3. Results

### 3.1. In vivo efficacy of VTP-50469 against pediatric MLL-r ALL PDXs

- **VTP-50469 was well tolerated**, with maximum average weight losses of 1.4-4.4% across treatment groups compared to vehicle control matched mice.
- **VTP-50469 induced significant decreases** in EFS distribution compared to control in 6 of the 8 of the expression, including the ALL-56 group. (Figure 1, Table 1).
- **Chromosomal translocations affecting the MLL gene at 11q23 involved in >10% translocation partners**. Of oncogenic MLL fusion proteins stimulate transcriptional deregulation which leads to dysregulated expression (Buchholz et al., 2017).

### 3.2. Study Methods

**Drug Administration:**
- VTP-50469 was administered at a dose of 120mg/kg by oral gavage, twice daily for 28 days.

**Study design and analysis:**
- Pediatric MLL-r ALL PDXs were established from direct patient ex vivo engraftment in the perivascular leukemic bone marrow (BM) tissue, and subsequently evaluated using a highly associated with leukemic infiltration (~90% of at least 2 major organs).
- The Kaplan-Meier method compared event-free survival (EFS) between treated and control groups.
- The drug response categories are as described in Houghton et al., 2007.
- The data are reported as mean (±SEM) or median (±range) values unless otherwise stated. *p* values were determined by one-way ANOVA with Dunnett’s post hoc testing. 
- *p* values less than 0.05 were considered statistically significant.
- The integral of the relative percentage of the minimal %huCD45+ cells in the BM at any point in time after treatment initiation relative to the %huCD45+ on the day of treatment initiation is known as the EFS to the median.
- Results are displayed as mean ± SEM for each group and presented as Kaplan-Meier plots. **Figure 1**, **Figure 2**, **Table 1**.

### 3.3. Results (continued)

- **Table 1. Responses of pediatric MLL-r ALL PDXs tested with VTP-50469 in vivo**.

### 4. Discussion and Conclusions

- **VTP-50469 exerted profound efficacy against ALL PDXs** derived from infants harboring MLL-ENL, ABL-ENL, and MMAL-ENL translocations.
- VTP-50469 as a single agent was well tolerated by naive NSG mice up to 120 mg/kg (highest dose tested).
- A significant reduction in leukemia BM infiltration was elicited by VTP-50469 in 6 of 7 evaluable MLL PDXs.
- The present activity of VTP-50469 was verified by its lack of effect against the A-Rh-ALL PDX harboring the BCR-ABL1 translocation.

### 5. References


**Figure 1.** Responses of MLL-r ALL PDXs to VTP-50469 in vivo. Engraftment plots of 3 MLL-r ALL PDXs (A) and 4 MLL-r ALL PDXs (B) were treated with VTP-50469. (A) Engraftment plots (B) comparing AML-fusion survival curves of MLL-r ALL PDXs.

**Figure 2.** Effects of VTP-5049 on leukemia infiltration into the femoral BM of mice engrafted with ALL PDXs. The proportion of human leukemia cells in specific femoral bone marrow regions was assessed prior to treatment (Day 0; black cross), in vehicle control mice at end of study (gray squares), and in vehicle control mice at end of study (red squares). **Figure 2**.

**Figure 3.** Dose response of MLL-r PDXs engrafted with 0.5 and 2.5 times the MTD. (A) Engraftment plots (B) comparing AML-fusion survival curves of MLL-r ALL PDXs.