Abstract #3835

In vivo evaluation of the menin inhibitor VTP-50469 against Ewing sarcoma preclinical models – A report from the Pediatric Preclinical Testing Consortium (PPTC)

Raushan T. Kurmasheva, Stephen W. Erickson, Gerald M. McGeehan, Beverly A. Teicher, Malcolm A. Smith, Peter J. Houghton

1Greehey Children’s Cancer Research Institute, San Antonio, TX; 2RTI International, Research Triangle Park, NC; 3Syndax Pharmaceuticals, Waltham, MA; 4National Cancer Inst., Bethesda, MD

1. Introduction

- MLL1 (KMT2A), a lysine methyltransferase, binds promoters of HOX genes resulting in H3 Lys 4 methylation and H3 and H4 acetylation.
- While the role of MLL1 translocations is well established for leukemia, less is known regarding the role of MLL1 in solid tumors.
- Posterior HOXD genes are overexpressed in Ewing sarcoma (EwS). Promoter regions for these genes are characterized by MLL1-mediated H3K4me3 marks and are devoid of recessive H3K27me3 marks (Svoboda, et al., 2014).
- In leukemias, the oncogenic activity of MLL1 fusion proteins is dependent on association with menin, a scaffolding protein that binds MLL1 and MLL4 (KMT2B) in the context of TTXG COMPASS complexes (Yokoyama, et al., 2005).
- Small molecules that inhibit the Menin-MLL1 interaction have shown profound activity against PPTC MLL-rearranged leukemia and solid tumors. (Borkin, et al., 2015).
- The role of MLL1 in solid tumors is less known.

2. Study Methods

Agent Administration: VTP-50469 was administered by oral gavage at 100 mg/kg twice daily for 28 days.

3. Results

- Tumor bearing mice were treated when tumors were 200-400 mm³. VTP-50469 was administered by oral gavage (PO), at 120 mg/kg or 100 mg/kg twice daily for a planned 28 days. Lines show growth of individual tumors, Control (red); VTP-50469 treated (blue). The solid (bold) lines show median response. Panel A: Tumor volume, Panel B: relative tumor volume, and Panel C: Kaplan-Meier probability curves for event-free survival (EFS).

4. Discussion and Conclusions

- VTP-50469 caused a statistically significant growth delay in 4 of 7 EwS models.
- Among models with significant slowing of tumor growth, the ratio of median time to event for the treated versus control groups (EFS T/C) ranged from 1.24 to 1.74.
- There were no tumor regressions, and the mean minimum relative tumor volumes (RTV) for treated groups ranged from 1.2 to 3.5.
- At the same dose and schedule at which VTP-50469 shows remarkably high in vivo activity against MLL-rearranged leukemia xenograft lines, it shows minimal levels of in vivo activity against EwS models.
- Our results and an examination of existing literature for menin inhibitors suggest that EwS cells are less dependent on the Menin-MLL1 interaction for survival in comparison to MLL-rearranged leukemias.

5. References

- Borkin, et al. The role of MLL1 in solid tumors is less known.

More Information

*Corresponding author: Raushan T. Kurmasheva
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