**Supplemental Figure Legends**

**Supplemental Figure 1. ABBV-075 displaces BRD4 from Myc promoter.**  SKM1 cells were incubated with DMSO or ABBV-075 for 6 hours, and the binding of BRD4 to the myc promoter or the reported super enhancer (Shi et.al Genes and Development, 2013) were determined by ChIP-qPCR. Results are representative of two independent experiments with triplicates for each data point. The primers specific for the heme lineage-specific enhancers were reported by Shi et al., Genes & Development (2013). Enrichment was calculated using the DDCT method using negative control region.

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**Supplemental Figure 2. Apoptotic responses to MS417 across cancer cell lines.** Cells were treated with 1 µM MS417 for 72 hours and the degrees of apoptosis were determined by FACS analysis using Annexin/7-AAD staining.

**Supplemental Figure 3. Degrees of apoptosis in CD34+ cells upon the treatment of BET inhibitors.** Cord blood cells were treated with DMSO, ABBV-075, or MS417 at the indicated concentration for 72 hours. Apoptosis was determined by FACS analysis using gating strategies to specifically detect Annexin positive cells within the CD34+ population. The average and standard deviation of % Apoptotic cells from two independent experiments is presented.

**Supplemental Figure 4. MS417-mediated downregulation of BCL-XL and BCL-2 preceded MCL-1 downregulation.** Cells were treated with 1 µM MS417 for the indicated duration, collected at each time point, and analyzed by Western blotting using indicated antibodies.

**Supplemental Figure 5. ABBV-075 downregulated BCL-XL in hematological cancer cell lines.** Cells were treated with 0.2 µM ABBV-075 for the indicated duration, collected at each time point, and analyzed by Western blotting using the indicated antibodies. Results are representative of two independent experiments.

**Supplemental Figure 6. Exogenously introduced BCL-XL expression rescued apoptosis induced by ABBV-075 in AML cell lines.** A) The AML2 parental cells (AML2 Parental) and AML2 cells with stable integrated empty vector (AML2 Vector) or BCL-XL expression cassette (AML2/BCL-XL) were incubated without or with (- or +) 0.2 µM ABBV-075 for 24 hours. Cells were then collected and analyzed by Western blotting. B) AML2 parental lines (grey bars), cells with stably integrated empty vector (black bars) or BCL-XL expression cassette (white bars) were incubated with DMSO or indicated concentrations of ABBV-075 for 72 hours, then analyzed by FACS using Annexin/7-AAD staining to determined degrees of apoptosis. C) Cells were incubated with DMSO or indicated concentrations of ABBV-075 for 24 hours, and cell cycle profiles were analyzed by FACS using PI staining. Results are representative of two independent experiments with biological duplicates in each experiment.

**Supplemental Figure 7. BET inhibitor triggered reversible cell cycle arrest in cell lines originating from solid tumors.** H1299 and MX-1 cells with continuous exposure to DMSO or 1 µM MS417 for 48 hours or a 48-hour exposure to MS417 followed by a 24-hour or 48-hour washout were analyzed for cell cycle profile by FACS using PI staining. Results are representative of two independent experiments with biological duplicates in each experiment.

**Supplemental Figure 8. Sustained exposure to a BET inhibitor over 7 days triggered senescence in cell lines originating from solid tumors.** H1299 and MX-1 cells were incubated with DMSO or 2 µM MS417 for 7 days then stained for senescence associated -galactosidase using the manufacturer’s suggested protocol. Results are representative of three independent experiments with biological duplicates in each experiment.

**Supplemental Figure 9. ABBV-075 inhibited cell cycle related genes.** SKM1 and H1299 cells were incubated with 0.2 µM ABBV-075 for 24 hours. Cells were then collected and analyzed for the expression of a set of cell cycle related genes using the bDNA assay. Results are representative of three independent experiments with biological duplicates in each experiment.

**Supplemental Figure 10. ABBV-075 downregulated *BCL-XL* at the mRNA level.** Cells were incubated with 0.2 µM ABBV-075 for 24 hours. Cells were then collected and analyzed for the expression of BCL-XL using the bDNA assay.

**Supplemental Figure 11. ABBV-075 displaced BRD4 from the *BCL-XL* promoter and super enhancer.** SKM1 cells incubated with DMSO or 0.1 µM ABBV-075 for 6 hours, and the binding of BRD4 to the *BCL-XL* promoter region was determined by ChIP-qPCR. Results are representative of two independent experiments. The primers specific for the promoter were reported by Pradhan et al, PLOS One (2011): SE-specific regions were ordered from Qiagen. Enrichment was calculated using the DDCT method using a negative control region.

**Supplemental Figure 12. PPZ did not sensitize H1299 and 22RV1 cells to ABBV-075.**  H1299 and 22RV1 cells were treated with DMSO or PPZ at 6 and 50 uM in the presence or absence of 0.2 uM ABBV-075 for 7 days. Apoptosis was determined by FACS analysis of Annexin and 7-AAD positive cells. Results are representative of two independent experiments with biological duplicates in each experiment.

**Supplemental Figure 13. Restoring Myc expression in MV4:11 did not rescue ABBV-075-induced cell cycle arrest or apoptosis.** Top panel: MV4:11 parental cells and MV4:11 cells containing a CMV-Myc expression cassette (MV4:11\_cMyc) by lentiviral infection were treated with 1 uM MS417 and collected for Western analysis at the indicated time points. Bottom panels: apoptosis and cell cycle arrest in MV4:11 and MV4:11 cMyc cells incubated with DMSO or 1 uM MS417 for 72 hours.

**Supplemental Figure 14. Differential expression of key Bcl-2 family proteins in hematological and solid tumor cell lines.** Expression data based on NGS platform was obtained from CCLE database.

**Supplemental Figure 15. A model for differential apoptotic responses to ABBV-075 in hematological versus solid tumor cell lines.** High levels of Bim expression confer an intricate balance of pro- and anti-apoptotic proteins in hematological cancer cells, making these cells exquisitely sensitive to a relatively strong down regulation of Bcl-XL by ABBV-075. In contrast, the lack of apoptotic stress from high Bim expression allow solid tumor cell lines maintain sufficient extra anti-apoptotic capacities to buffer the apoptotic stress from a moderate down regulation of Bcl-XL by ABBV-075 in these cells.

**Supplemental Figure 16. Reduction of ABBV-075-induced apoptosis in Granta519 cells with low Bim expression.** Left panel: the parental Grenta519 cell line and a derivative cell line with low Bim expression were treated with 1 uM of ABBV-075 for 72 hours, and the degree of apoptosis was determined by FACS analysis of Annexin and 7-AAD staining. Right panel: Western analysis of Bim expression in the parental and the derivative low Bim cell line. Results are representative of two independent experiments with biological duplicates in each experiment.

**Supplemental Figure 17. Distribution of CCLE cell lines with concomitant high levels of Bim and Bcl-2 expression within different cancer types.** Cell lines with FPKM > 10 for both Bim and Bcl-2 was identified using the CCLE cell panel expression data that was obtained from the NGS platform. Numbers on top of each column represent the number of cell lines with high expression of both Bim and Bcl-2 and the total number of cell lines within indicated cancer type. Y-axis represent the percentage of Bim/Bcl-2 high expression cell lines within a given cancer type.

**Supplemental Figure 18. Global gene expression analysis of SKM1 flank tumors upon azacitidine and ABBV-075 single agent and combination treatment.** Mice bearing SKM1 flank tumors were administrated with vehicle (n=4), azacitidine (n=3), ABBV-075 (n=3), and Azacitidine/ABBV-075 combination with the same dose and schedule used in tumor efficacy studies: azacitidine i.v. 6 mg/kg, qdx1, ABBV-075 p.o. 0.67 mg/kg, qdx3, and combination at the same dose/schedule. Tumors were collected for microarray analysis 6 hours after the last dose of ABBV-075, which is 72 hours post azacitidine administration. Top panel: clustering of all experiments based on fold changes (>2 fold, p<0.01). Lower panel: break down of genes that are modulated by single agent and combination treatment, and examples of subsets of ABBV-075 responsive genes whose regulation by ABBV-075 were enhanced by the combination with azacitidine.

**Supplemental Figure 19. Hypoxia and/or the presence of pro-survival factor IL-6 did not significantly alter cell sensitivity to ABBV-075.** Cells that exhibited low levels of apoptosis (FaDu) or high levels of apoptosis (OPM2, SKM1) upon ABBV-075 treatment were incubated with series dilution of ABBV-075 under normal tissue culture conditions or under hypoxia or in the presence of IL-6 or hypoxia+IL6 for 5 days and IC50s of ABBV-075 under each condition is presented.

**Supplemental Figure 20. ABBV-075 impacted components of the agiogenesis machinery.** Top panel: Activity of ABBV-075 on HUVEC cell proliferation. Bottom panel: does response of ABBV-075 in blocking VEGF-A and FGF2 transcription under hypoxia. Results are representative of two independent experiments with biological duplicates in each experiment.

**Supplemental Figure 21. ABBV-075 induces differentiation markers in HL-60 cells.** HL-60 cells were incubated with ABBV-075 or known differentiation agents Bexa or ATRA at the indicated concentration for 7 days. The expression of differentiation markers CD11b and CD14 were determined using FACS analysis. Results are representative of two independent experiments with biological duplicates in each experiment.

**Supplemental Table 1. IC50s of ABBV-075 in the 5-day proliferation assay across cancer cell lines.**

**Supplemental Table 2. IC50s of MS417 in the 5-day proliferation assay across cancer cell lines.**

**Supplemental Table 3. Degrees of apoptosis triggered by ABBV-075 across cancer cell lines.** Cells were treated with 0.2 µM ABBV-075 for 72 hours and the degrees of apoptosis were determined by FACS analysis using Annexin/7-AAD staining.

**Supplemental Table 4. Degrees of apoptosis triggered by MS417 across cancer cell lines.** Cells were treated with 1 µM MS417 for 72 hours and the degrees of apoptosis were determined by FACS analysis using Annexin/7-AAD staining.