**Figure Legends – Supplementary Figures**

**Supplementary Fig. S1. Histology and immunohistochemistry identify the xenograft model BT183 and the new PDX model NCH3602 as ETMR tumors.** Whole-mount sagittal brain section of H&E immunohistochemistry of the ETMR xenograft model BT183 (**A**) and the ETMR PDX model NCH3602 (**B**). Higher magnification of H&E immunohistochemistry of the primary tumor BT183 (**C**) and its xenograft tumor (**D**), and of the primary tumor NCH3602 (**E**) and its PDX tumor (**F**). LIN28A immunohistochemistry of the primary tumor BT183 (**G**) and its xenograft tumor (**H**), and of the primary tumor NCH3602 (**I**) and its PDX tumor (J). C19MC FISH of the primary tumor BT183 (**K**) and its xenograft tumor (**L**), and of the primary tumor NCH3602 (**M**) and its PDX tumor (**N**). Scale bars: 1 mm (**A**,**B**), 100 µm (**C**-**J**), 5 µm (**K**-**N**).

**Supplementary Fig. S2. Gene expression profiling of drug target genes in pediatric brain tumor entities, normal embryonal and infant brain and the ETMR cell line BT183.** Dot plots of gene expression in human pediatric brain tumor samples. Comparison of gene expression across various pediatric brain tumor subgroups, the ETMR cell line BT183 (red dot within the ETMR group) and normal brain tissue (‘Normal Brain’) is shown for MYCN (**A**), DNMT3B (**B**), EZH2 (**C**), 4EBP1 (**D**), HES5 (**E**), NOTCH1 (**F**) and PTCH1 (**G**). Data are shown in log scale and were extracted from the r2 database (http://hgserver1.amc.nl/cgi-bin/r2/main.cgi) using the published ‘brain tumor’ and ‘normal brain’ dataset (see GEO reference numbers) representing the subgroups for CNS-PNETs: NB-FOXR2 (n = 10), EFT-CIC (n = 4), HGNET-MN1 (n = 7), HGNET-BCOR (n = 15); the subgroups for medulloblastoma: MBWNT (n = 30), MBSHH (n = 30), MBGRP3 (n = 30), MBGRP4 (n = 30); the subgroups for AT/RTs: AT/RTTYR (n = 25), AT/RTSHH (n = 20), AT/RTMYC (n = 17) and ETMRs; the ETMR cell line BT183 is indicated in *red* within the ETMR group; for ‘Normal Brain’ a dataset of adult brain tissue was used with overall 169 samples composing of neural tissue of various brain regions.

**Supplementary Fig. S3.** IC50 curves of all 35 drugs in the screen sorted by their target mechanism or pathway, presenting topoisomerase inhibitors (**A**), pathway specific compounds (**B**), epigenetic compounds (**C**), cell cycle and proteasome inhibitors (**D**) and DNA synthesis and replication inhibitors (**E**). Compounds and their respective IC50 values are listed on the right of each graph. IC50 values were calculated with Graphpad Prism Software; n/a indicates that the IC50 could not be determined; error bars represent the mean ±SD.

**Supplementary Fig. S4. Apoptosis and cell cycle arrest are induced in BT183 cells by treatment with the top drug candidates. A-F** 7AAD/Annexin flow cytometry assay of BT183 cells treated with the different inhibitors in four increasing concentrations respectively. **G-L** Western blot of BT183 cells treated with the different inhibitors in four increasing concentrations for either 48 hours (for topotecan, doxorubicin, panobinostat and decitabine) or for 72 hours (for volasertib, alisertib and MLN0128). Protein levels for PARP, BAX and for GAPDH as loading control are shown. **M,N** Cell cycle analysis with flow cytometry for BT183 cells treated with alisertib and volasertib for 72 hours. Experiments were performed in triplicate, error bars represent the mean ±SD and p values were calculated using an unpaired, one-tailed t test; p values are shown as follows: \* signifies p < 0.05, \*\* signifies p < 0.01, \*\*\* signifies p < 0.001 and \*\*\*\* signifies p < 0.0001.

**Supplementary Fig. S5. Validation of mode of action of topotecan, doxorubicin, alisertib, volasertib and MLN0128 treatment in BT183 cells.** **A,B** Western blot analysis of TOP1, H2A.X and p-H2A.X in topotecan treated BT183 cells and quantification of protein levels. **C,D** Western blot analysis of TOP1, H2A.X and p-H2A.X in doxorubicin treated BT183 cells and quantification of protein levels. **E-H** Western blot analysis of PLK1-3 in volasertib treated BT183 cells and quantification of protein levels. **I-L** Western blot analysis of AURKA, p-AURKA and MYCN in alisertib treated BT183 cells and quantification of protein levels. **M-O** Western blot analysis of 4E-BP1 and p-4E-BP1 in MLN0128 treated BT183 cells and quantification of protein levels.

**Supplementary Fig. S6.** IC50 curves for topotecan, doxorubicin, volasertib, MLN0128, alisertib and decitabine (**A**) and for panobinostat, carboplatin, irinotecan, vincristine, methotrexate and etoposide (**B**) in NCH360 cells (2 NCH3602 PDX animals, animal #231 and #233). Inhibitors and their respective IC50 values are listed on the right. IC50 values were calculated with Graphpad Prism Software; n/a indicates that the IC50 could not be determined; error bars represent the mean ±SD.