Table S1. Summary of RNAseq gene expression analyses of mouse and human cells.
RNAseq analysis of differential gene expression of: *MxCreNpm1c*$^{flox\text{-}cA/+}$ versus WT GMPs and LSKs, 4 weeks post pIpC injection; Mouse *MIG-CreNPM1c/DNMT3a* mutant leukemic GMPs compared to WT GMPs; OCI-AML3 cells treated with DMSO versus 330 nM VTP-50469 for 3, 5, and 7 days; *Npm1*$^{flox\text{-}cA/+}$*Dnmt3a*$^{R878H/+}$ mouse cell line (SIIIL12) treated with DMSO versus 30 nM VTP-50469 for 3 days; Mouse *MxCreNpm1*$^{flox\text{-}cA/+}$*Dnmt3a*$^{R878H/+}$ LT-GMPs treated with control versus 0.1% VTP-50469 spiked chow *in vivo* for 5 days.

Table S2. Summary of Menin and MLL1 ChIPseq analyses in OCI-AML3 cells.
Differential occupancy at TSSs of MLL1 and Menin in DMSO versus 330 nM VTP-50469 (4 days) treated OCI-AML3 cells.

Table S3. Lists of gene signatures used for GSEA analyses.
List of all gene sets used in this study including custom made gene sets "OCI-AML3_VTP-50469_MLL_LOSS" (top 200 genes that lose MLL TSS occupancy in response to VTP-50469 treatment determined by ChIPseq analysis) and "UP_IN_LSK_VS_GMP" (genes significantly upregulated in wildtype LSKs versus GMPs determined by RNAseq analysis).

Table S4. Summary of sequencing results to verify MLL1, MLL2 Meis1 editing.
CLUSTAL O(1.2.0) multiple sequence alignment of amplicons of targeted genomic DNA for sg*MLL1*, sg*MLL2,* and mouse *sgMeis1*.

Table S5. Patient derived xenograft sample information.
Summary of age, gender, and therapy information available for patient samples used in PDX studies.

Table S6. Detailed patient information for matched NPM1c^{+} MDS and sAML samples.
Summary of age, type, and time to relapse information for matched NPM1c^{+} MDS and sAML samples**.**