1. Introduction

Malignant transformation of the mixed lineage leukemia (MLL, KMT2A) gene (MLL) occurs predominantly in acute leukemia, in 80% of infant acute lymphoblastic leukemia (ALL) cases, and in 30% of adult acute leukemia. MLL encodes a histone methyltransferase responsible for the regulation of gene expression. Chromosomal translocations affecting the MLL gene at 11q23 involve > 90 translocation partners. Oncogenic MLL fusion proteins stimulate transcription elongation which leads to dysregulated expression of target genes (Molenaar et al., 2007).

Interaction of MLL with the nucleolar protein exin drives transcription of hundreds of MLL target genes. MLL fusion proteins regulate the expression of the protein Menin, which is a ubiquitously expressed tumor suppressor protein that localizes to the nucleolus. The menin-MLL interaction acts as a critical oncogenic cofactor of MLL fusion proteins and together associates with the MLL-SET1 like histone methyltransferase complex and acts as a transcriptional repressor. The menin-MLL interaction is dysregulated in most MLL-rearranged leukemia models of infant acute lymphoblastic leukemia.

2. Study Methods

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

3. Results

3.1. In vivo efficacy of VTP-50469 against pediatric MLLr ALL PDXs

- VTP-50469 was well-tolerated, with maximum average weight losses of 1.6-4.4% across treatment groups compared with poor outcome.
- VTP-50469 induced significant differences in EFS distribution compared to control in all 6 of the expression, including the all-MLL group.
- Chromosomal translocations affecting the MLL gene at 11q23 involve > 90 translocation partners.
- Oncogenic MLL fusion proteins stimulate transcription elongation which leads to dysregulated expression of target genes (Molenaar et al., 2007).
- Interaction of MLL with the nucleolar protein exin drives transcription of hundreds of MLL target genes. MLL fusion proteins regulate the expression of the protein Menin, which is a ubiquitously expressed tumor suppressor protein that localizes to the nucleolus.

3.2. Study Methods

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

3.3. Results (continued)

Figure 1. Responses of pediatric MLLr ALL PDXs tested with VTP-50469 in vivo.

Figure 2. Effects of VTP-50469 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 circles), in vehicle control mice at event (grey squares), or in VTP-50469-treated mice at Day 28 post treatment initiation (red triangles). Control mice were assessed prior to treatment (Day 0, black circles), in vehicle control mice at event (grey squares), or in VTP-50469-treated mice at Day 28 post treatment initiation (red triangles) or at Day 28 post treatment initiation at all events (whichever occurred first) in control and VTP-50469-treated animals.

Table 1. Response of pediatric MLLr ALL PDXs tested with VTP-50469 in vivo.

Table 1. Response of pediatric MLLr ALL PDXs tested with VTP-50469 in vivo.

VTP-50469 was also effective across a broad dose range, indicating that it may represent a novel small molecule inhibitor.

4. Discussion and Conclusions

VTP-50469 was well-tolerated to evaluate its pharmacodynamic efficacy against an ALL PDX panel across a broad dose range, indicating that it may represent a novel small molecule inhibitor.

5. References

