacy of single agent VTP-5049. Figure 5. In vivo efficacy of single agent VTP-5049.

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