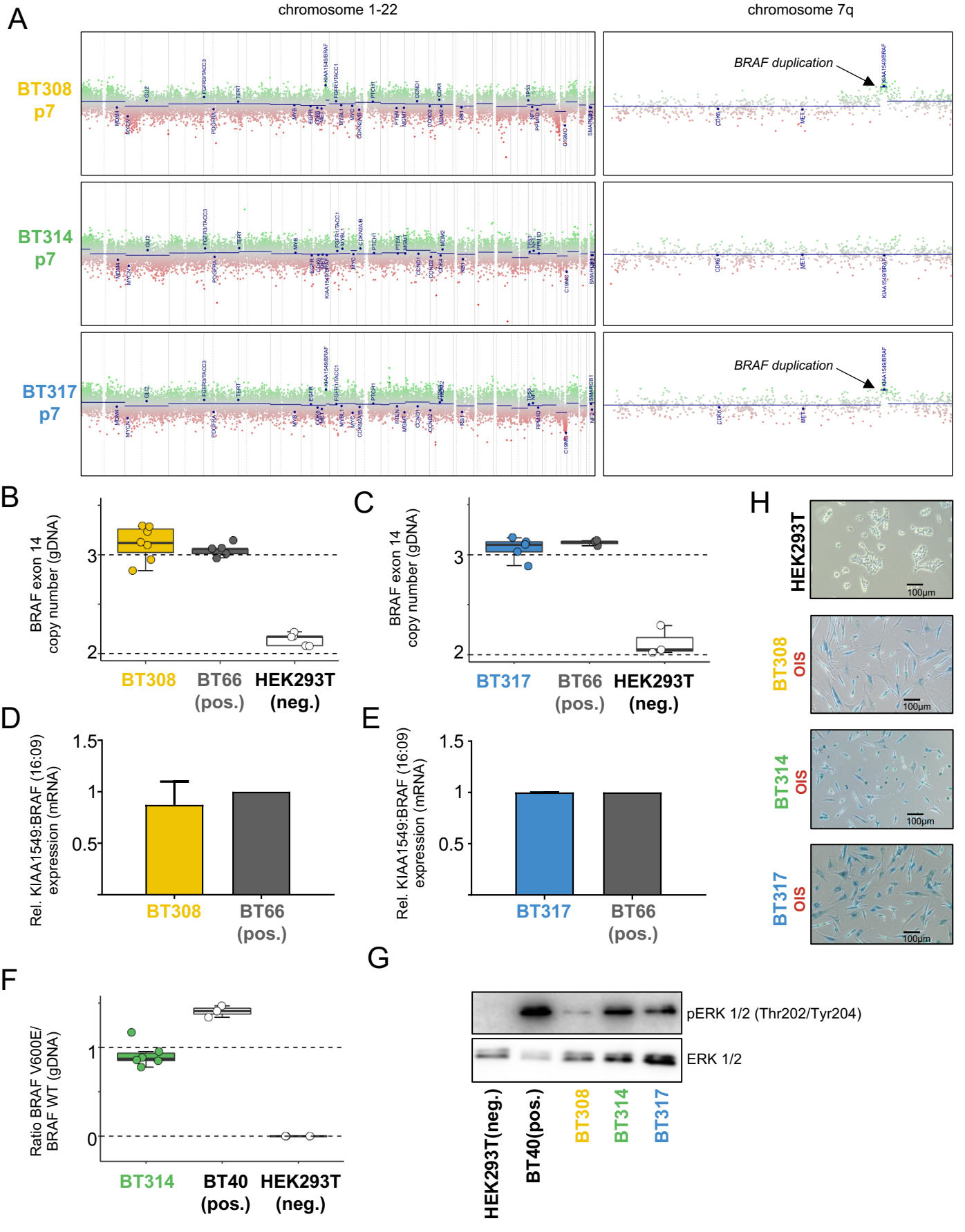
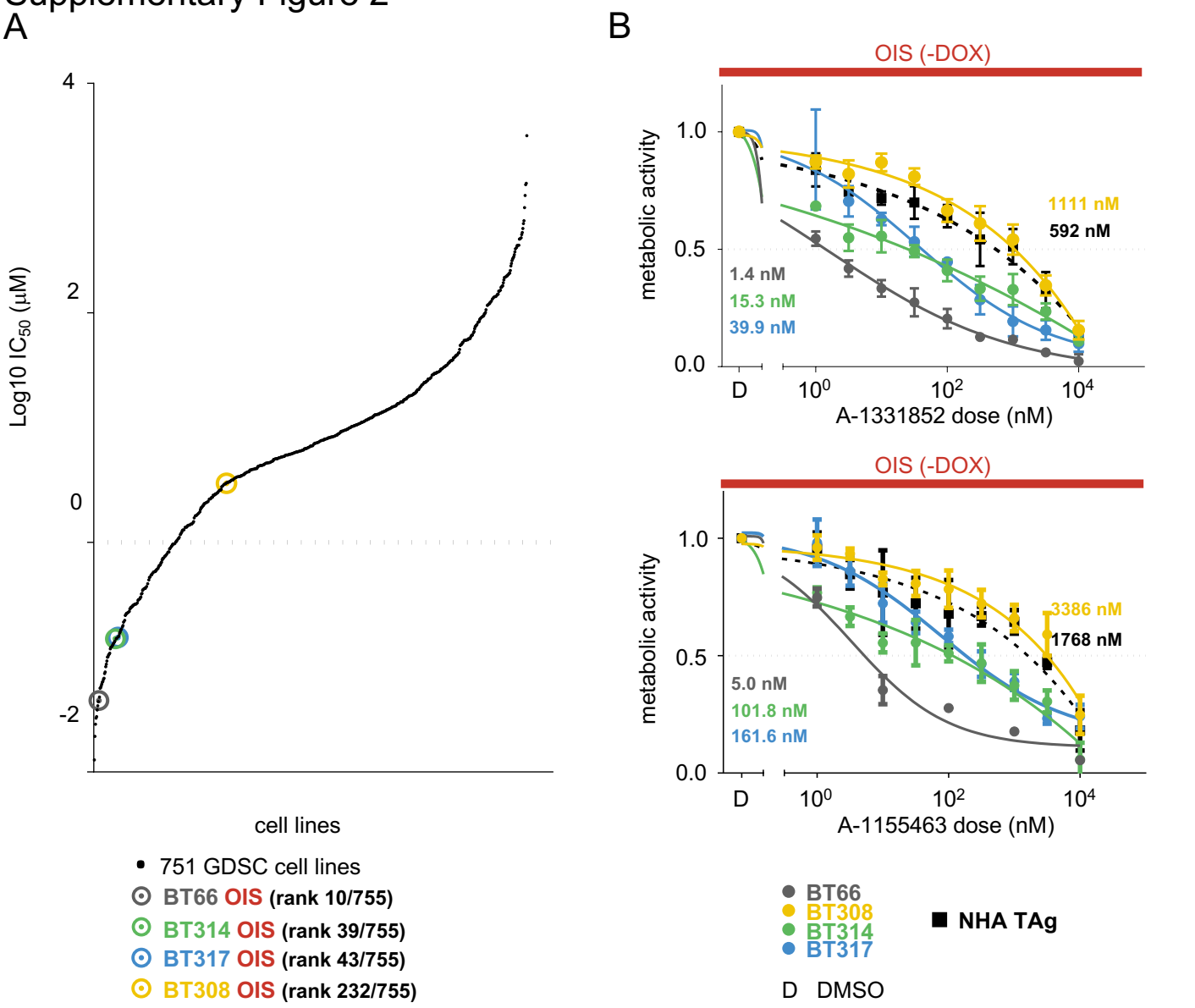
Supplementary Figure 1



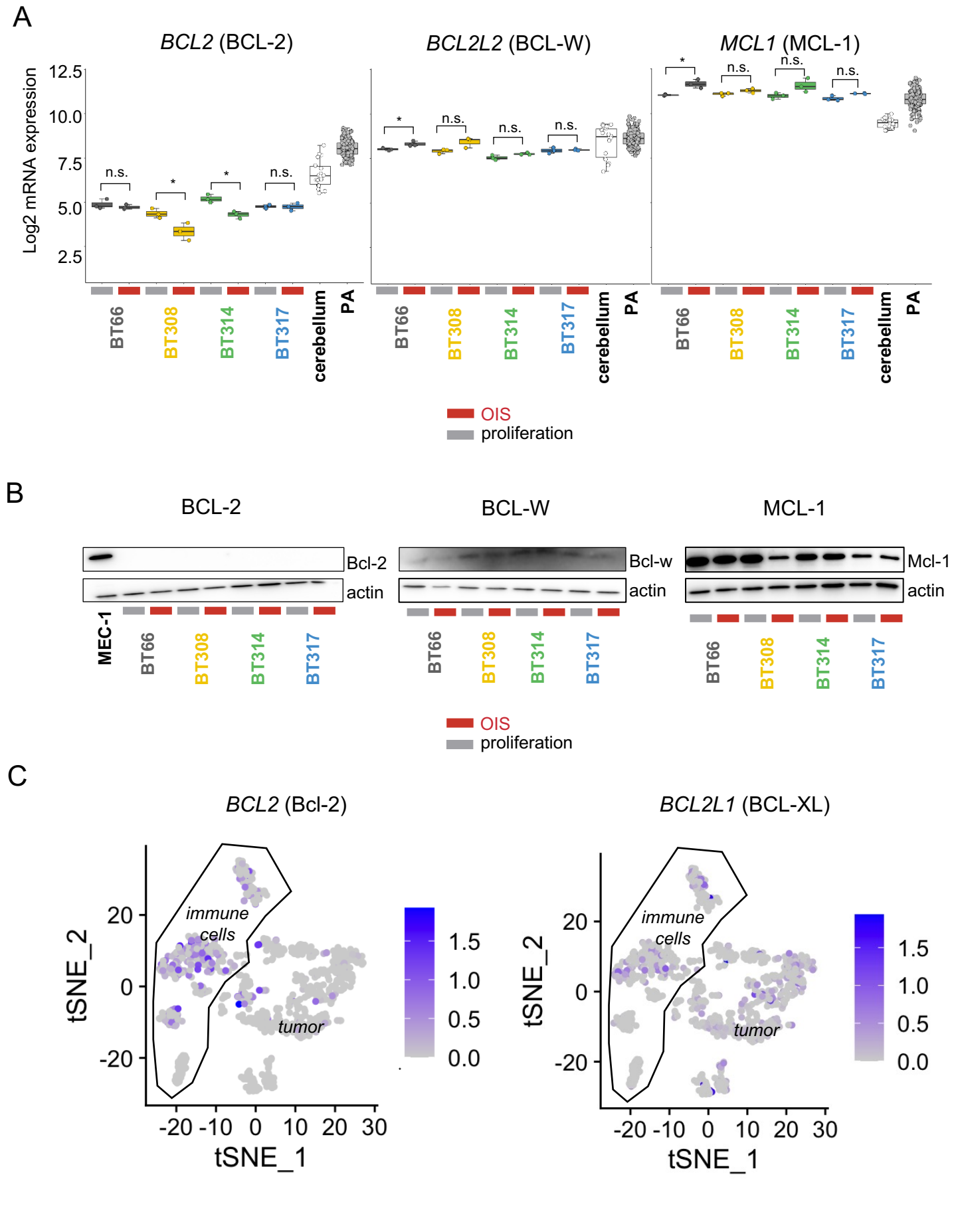
Supplementary Figure 1: Characterization of new patient-derived PA *in vitro* models DKFZ-BT308 (BT308), DKFZ-BT314 (BT314) and DKFZ-BT317 (BT317). A DNA methylation derived copy number plots of PA cell lines in proliferation mode at passage 7. Enlarged depiction of chromosome 7q highlights a focal gain indicating the presence of a BRAF duplication. **B, C** Copy number of BRAF exon 14 measured by ddPCR on genomic DNA level (at least n=3 biological replicates) indicating the presence of a BRAF duplication in BT308 and BT317 cells, respectively. DKFZ-BT66 served as positive control (BRAF duplicated) and HEK293T cells were used as BRAF WT control. **D, E** RTqPCR with specific primers detecting the expression of a KIAA1549 (exon 16): BRAF (exon 9) fusion in BT308 (n=3; mean +/-SD) and BT317 (n=3; mean +/- SD), respectively. DKFZ-BT66 served as reference. **F** Ratio of BRAF-V600E/BRAF WT on genomic DNA level (at least n=3 biological replicates) measured by ddPCR mutation assay detecting a BRAF V600E mutation in BT314 cells. A ratio close to 1 indicated a high tumor cell purity. BT40 cells served as positive control (5 copies of BRAF-V600E/cell). **G** Western blot of pERK/ERK expression in 3 PA models compared to MAPK negative control (HEK293T) and MAPK positive control (BT40) **H** Staining for SA-β-galactosidase in three PA cell lines in OIS mode (5 days after doxycycline withdrawal, representative pictures). HEK293T cells served as negative control.

Supplementary Figure 2



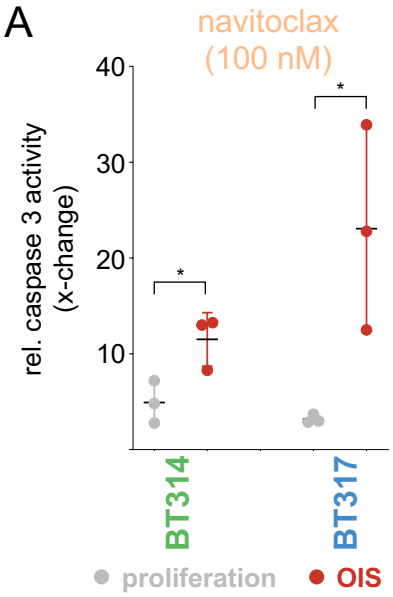
Supplementary Figure 2: Impact of BH3 mimetics on the metabolic activity of PA cell lines DKFZ-BT66 (BT66), DKFZ-BT308 (BT308), DKFZ-BT314 (BT314) and DKFZ-BT317 (BT317). A ranking of IC_{50} values of navitoclax in 751 cell lines from GDSC database (GDSC2) and the four PA models in OIS mode. **B** Dose-response curve of A-1331852 and A-1155463, respectively, in four PA cell lines in OIS and normal human astrocytes NHA TAg (5 days doxycycline withdrawal). Depicted are means +/- SD of at least n=3 biological replicates. Absolute IC_{50} values are given in nM for each cell line.

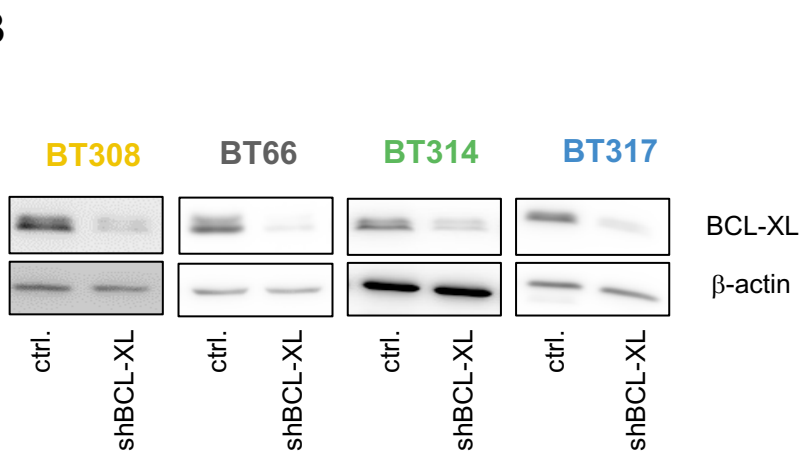
Supplementary Figure 3

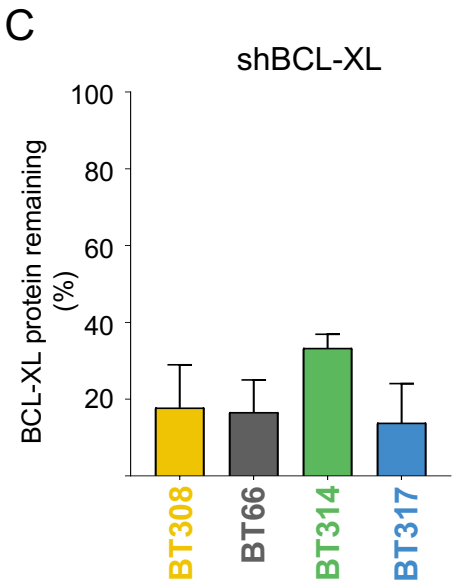


Supplementary Figure 3: Expression of anti-apoptotic BCL-2 members in PA. A Boxplots depicting *BCL2*, *BCL2L2* and *MCL1* mRNA expression in four PA cell lines in proliferation vs. OIS compared to normal cerebellum (n=18) and primary PA (n=191) (Tumor Pilocytic astrocytoma (DKFZ) - Kool; R2 internal identifier: ps_mkheidel_mkdkfz209_u133p2)**.** Differences between two groups were analyzed using unpaired t-test. * $p<0.05$, ** $p<0.01$, *** $p<0.001$. **B** Western blots of BCL-2, BCL-W and MCL-1 protein expression in four PA cell lines in proliferation and OIS mode. **C** tSNE analysis of *BCL2* and *BCL2L1* mRNA expression in PA single cell RNA sequencing data. Bcl-2 is predominantly expressed in the immune cell clusters.

Supplementary Figure 4



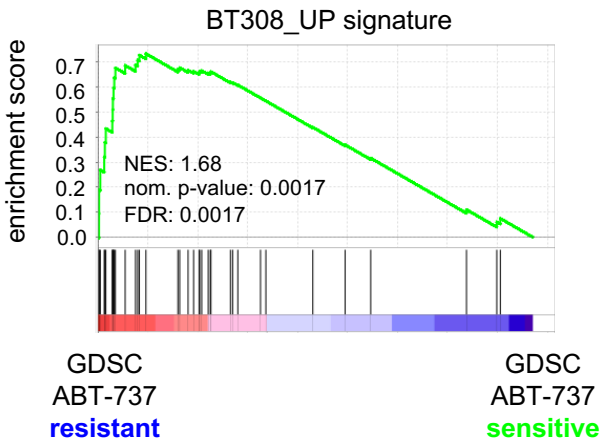




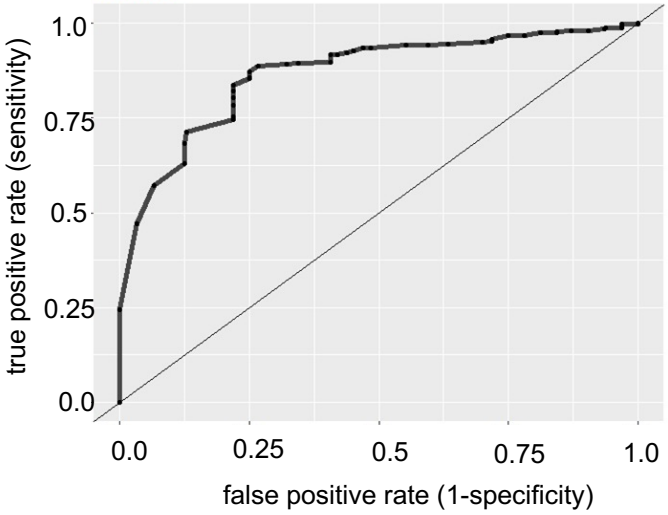
Supplemetary Figure 4: Caspase 3 activity in proliferation vs. OIS and dependence of PA cell lines on BCL-XL. A Caspase 3 activity relative to DMSO control in proliferation vs. OIS after 24h treatment with 100 nM navitoclax (mean +/- SD, n=3). Unpaired t-test: * $p<0.05$. **B** Representative western blots. PA cell lines in OIS were transduced with lentiviral shRNA against BCL-XL or non-silencing control shRNA (ctrl.) 96h before lysis. **C** Densitometric quantification of western-blot data. Band intensity of BCL-XL protein in BCL-XL knocked cells (96h after lentiviral infection) was measured and normalized to the intensity in cells transduced with control shRNA (n= 3 biological replicates; mean +/- SD).

Supplementary Figure 5

A



B



Supplementary Figure 5: Difference in gene expression between the BCL-XLi resistant cell line DKFZ-BT308 (BT308) and the BCL-XLi sensitive cell lines DKFZ-BT66 (BT66), DKFZ-BT314 (BT314) and DKFZ-BT317 (BT317). A GSEA enrichment plot depicting the comparison of BT308_UP signature expression between the two GDSC2 cell line groups “ABT-737 resistant” (IC_{50} z-score >0; n=402) and “ABT-737 sensitive” (IC_{50} z-score <-2; n=48) **B** ROC curve of the binary logistic regression analysis of the BT308_UP signature in 412 GDSC cell lines assigned to two groups “navitoclax resistant” and “navitoclax sensitive”.