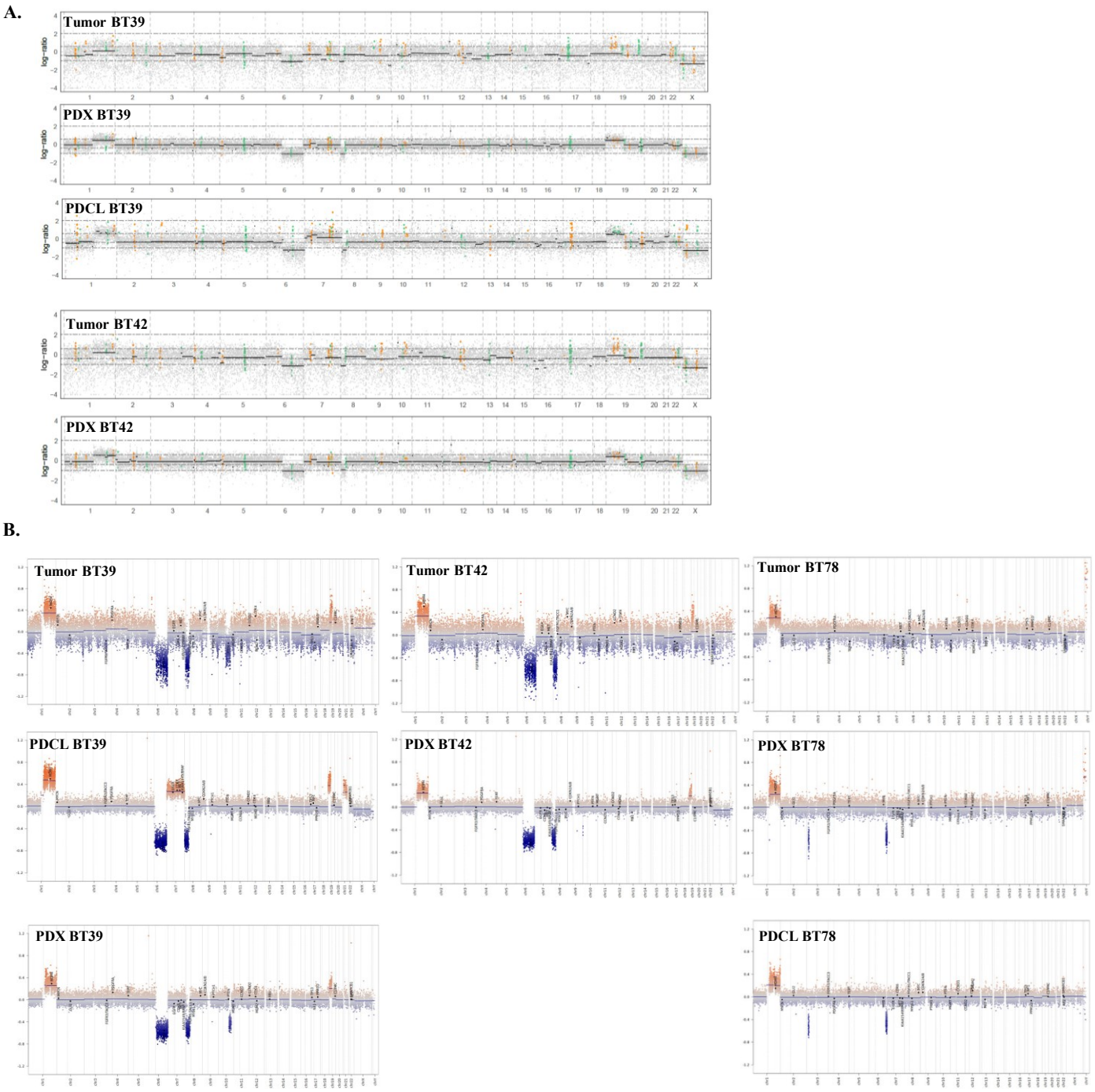


Figure S1. Concordant copy-number variation (CNV) profiles generated by targeted next-generation sequencing and DNA methylation analyses in representative pediatric ependymoma models. (A) Genome-wide CNV profiles inferred from targeted next-generation sequencing (NGS; DRAGON pipeline) for primary tumors, paired patient-derived xenografts (PDXs), and patient-derived cell lines (PDCLs) from BT39 and its matched relapse specimen BT42**. (B) Corresponding CNV profiles inferred from DNA methylation array data for BT39, BT42, and BT78** parental tumors and their matched PDXs and/or PDCLs. The strong concordance between sequencing- and methylation-derived CNV profiles confirms the robustness of copy-number alterations across patient-derived models and highlights the complementary value of integrating genomic and epigenomic analyses for accurate molecular characterization and assessment of clonal evolution.

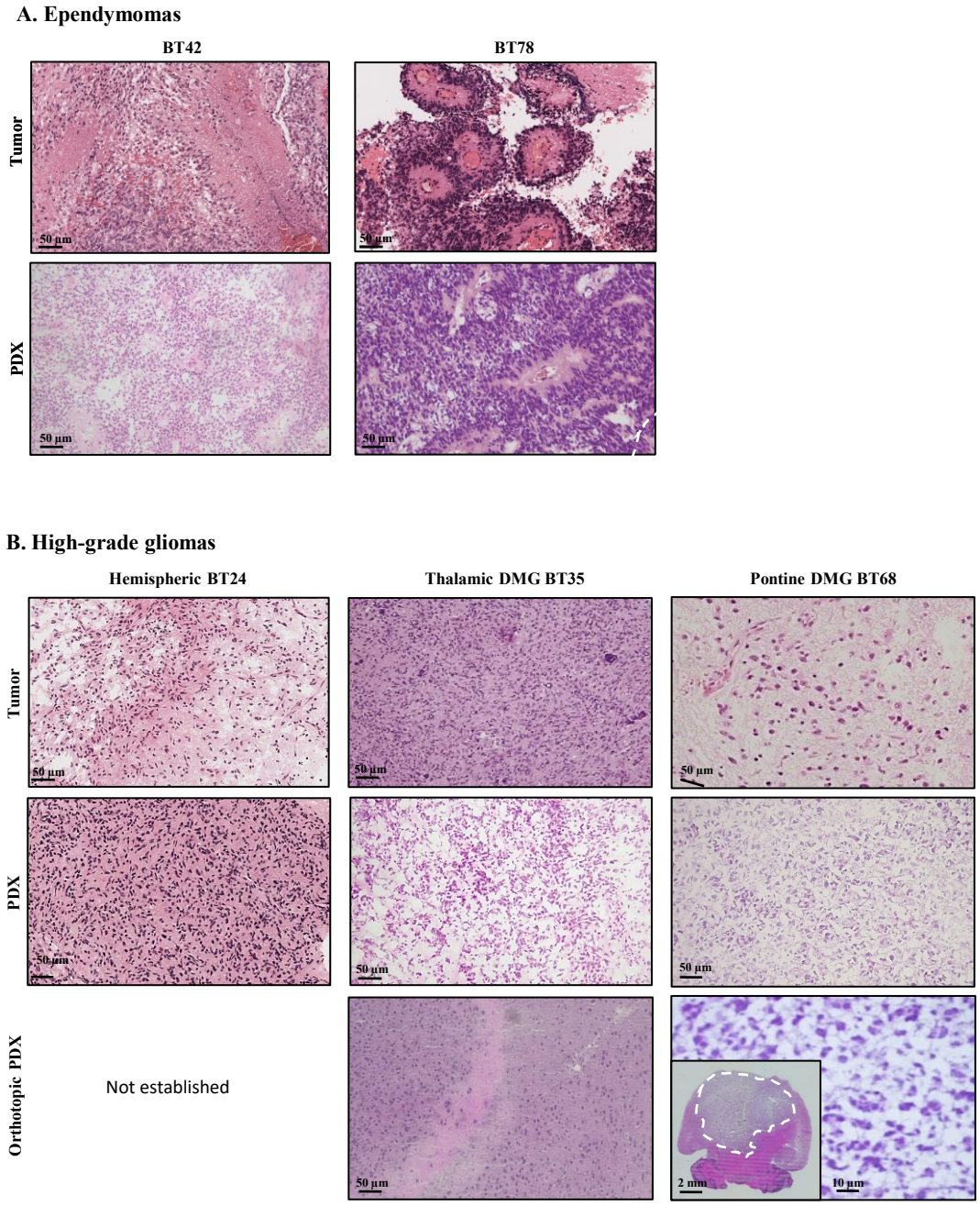
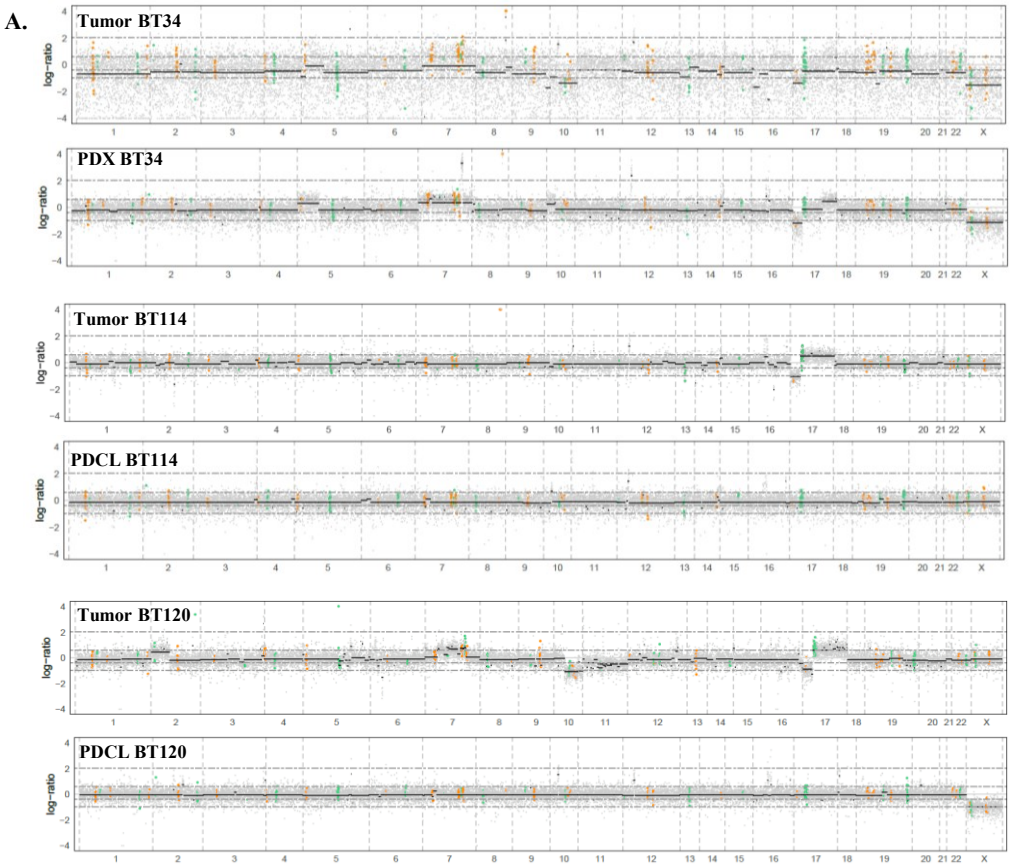


Figure S2. Histopathological comparison of primary tumors and matched patient-derived xenografts. Representative hematoxylin and eosin (H&E)-stained sections of primary tumors and their corresponding patient-derived xenografts (PDXs) from **ependymomas** (A) and **high-grade gliomas** (B), demonstrating the preservation of the characteristic histopathological architecture and cellular morphology across the different HGG entities including in orthotopic injections.



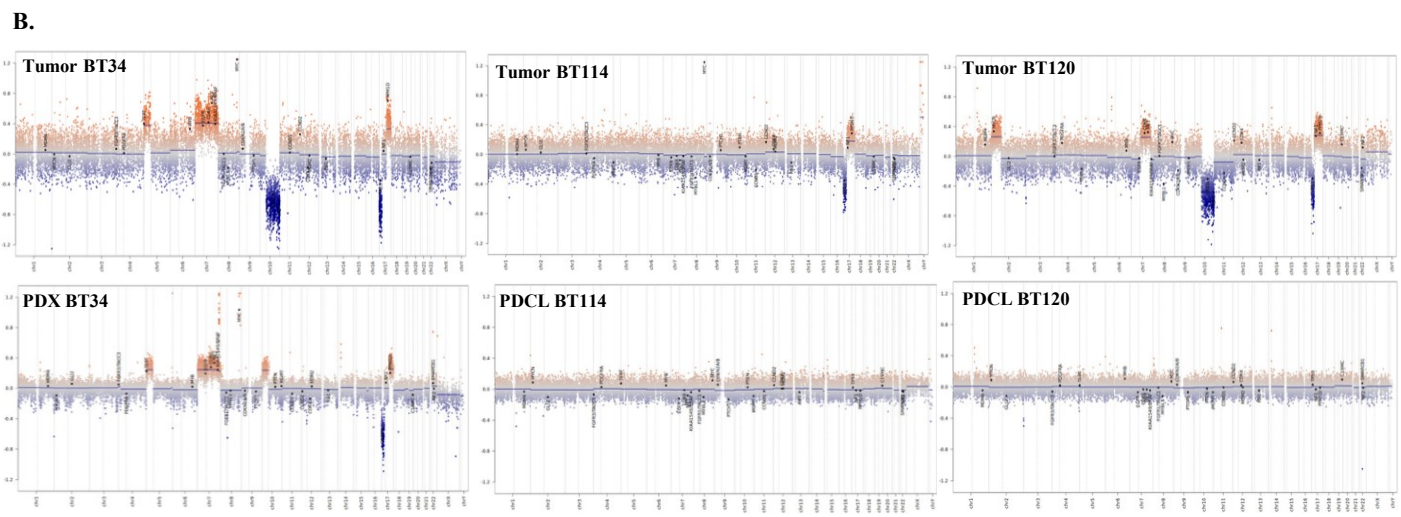


Figure S3. Concordant copy-number variation (CNV) profiles generated by targeted next-generation sequencing and DNA methylation analyses in representative. (A) Genome-wide CNV profiles inferred from targeted next-generation sequencing (NGS; DRAGON pipeline) for primary tumors and their matched patient-derived xenografts (PDXs) and/or patient-derived cell lines (PDCLs) from BT34, BT114 and BT120. (B) Corresponding CNV profiles inferred from DNA methylation array data for the same tumor-model pairs. The concordance between sequencing- and methylation-derived CNV profiles confirms the robustness of copy-number alterations across patient-derived models and highlights the complementary value of integrating genomic and epigenomic analyses for accurate molecular characterization and assessment of tumor evolution.

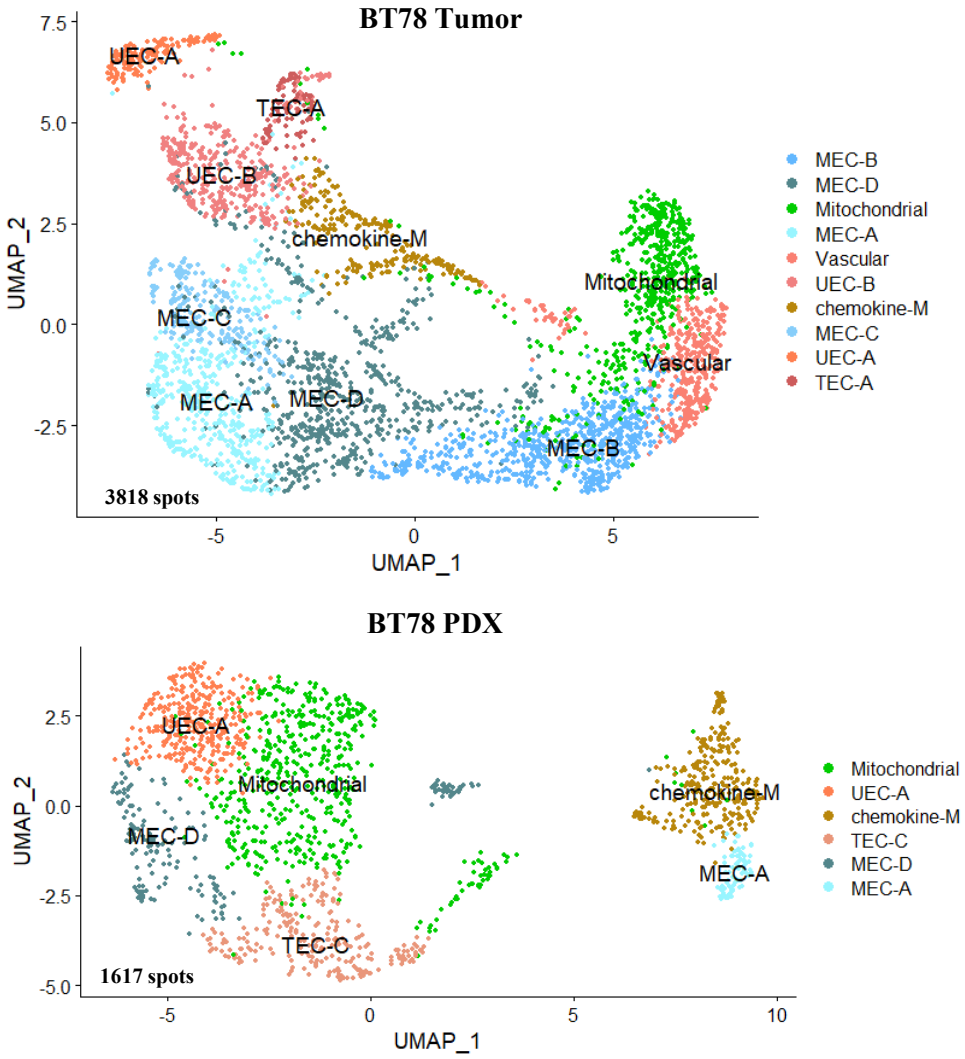


Figure S4. Cell-to-cell interactions in patient-derived xenograft (PDX) models captured by spatial transcriptomics. Projection of BT78 primary tumor and matched PDX spatial transcriptomic spots onto the pediatric ependymoma reference dataset from Fu *et al.* (2023). UMAP clustering demonstrates that both the primary tumor and the corresponding PDX comprise distinct epithelial and mesenchymal cell populations, highlighting the preservation of the tumor cellular architecture and microenvironmental organization in the PDX model.

Table S1. List of 83 compounds and their corresponding drug classes.

Drug ID	Group
Doxorubicin	Chemotherapy
Etoposide	Chemotherapy
Gemcitabine	Chemotherapy
Melphalan	Chemotherapy
Paclitaxel	Chemotherapy
SN38	Chemotherapy
Topotecan	Chemotherapy
Vincristine	Chemotherapy
Vinorelbine	Chemotherapy
Berzosertib	DNA repair inhibitor
KU-60019	DNA repair inhibitor
Nutlin 3	DNA repair inhibitor
Prexasertib	DNA repair inhibitor
Prima1	DNA repair inhibitor
Afatinib	EGFR inhibitor
Erlotinib	EGFR inhibitor
Osimertinib	EGFR inhibitor
Doramapimod	MAPK / AKT / PI3K inhibitor
Fimepinostat	MAPK / AKT / PI3K inhibitor
Paxalisib	MAPK / AKT / PI3K inhibitor
Ralimetinib	MAPK / AKT / PI3K inhibitor
Mirdametinib	MEK inhibitor
Selumetinib	MEK inhibitor
Trametinib	MEK inhibitor
Everolimus	MTOR inhibitor
Omipalisib	MTOR inhibitor
Temsirolimus	MTOR inhibitor
Vistusertib	MTOR inhibitor
Axitinib	Receptor inhibitor
Lapatinib	Receptor inhibitor
Lenvatinib	Receptor inhibitor
Ningetinib	Receptor inhibitor
Rigosertib	Receptor inhibitor
RU-301	Receptor inhibitor
Savolitinib	Receptor inhibitor
Entrectinib	TRK inhibitor
Larotrectinib	TRK inhibitor
Selitrectinib	TRK inhibitor
Alisertib	Aurora / PLK / CDK inhibitor
Dinaciclib	Aurora / PLK / CDK inhibitor
Palbociclib	Aurora / PLK / CDK inhibitor
Ribociclib	Aurora / PLK / CDK inhibitor
Volasertib	Aurora / PLK / CDK inhibitor
VX680	Aurora / PLK / CDK inhibitor
Entinostat	HDAC inhibitor
Panobinostat	HDAC inhibitor
Vorinostat	HDAC inhibitor
HS-243	IRAK inhibitor
IRAK-1	IRAK inhibitor
FK866	NAMPT inhibitors
GMX-1778	NAMPT inhibitors
OR0642	Other targeted agent
AGI-5198	Other targeted agents
Bortezomib	Other targeted agents
Dabrafenib	Other targeted agents
Enasidenib	Other targeted agents
ONC201	Other targeted agents
ONC206	Other targeted agents
Sonidegib	Other targeted agents
Vismodegib	Other targeted agents
YM155	Other targeted agents
ABBV-744	BET inhibitors
Birabresib	BET inhibitors
GSK-046	BET inhibitors
Molibresib	BET inhibitors
PFI-1	BET inhibitors
RVX-208	BET inhibitors
GSK-126	Other Epidrugs
GSK-J4	Other Epidrugs
SGC 0946	Other Epidrugs
Birinapant	Apoptosis targeting
GDC-0152	Apoptosis targeting
LCL-161	Apoptosis targeting
Navitoclax	Apoptosis targeting
Olaparib	Apoptosis targeting
Venetoclax	Apoptosis targeting
Astemizole	other repurposed drugs
Buparlisib	other repurposed drugs
Disulfiram	other repurposed drugs
Fluphenazine	other repurposed drugs
Metergoline	other repurposed drugs
Paroxetine	other repurposed drugs
Sertraline	other repurposed drugs