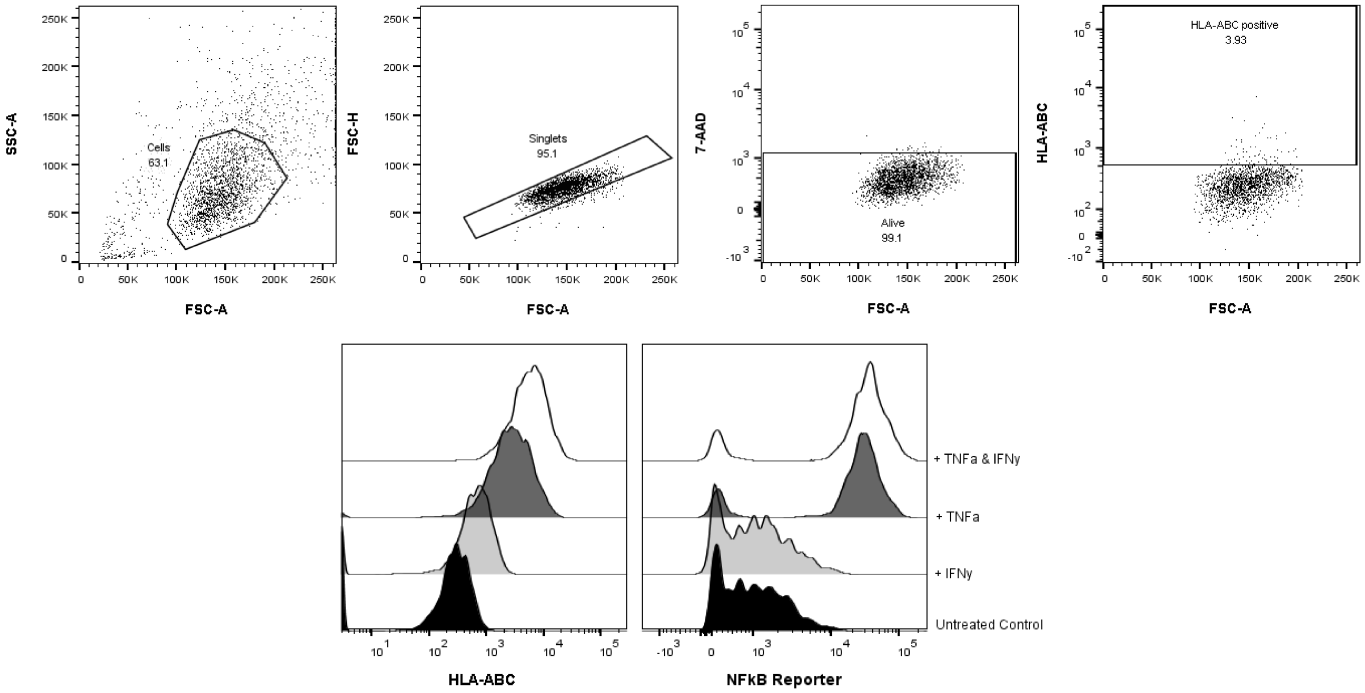
Supplementary Material

Supplementary table 1 – List of HDAC inhibitors upregulating MHC-I expression in GIMEN reporter cells. *HDAC = Histon Deacetylase, % HLA-ABC expression standardized to untreated control cells*

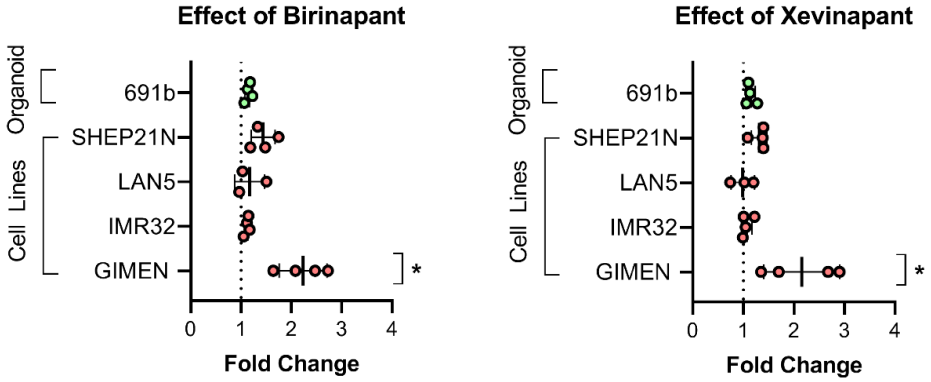
Compound	Alternative Names	Target	% HLA-ABC expression
Citarinostat	ACY-241, HDAC-IN-2	HDAC3/6	10.2%
Fimepinostat	CUDC-907	PI3K, & HDAC1/2/3/10	49.9%
Pracinostat	SB939	panHDAC	41.9%
Abexinostat	PCI-24781, CRA-024781	panHDAC, most potent against HDAC1	40.3%
Mocetinostat	MGCD0103, MG0103	HDAC 1/2/3/11	34.9%
Entinostat	MS-275, SNDX-275	HDAC1/3	26.8%
Sodium Phenylbutyrate	4-BPA, 4-phenylbutyric acid	HDAC1/2a	25.7%
Tucidinostat	Chidamide, HBI-8000, CS-055	HDAC1/2/3/10	22.8%
Dacinostat	LAQ824, NVP-LAQ824	panHDAC	21.2%
Resminostat	RAS2410	HDAC1/3/6	19.7%
CUDC-101	-	HDAC1/2, EGFR, HER2	14.1%
LMK-235	-	HDAC4/5	10.7%
Citarinostat	ACY-241, HDAC-IN-2	HDAC3/6	10.2%
Droxinostat	NS41080	HDAC3/6/8	9.9%
Tubastatin A	-	panHDAC, most potent against HDAC6	9.9%
RGFP96	-	panHDAC, most potent against 3	9.4%

Supplementary table 2 – List of IAPi upregulating MHC-I expression in GIMEN reporter cells. *IAP = inhibitor of apoptosis, % HLA-ABC expression standardized to untreated control cells*

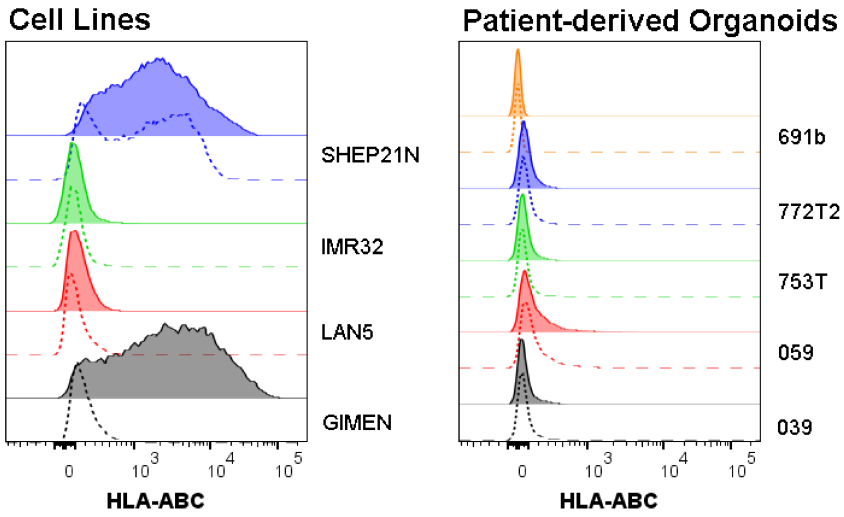
Compound	Alternative Names	Target	% HLA-ABC expression
MX69		MDM2, XIAP	46.8%
GDC-0152		cIAP1+2, XIAP, ML-IAP	27.8%
AZD-5582		cIAP1+2, XIAP	24.4%
Xevinapant	AT-406	cIAP1+2, XIAP	20.5%
Birinapant	TL32711	cIAP1 mostly, less potent against XIAP	20.0%
LCL-161		cIAP1+2, XIAP	19.8%



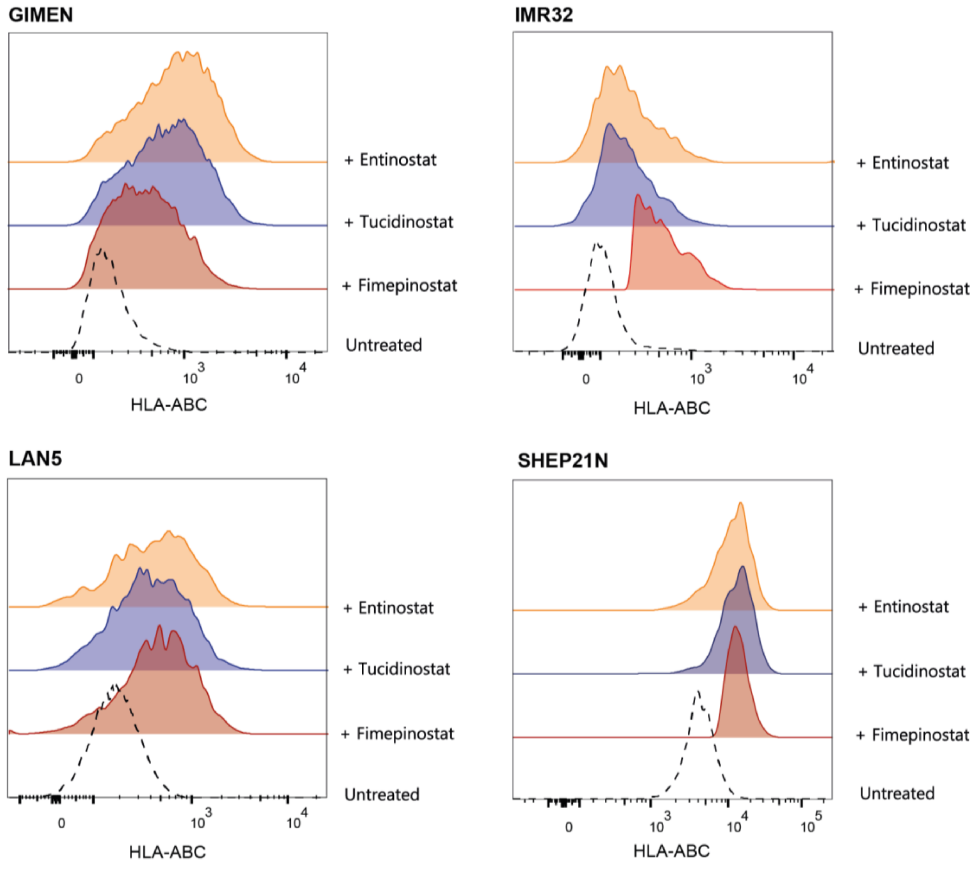
Supplementary Figure 1 – Drug Library Screen Gating Strategy & Representative Controls. *Upper Panel: Gating strategy to identify HLA-ABC expressing cells. Lower Panel: MHC-I (left) and NFkB Reporter (right) induction upon cytokine incubation. Untreated cells were used as negative controls. Cells treated with 1000 U/mL IFNγ, and/or 50 ng/mL TNFα were used as a positive control for MHC-I expression (HLA-ABC AF647) or NFkB Reporter (GFP) induction.*



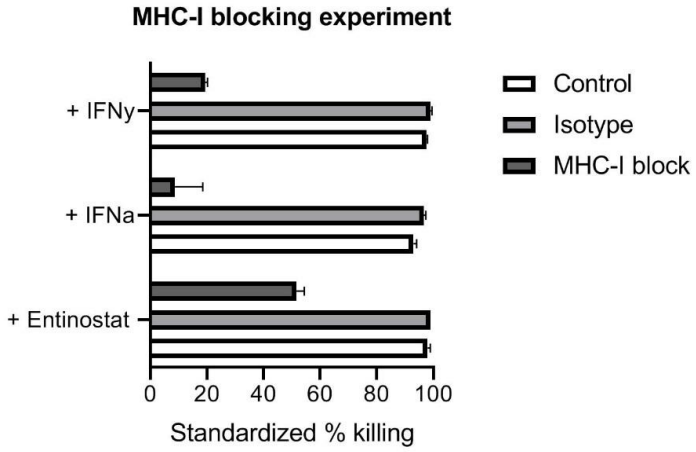
Supplementary Figure 2 – Effect of two other IAPi across a panel of NBL lines. *Fold Induction of MHC-I expression relative to untreated control cells after 48h of incubation with 250 nM Birinapant or 500 nM Xevinapant. Data depicted as mean ± SD. LAN5: n=3, rest: n=4, Statistical differences between MFIs were calculated with the Mann Whitney U test, *p<0.05.*



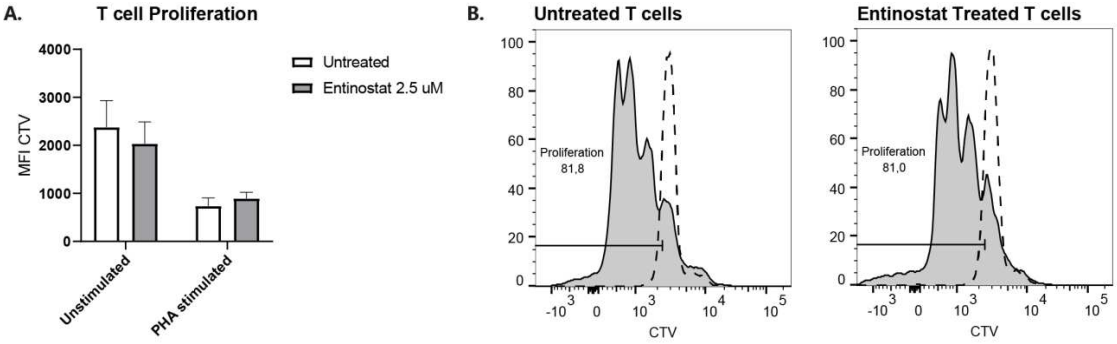
Supplementary Figure 3 – Sensitivity of NBL models to TNFα-mediated NFkB pathway activation. *Dotted lines reflect unstimulated cells, filled histograms are stimulated with TNFα (0.5 ng/mL).*



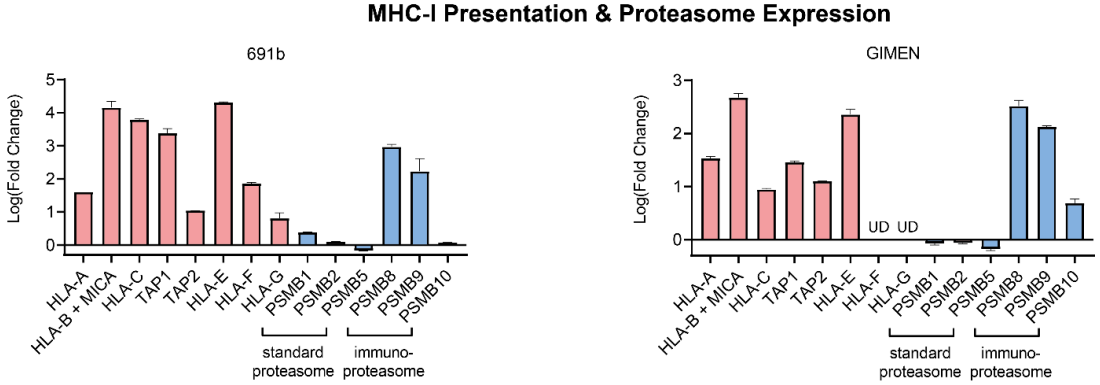
Supplementary Figure 4 – Effect of two other HDACi, tucidinostat and fimepinostat, across a panel of NBL lines. *MHC-I upregulation after 48h treatment with Tucidinostat (GIMEN & LAN5: 5 uM, SHEP21N: 2.5 uM, IMR32 1.25 uM) or Fimepinostat (GIMEN: 100 nM, LAN5 & SHEP21N: 25 nM, IMR32: 12.5 nM). Dotted line reflects untreated control cells.*



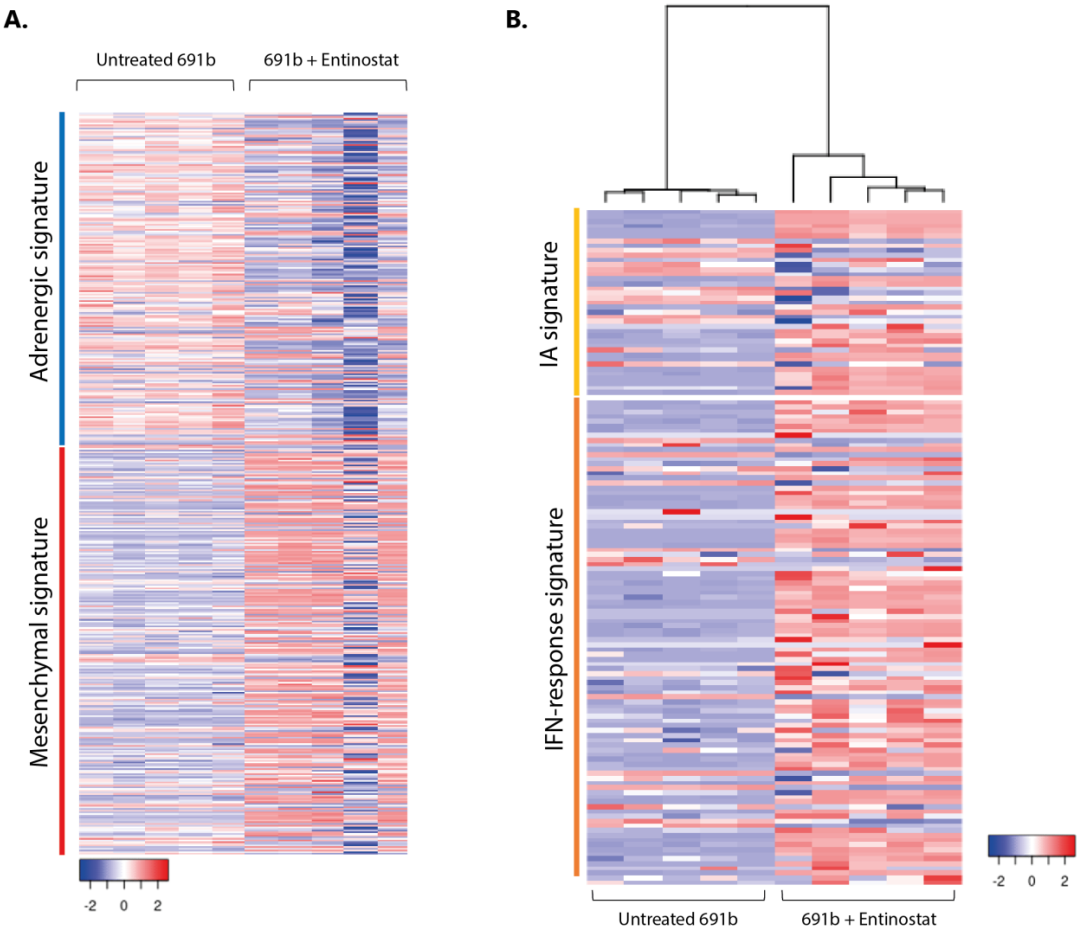
Supplementary Figure 5 – Entinostat-induced T cell cytotoxicity is MHC-I dependent. *Luminescence-based cytotoxicity against luciferase-transduced 691b organoids after 48h pre-incubation with 2.5 μM Entinostat, 1000 U/mL IFNα, or 100 U/mL IFNγ. Co-cultures were performed either without presence of blocking antibody, with an isotype control, and with an MHC-I blocking antibody. Cells were co-cultured overnight at an E:T of 1:1. Data are shown as mean ± SEM.*



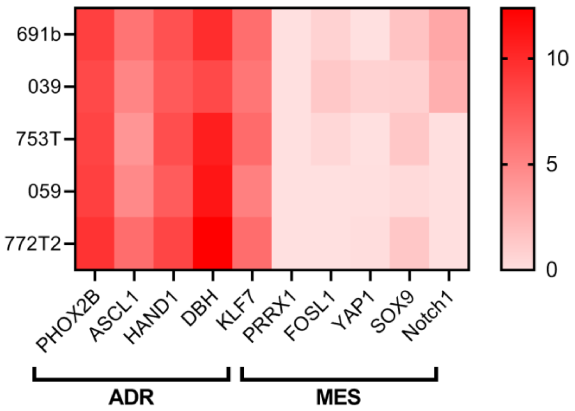
Supplementary Figure 6 – Intact proliferative capacity of Entinostat pre-treated healthy-donor T cells. *Proliferative capacity of T cells based on CTV-dilution. (A) Shows the MFI in CTV in untreated and 2.5 uM Entinostat pre-treated healthy-donor CD3+ T-cells. Data is shown from four donors, no significant differences based on the Mann Whitney U test. (B) shows the CTV division pattern in untreated (left) and entinostat pre-treated T cells (right).*



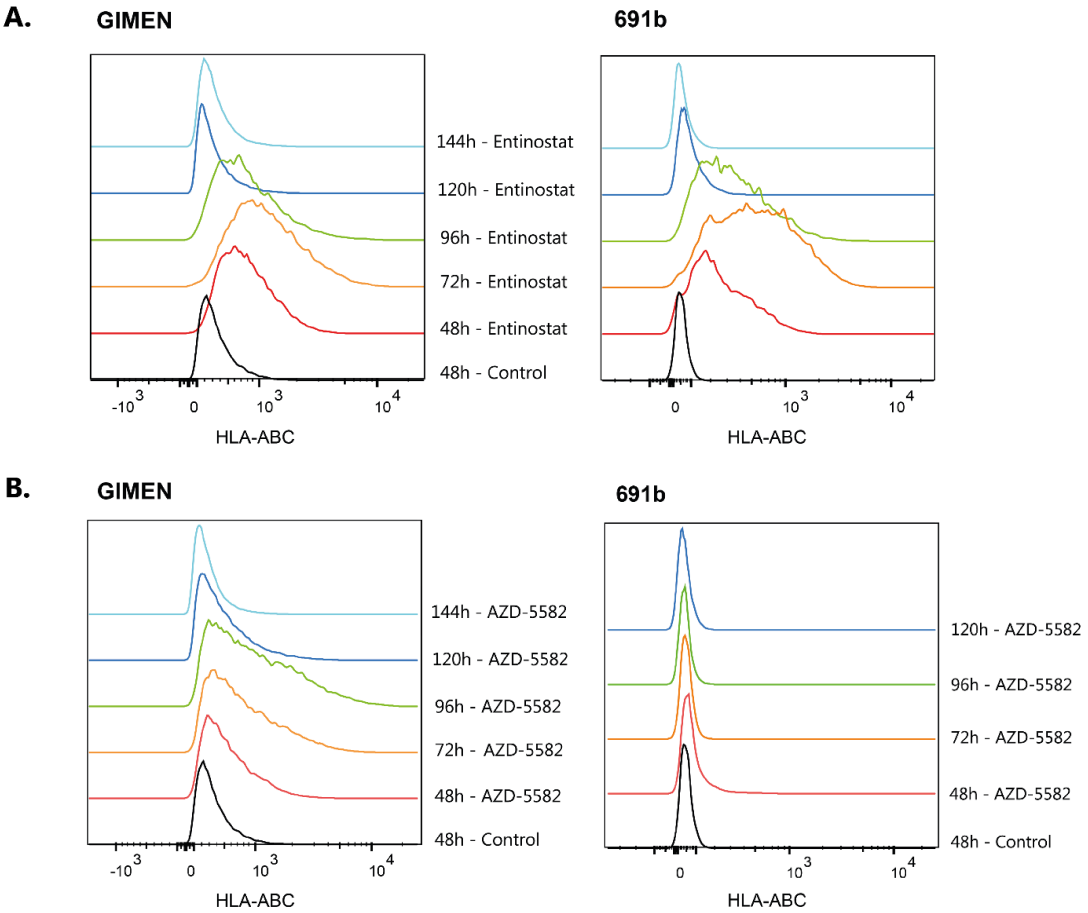
Supplementary Figure 7 – qPCR validation of increases in transcript abundance observed with RNAseq
Data is depicted as log(fold change) between untreated and entinostat-treated 691b organoids (B) or GIMEN (C). Data relative to GAPDH. 691b: All log(fold changes) are significant, except HLA-G and PSMB9 (p=0.09 and 0.08, respectively). GIMEN: all log(fold changes) are significant, except PSMB1/2/5. UD = undetected. Duplos are shown as mean ± SD. Statistical differences between log(fold changes) were calculates with a one sample T test.



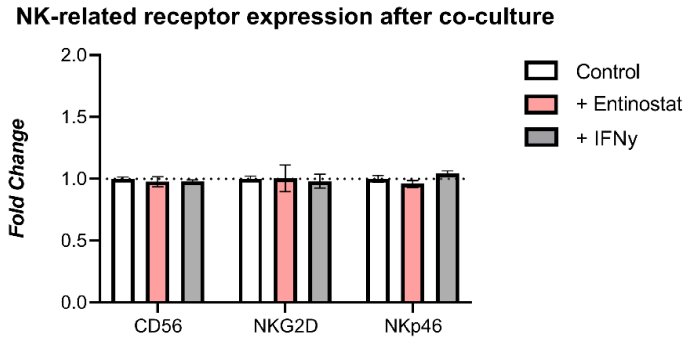
Supplementary Figure 8 – Increased mesenchymal-, immune activation-, and IFN-response signature upon Entinostat treatment of 691b organoids. *Heatmap showing individual signature components of cell lineage **(A)** and immune activation (IA) / IFN-response **(B)** in untreated and 691b Entinostat-treated organoids (48h, 2.5 uM Entinostat). Log2 gene expression values were z-score transformed for heatmap visualization.*



Supplementary Figure 9 – Neuroblastoma cel lineage markers in utilized patient-derived organoid models. *ADR = adrenergic, MES = mesenchymal*.



Supplementary Figure 10 – MHC-I upregulation kinetics after drug incubation. *GIMEN (left) and 691b (right) were incubated with 2.5 uM entinostat **(A)** or 62.5 nM AZD-5582 **(B)** for 48h, after which media was refreshed. Effect on MHC-I expression was determined at indicated timepoints. HLA-ABC expression in controls remained unchanged overtime, expression after 48h is shown as an example of baseline expression.*



Supplementary Figure 11 – Expression of three NK-related receptors on NK-cells after 5h co-culture with 691b organoids. *Expression of NK-related receptors CD56, NKG2D and NKp46 on NK-cells after 5h co-culture with either untreated 691b control cells or 691b pre-treated for 48h with 2.5 uM Entinostat or 100 U/mL IFNγ. Expression is shown relative to untreated controls.*