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Exploring Novel Applications: Repositioning Clinically Approved Therapies for Medulloblastoma Treatment

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Key Points

- Overexpression of targets of clinically approved treatments correlates with either longer or shorter survival.
- A treatment designed for hematological tumors, venetoclax, appear relevant for medulloblastoma.
- The presence of mutations may warrant treatment efficacy as personalized medicine.

Abstract

Background/Objectives: The advent of kinase inhibitors (TKI), therapeutic antibodies and inducers of apoptosis has revolutionized cancer treatment, yet their application in pediatric tumors, particularly medulloblastoma, remains understudied. Understanding the expression of these targets in specific genetic subgroups could unveil potential repositioning opportunities for already approved drugs. **Methods**: We analyzed RNA-sequencing data from the R2 Genomics Analysis and Visualization Platform (N = 763 patients, multiple cohorts) and the TCGA database (six individual cohorts 828 patients) to assess the expression of 73 potential targets of TKIs and antibodies targeting immune checkpoint inhibitors (ICI) or membrane receptors and inducers of apoptosis. These treatments, FDA-approved or in phase II clinical trials for solid or hematologic cancers, and their targets were evaluated in both non-metastatic and metastatic patients when data was available. Additionally, we examined treatments tailored to mutated targets crucial for tumorigenesis or resistance to conventional therapies. **Results**: Overexpression of certain targets beyond predefined cutoff values in Kaplan-Meier analyses correlated with either prolonged or shortened overall survival. Targets associated with shorter survival suggested potentially relevant treatments, thereby highlighting the importance of defining specific treatments for distinct genetic subgroups. Notably, certain immune checkpoint inhibitors showed relevance for specific subgroups but detriment for others. As a positive control, our analysis confirmed the use of axitinib, an anti-angiogenic treatment, as demonstrated by our recent publication. Surprisingly, a treatment developed for hematological tumors, venetoclax, demonstrated potential efficacy in medulloblastoma. **Conclusions**: Medulloblastoma displays subtype-specific expressions of FDA-approved TKI, ICI and pro-apoptotic drug targets, impacting overall survival. Clinical trials investigating these approved treatments in medulloblastoma are therefore warranted.

Keywords: Medulloblastoma**;** kinase inhibitors**;** immune check point inhibitors**;** mutations**;** non-metastatic/metastatic tumors; BCL2; Venetoclax

1. Introduction

Medulloblastoma patients undergo highly intensive treatments involving surgery, radiotherapy (for patients above 3 years old), and intensive multimodal chemotherapies. However, such aggressive

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treatments pose significant risks for young patients during critical growth periods. Consequently, there is a pressing need to explore strategies for de-escalating treatment intensities without compromising efficacy or exacerbating side effects. Targeted, less toxic therapies are imperative to enhance cure rates, manage relapses, and mitigate the adverse effects associated with current intensive regimens.

Over the past 15 years, considerable advancements have been made in cancer treatments across various types. Yet, the challenge persists in developing innovative therapies, often constrained by logistical hurdles and financial constraints. Herein lies an opportunity to reposition existing treatments through a molecular pathology approach, leveraging the analysis of specific mutation expressions in newly diagnosed patients or those experiencing relapses. By harnessing available data from public databases, we can tailor treatments to specific genetic subgroups of medulloblastoma, thus creating a customized treatment landscape.

This inclusive genetic approach allows us to construct a comprehensive performance profile for existing treatments. Surprisingly, treatments approved for hematological cancers show promise in medulloblastoma, suggesting potential avenues for repurposing therapies. By adopting this streamlined methodology, we uncover compelling opportunities for treatments to undergo evaluation in early-phase clinical trials, paving the way for meaningful advancements in medulloblastoma management.

Medulloblastoma ranks as the second most prevalent solid pediatric tumor. Pediatric medulloblastoma is composed of several molecular subgroups: Wingless (WNT), Sonic Hedgehog (SHH), Group 3 and Group 4. Groups WNT and SHH are characterized by abnormal activation of the corresponding signal transduction. Group 3 and Group 4 show overexpression of N- and c-Myc, inactivation of p53 and deleterious chromosomal abnormalities [1]. Patients undergo rigorous treatments comprising surgery, radiotherapy (administered to patients above 3 years old), and chemotherapy regimens incorporating agents like etoposide, carboplatin, and vincristine. While these intensive interventions yield a 70% long-term remission rate, most patients suffer from the severe side effects of these treatments [2,3] and approximately 30% of cases experience relapse, with fatal outcomes being commonplace. Therefore, physicians face two paramount challenges in managing medulloblastoma: 1) **Reducing Treatment Intensity**: The primary objective is to mitigate the high detrimental side effects associated with intensive therapies, which can encompass mobility issues, cognitive impairments, language deficits, and motor function limitations. This reduction must be achieved without compromising treatment efficacy; 2) **Identifying Relevant Therapies for Relapse**: Another critical goal is to propose effective treatments in instances of relapse, with the aim of extending survival and potentially achieving a second long-term remission. Addressing these challenges demands a delicate balance between treatment effectiveness and the minimization of adverse effects, underscoring the importance of tailored therapeutic strategies in the management of medulloblastoma.

Despite advancements in treatment strategies, the development of new therapies for pediatric cancers remains challenging, largely due to historical underinvestment by the pharmaceutical industry. Treatment repositioning represents a promising alternative, leveraging the efficacy of several targeted therapies that have been successfully utilized for decades in adult cancers sharing similar mechanisms of tumor aggressiveness with medulloblastomas. For instance, reverse genetic analysis conducted by Coy et al. [4] demonstrated the potential application of antibody-drug conjugates for pediatric brain tumors.

Given the hyper vascularized nature of medulloblastomas and considering that increased angiogenesis is associated with the most aggressive medulloblastomas [5]. We, along with German collaborators, have highlighted the utility of Axitinib, a tyrosine kinase inhibitor initially approved for metastatic kidney cancer [6] or combined with immune checkpoint inhibitors. Axitinib has shown promise both as a monotherapy and in combination with immune checkpoint inhibitors for kidney cancers [7] but also for treating medulloblastomas [8,9]. This approach has led to the initiation of the clinical trial **Mependax** (NCT06485908), which is currently enrolling patients with relapsed

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medulloblastoma and ependymoma, building upon encouraging findings in six children treated with Axitinib and metronomic etoposide [10].

To identify additional therapeutic candidates, we implemented a systematic approach. First, we cataloged available targeted therapies, including older and next-generation agents, alongside their molecular targets. Utilizing publicly accessible datasets via the R2 platform https://hgserver1.amc.nl/cgi-bin/r2/main.cgi?open_page=login and the TCGA database through cBioportal https://www.cbioportal.org/, we analyzed the expression of target genes and their correlation with survival outcomes. Specific activating mutations in target genes were also evaluated, given that many therapies are indicated only for tumors harboring such mutations.

This strategy identified several unexpected candidates for repositioning in medulloblastoma, including therapies traditionally used for hematological malignancies. The validity of our approach was supported by the identification of Axitinib [8] and HER2 inhibitors [4,11], as relevant treatment options. Furthermore, we demonstrated the potential of Venetoclax, typically used in hematological tumors, as a promising therapeutic candidate for medulloblastoma.

2. Materials and Methods

2.1. Expression and Mutation Profiling

Gene expression levels and survival correlations using the Kaplan Meier method were analyzed using the R2 Genomics Analysis and Visualization Platform (https://hgserver1.amc.nl/cgi-bin/r2/main.cgi?open_page=login) and the cBioportal platform (https://www.cbioportal.org). For the R2 platform, medulloblastoma datasets included the following:

GSE85217 (Cavalli, [12])
GSE67851 (Hsieh, TH [13])
GSE37418 (Gilbertson, RJ [14])
GSE74195 (den Boer, M [15])
GSE10327 (Kool, M [16])
GSE49243 (Pfister 2, [17])
GSE12992 (Delattre, [18])
GSE3526 (Roth, [19])
Cohort Pfister 1 [20]

For the cBioportal platform, the following data set were analyzed:
Medulloblastoma (PCGP, Nature 2012, [14])
Medulloblastoma (Broad, Nature 2012, [21])
Medulloblastoma (DKFZ, Nature 2017, [20])
Medulloblastoma (ICGC, Nature 2012, [22])
Medulloblastoma (Sickkids, Nature 2016, [23])

These datasets provided robust platforms for exploring gene expression profiles and their association with clinical outcomes.

2.2. Establishment of the List of Targeted Therapies

The compilation of targeted therapies, including kinase inhibitors, immune system modulators, and specific monoclonal antibodies, was carried out using the resources provided by the National College of Medical Pharmacology (https://pharmacomedicale.org) (**Table 1**). This approach ensured a comprehensive and up-to-date selection of therapeutic agents relevant to the study's focus.

2.3. Cell Lines

The human medulloblastoma cell lines (ONS76, DAOY, HD-MB03) and the normal microglial cells (HMC3) were purchased from American Type Culture Collection (ATCC). DAOY, ONS76 and HMC3 cells were maintained in MEM alpha (Gibco, Life Technologies Corporation, Loughborough, UK) supplemented with 10% fetal bovine serum (FBS, SIGMA, Burlington, MA, USA). HD-MB03

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cells were maintained with RPMI 10% fetal bovine serum (FBS, SIGMA, Burlington, MA, USA). Cells were monitored routinely, and the absence of mycoplasma was verified monthly using the PlasmoTest kit (Invivogen, San Diego, CA, USA).

2.4. Cell Death Assay

Cell viability was assessed using the propidium iodide (PI) exclusion assay. Following treatment, cells were harvested and incubated with PI (10 μg/ml) for 5 minutes. The percentage of PI-positive cells was subsequently analyzed by flow cytometry using a MACSQuant Analyzer (Miltenyi Biotec, catalog number 130-092).

2.5. Immunoblot

Cells were lysed with Laemmli buffer and protein amounts were determined by the Pierce TM BCA Protein Assay Kit (Thermo Fisher). Then, 20 μg of protein were resolved by SDS-PAGE. The proteins were transferred onto PVDF membranes in Tris–glycine buffer. Membranes were blocked with 5% milk at room temperature and then immunoblotted overnight in 3% milk with the anti-BCL2 antibody (Cell signaling Technology #2872). Membranes were washed with PBS–Tween 0.1% and incubated with HRP-conjugated secondary antibodies at room temperature for 1 h. The Advansta Western Bright Quantum HRP substrate was used as a detection reagent.

3. Results

3.1. Identifying Medulloblastoma Patients Eligible for Targeted Therapies

Table 1 highlights kinase and apoptosis inhibitors that target specific genes in tumor cells and are used in the treatment of both hematological and solid tumors. It also includes immunological modulators that act on specific targets expressed by transformed immune cells or on pathways involved in immune tolerance. Our aim was to explore the potential of repositioning these clinically validated therapies for the treatment of pediatric medulloblastoma.

To validate their relevance, we analyzed the relationship between these genes and overall patient survival (OS) using the Cavalli et al. cohort, the only publicly available dataset with survival data [12]. For each gene associated with a targeted therapy, Kaplan-Meier survival curves were generated via the R2 platform, employing the optimal cutoff values. Initially, Kaplan-Meier survival curves were generated for each gene, accompanied by their respective raw P-values and Bonferroni-corrected P-values. Approximately 300 curves were produced, which are presented in **Supplementary Figure S1**. Based on this analysis, **Table 2** summarizes the raw and Bonferroni-corrected P-values for each gene across the molecular subgroups of medulloblastoma (WNT, SHH, Group 3, and Group 4).

From **Table 2**, several genes were identified as relevant therapeutic targets due to their overexpression being associated with shorter OS. The corresponding treatments are outlined in **Table 3**. Genes with statistically significant associations (raw and Bonferroni-corrected P-values < 0.05) were prioritized for potential efficacy of targeted therapy within specific genetic subgroups:

SHH subgroup: Relevant targets included BCR-ABL, FILP1, PDGFR, Kit, CD52, FGFR, RET, RAF, TIM3, and VEGFR, with corresponding treatments Imatinib, Alemtuzumab, Pemigatinib, Regorafenib, Sabatolimab, Axitinib and Lenvatinib.

Group 3 tumors: Key genes identified were BCL2 and MEK2, with potential treatments Venetoclax and MEK inhibitors such as Cobimetinib, Trametinib, or Selumetinib.

WNT subgroup: Targetable genes included ABL1, CDK4/6, FGFR, HER2, and SMO, with suggested therapies such as Asciminib, Abemaciclib, Palbociclib, Ribociclib, Pemigatinib, Trastuzumab, Pertuzumab, T-DM1, T-DXd, Lapatinib, Tucatinib, and Sonidegib.

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Table 1. Overview of Approved Targeted Therapies for Solid and Hematologic Tumors. This table provides a detailed summary of targeted therapies currently approved for the treatment of solid and hematologic tumors. It includes the associated pathologies, the generic names of the treatments, their corresponding brand names, and the specific genes they target.

	Name of "INIB" and "UMAB"	Brand name	Target gene(s)
Immunomodulation	Baricitinib	OLUMIANT	JAK1, JAK2
	Tofacitinib	XELJANZ	JAK1, JAK3
Hematology	Ruxolitinib	JAKAVI	JAK (+JAKV617F)
	Acalabrutinib	IMBRUVICA	BTK (Bruton)
	Idelalisib	ZYDELIG	PI3K
	Venetoclax	VENCLYXTO	BCL2
	Midostaurine	RYDAPT	FLT3, KIT, VEGFR, PKC
	Ivosidenib	TIBSOVO	IDH1
	Gilteritinib	XOSPATA	FLT3, AXL
	Asciminib	SCEMBLIX	ABL1, BCR-ABL1
	Bosutinib	BOSULIF	BCR-ABL, SRC, LYN, HCK, PDGFR
	Dasatinib	SPRYCEL	BCR-ABL, SRC-KINASES
	Ponatinib	ICLUSIG	KIT, FLT3, RET, PDGFR, VEGFR
	Nilotinib	TASIGNA	BCR-ABL
	Imatinib	GLIVEC	BCR-ABL, FILP1, PDGFR, KIT
Solid Tumors	Avapritinib	AYVAKYT	PDGFR, KIT
	Sunitinib	SUTENT	VEGFR, PDGFR, KIT, FLT3
	Pazopanib	VOTRIENT	VEGFR, PDGFR, KIT, FLT3
	Axitinib	INLYTA	VEGFR, PDGFR, KIT, FLT3
	Cabozantinib	CABOMETYX	VEGFR, MET, RET
	Sorafenib	NEXAVAR	VEGFR, PDGFR, KIT, FLT3, RAF-KINASES
	Lenvatinib	LENVIMA	VEGFR, FGFR, RET, PDGFR, KIT
	Vandetanib	CAPRELSA	VEGFR, EGFR, RET
	Pemigatinib	PEMAZYRE	FGFR
	Regorafenib	STIVARGA	KIT, RET, RAF-KINASES
	Sonidegib	ERIVEDGE	SMO (Hedgehog pathway)
	Lorlatinib	LORVIQUA	ALK, ROS1
	Brigatinib	ALUNBRIG	ALK, ROS1
	Ceritinib	ZYKADIA	ALK
	Crizotinib	XALKORI	HGFR, c-MET
	Alectinib	ALECENSA	ALK, RET
	Afatinib	GIOTRIF	HER1, 2, 3, 4
	Dacomitinib	VIZIMPRO	HER1, 2, 4, DDR2
	Erlotinib	TARCEVA	HER1
	Gefitinib	IRESSA	HER1
	Osimertinib	TAGRISSO	EGFR T790M
	Dabrafenib	TAFINLAR	BRAF V600E
	Encorafenib	BRAFTOVI	BRAF V600E
	Vemurafenib	ZELBORAF	BRAF V600E
	Cobimetinib	COTELLIC	MEK
	Trametinib	MEKINIST	MEK
	Selumetinib	KOSELUGO	MEK
	Capmatinib	TRABECTA	RET fusion
	Selpercatinib	RETSEVMO	RET fusion
	Praseltinib	GAVRETO	RET fusion
	Larotrectinib	VITRAKVI	TRK
	Alpelisib	PIQRAY	PI3Ka
	Lapatinib	TYVERB	HER2
	Tucatinib	TUKYSA	HER2
	Abemaciclib	VERZENIOS	CDK4/6
	Palbociclib	IBRANCE	CDK4/6
	Ribociclib	KISQALI	CDK4/6
	Olaparib	LYNPARZA	PARP
	Rucaparib	RUBRACA	PARP
	Talazoparib	TALZENNA	PARP
Immune cell targeting	Blinatumomab	BLINCYTO	CD19
	Basiliximab	SIMULECT	CD25
	Gemtuzumab ozogamicin	MYLOTARG	CD33
	Alemtuzumab	CAMPATH	CD52
	Sabatolimab		TIM3
	Ipilimumab	YERVOY	CTLA4
	Adecatumumab		EPCAM
	Atezolizumab, avelumab, durvalumab	TECENTRIQ, BAVENCIO, IMFINZI	PDL1

Group 4 tumors: Although no targets were highly statistically significant, several potential candidates were identified, including ABL1 (Asciminib), BCR-ABL, FILP1, PDGFR, Kit (Imatinib), BCL2 (Venetoclax), CD33 (Gemtuzumab), CD52 (Alemtuzumab), CDK4/6 (Abemaciclib, Palbociclib, Ribociclib), CTLA4 (Ipilimumab), JAK1/3 (Tofacitinib), MEK (Cobimetinib, Trametinib, Selumetinib), PARP (Olaparib, Rucaparib, Talazoparib), PDL1 (Atezolizumab, Avelumab, Durvalumab), PDGFR/KIT (Avapritinib), and TIM3 (Sabatolimab).

This classification provides a framework for repositioning specific drugs to treat pediatric medulloblastoma, offering novel therapeutic opportunities tailored to the genetic profiles of the tumor subgroups.

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Table 2. Association Between Targeted Genes and Patient Survival Across Medulloblastoma Subgroups. This table illustrates the relationship between genes targeted by the therapies listed in Table 1 and overall survival (OS) across various genetic subgroups of medulloblastoma. The analyzed genes or gene families are displayed alongside their respective P-values, calculated using the R2 platform with the optimal cutoff method. Two P-values are provided for each gene: the first represents the raw significance, while the second reflects the Bonferroni-corrected significance. Genes are visually categorized based on their prognostic association using background colors: **White background**: Genes linked to shorter OS; **Black background**: Genes linked to longer OS; **Dark grey background with enlarged text**: Genes associated with a poor prognosis, indicated by both raw and Bonferroni-corrected P-values < 0.05; **Light grey background**: Non-significant (NS) genes with no clear survival impact. This classification provides an intuitive visual summary of the survival impact of specific genes across medulloblastoma subgroups, facilitating a better understanding of their prognostic relevance.

	ALK	BCL2	BCL2L1	BCL2L2	BTK	CD3D	CD19	CD20	CD25	CD33	CD52	CDK		DDR2	EPCAM	FGFR			FLT3
	ALK	BCL2	BCL2L1	BCL2L2	BTK	CD3D	CD19	CD20	CD25/ISG20	CD33	CD52	CDK4	CDK6	DDR2	EPCAM	FGFR1	FGFR2	FGFR3	FLT3
WNT	NS	NS	NS	NS	3e-3/NS	NS	NS	0.02/NS	NS	NS	NS	0.057/NS	NS	NS	NS	0.06/NS	NS	NS	0.04/NS
SHH	1e-2/NS	0.03/NS	NS	NS	0.01/NS	2e-2/NS	0.046/NS	1.4e-3/NS	0.01/NS	2e-3/NS	2.8e-4/0.04	9e-3/NS	0.07/NS	1.4e-3/NS	NS	NS	0.03/NS	9e-5/0.01	0.04/NS
GR4	0.02/NS	0.02/NS	1e-2/NS	NS	NS	9e-5/0.02	4.5e-4/NS	3e-4/0.07	NS	0.015/NS	5.5e-4/NS	0.01/NS	2e-3/NS	3e-3/NS	NS	9e-4/NS	5e-3/NS	7e-4/NS	7e-3/NS
GR3	1.5e-3/NS	5e-4/0.05	NS	3e-3/NS	0.04/NS	0.03/NS	0.05/NS	NS	6.7e-4/NS	NS	0.01/NS	2e-4/0.02	0.03/NS	0.04/NS	0.015/NS	0.03/NS	NS	NS	0.035/NS

	HER				Immune check points						IDH1	JAK			MAPK		
	EGFR/HER1	ERBB2/HER2	ERBB3/HER3	ERBB4/HER4	PD1	PD2	PDL1	PDL2	CTLA4	TIM3	LAG3	IDH1	JAK1	JAK2	JAK3	MAP2K2	MAPK1	MAPK3
WNT	5e-3/NS	0.05/NS	NS	NS	NS	NS	NS	NS	NS	0.08/NS	NS	0.07/NS	NS	0.095/NS	NS	NS	0.03/NS	NS
SHH	NS	0.04/NS	2e-5/3.5e-3	0.02/NS	0.03/NS	NS	9e-3/NS	0.02/NS	0.07/NS	3e-5/5e-3	NS	NS	4e-3/0.6	3e-3/0.8	8e-3/NS	0.04/NS	NS	1.2e-3/NS
GR4	NS	0.01/NS	0.03/NS	0.01/NS	NS	0.02/NS	3e-3/NS	NS	0.02/NS	0.06/NS	NS	0.05/NS	0.07/NS	NS	0.06/NS	0.05/NS	4e-3/NS	0.05/NS
GR3	0.02/NS	0.01/NS	NS	0.02/NS	6e-3/NS	8e-4/0.08	NS	0.03/NS	7e-3/NS	0.03/NS	NS	0.08/NS	0.05/NS	NS	NS	5e-4/0.05	0.04/NS	6e-3/NS

	MET	MTOR	NTRK		PARP1	PDGFR				PIK3G							
	MET	MTOR	NTRK1	NTRK2	NTRK3	PARP1	PDGFRA	PDGFRB	FIP1L1	KIT	PIK3CA	PIK3CB	PIK3CD	PIK3G	PIK3C2B	PIK3C2B	PIK3C2G	PIK3C3
WNT	NS	NS	NS	4e-4/NS	0.04/NS	NS	NS	NS	0.04/NS	NS	NS	0.04/NS	0.04/NS	0.02/NS	0.05/NS	0.01/NS	6e-3/NS	NS
SHH	0.03/NS	NS	1e-7/1.5e-5	0.01/NS	5e-5/9e-3	5e-3/NS	7e-5/0.01	5e-8/6e-6	3.5e-7/5.5e-5	9e-5/0.01	8.9e-3/NS	0.02/NS	0.06/NS	4e-4/0.06	0.04/NS	3e-3/NS	5e-8/6e-5	5e-3/NS
GR4	0.08/NS	NS	0.07/NS	NS	8e-7/2e-4	0.02/NS	0.06/NS	0.02/NS	0.04/NS	0.08/NS	0.03/NS	0.02/NS	0.01/NS	3e-4/0.07	0.095/NS	0.04/NS	0.05/NS	2e-3/NS
GR3	0.02/NS	0.01/NS	0.02/NS	NS	0.03/NS	0.01/NS	0.01/NS	0.02/NS	0.07/NS	0.04/NS	0.057/NS	0.05/NS	0.08/NS	0.05/NS	0.03/NS	NS	1.4e-3/NS	1.6e-3/NS

	PKC				RAF			RET	ROS1	SMO	SRC					VEGFR		
	ITPKC	PRKCA	PRKCB	PRKCD	ARAF	BRAF	RAF1	RET	ROS1	SMO	ABL1	SRC	FYN	YES	LYN	FLT1	KDR	FLT4
WNT	NS	NS	NS	2e-8/1.2e-4	NS	NS	NS	NS	NS	0.02/NS	0.06/NS	0.035/NS	NS	NS	7e-3/NS	NS	NS	NS
SHH	NS	0.014/NS	0.04/NS	1.6e-3/NS	NS	0.03/NS	8e-4/NS	NS	7e-3/NS	0.05/NS	3e-3/NS	4e-3/NS	2e-5/3e-3	6.5e-3/NS	NS	6e-3/NS	5e-3/NS	0.02/NS
GR4	NS	0.03/NS	1e-2/NS	1e-4/0.024	0.07/NS	1e-2/NS	0.02/NS	0.07/NS	NS	0.03/NS	0.02/NS	NS	0.05/NS	0.04/NS	0.02/NS	5e-3/NS	0.04/NS	NS
GR3	0.03/NS	0.04/NS	0.07/NS	NS	0.01/NS	0.01/NS	0.02/NS	0.05/NS	0.01/NS	NS	NS	0.04/NS	6e-3/NS	0.01/NS	NS	0.04/NS	NS	0.08/NS

Table 3. Alignment of Targeted Therapies with Gene-Survival Associations Across Medulloblastoma Subgroups. This table outlines the positioning of targeted therapies based on the survival impact of their corresponding genes across medulloblastoma subgroups. It highlights the most suitable treatments for each subgroup, determined by the lowest P-value: **Small characters**: Indicate a trend toward significance. **Medium characters**: Denote a statistically significant raw P-value. **Large characters**: Represent both raw and Bonferroni-corrected P-values as statistically significant. This table aids in identifying the most effective targeted therapies for each medulloblastoma subgroup, guided by gene-survival correlations.

TARGET	WNT	SHH	GR4	GR3
ABL1	Asciminib	Asciminib	Asciminib	
BCR-ABL, FILP1, PDGFR, KIT		**Imatinib**	Imatinib	
BCL2		Venetoclax	Venetoclax	**Venetoclax**
BTK		Acalabrutinib		Acalabrutinib
CD19/CD3		Blinatumomab		
CD25		Basiliximab		
CD33		Gemtuzumab	Gemtuzumab	
CD52		**Alemtuzumab**	Alemtuzumab	Alemtuzumab
CDK4/6	Abemaciclib, Palbociclib, Ribociclib	Abemaciclib, Palbociclib, Ribociclib	Abemaciclib, Palbociclib, Ribociclib	
CTLA4		Ipilimumab	Ipilimumab	Ipilimumab
EPCAM				Adecatumumab
FGFR	Pemigatinib	**Pemigatinib**		
FLT3				Gilteritinib
HER2	Trastuzumab, Pertuzumab, TDM1, TDXd, Lapatinib, Tucatinib			Trastuzumab, Pertuzumab, TDM1, TDXd, Lapatinib, Tucatinib
JAK1, 3			Tofacitinib	
Kit RET RAF		**Regorafenib**		
MEK		Cobimetinib, Trametinib, Selumetinib	Cobimetinib, Trametinib, Selumetinib	**Cobimetinib, Trametinib, Selumetinib**
MET				Crizotinib
PARP		Olaparib, Rucaparib, Talazoparib	Olaparib, Rucaparib, Talazoparib	Olaparib, Rucaparib, Talazoparib
PDL1			Atezolizumab, Avelumab, Durvalumab	
PDGFR, KIT			Avapritinib	
PIK3CA		Idelalisib		Idelalisib
SMO	Sonidegib	Sonidegib		
TIM3		**Sabatolimab**	Sabatolimab	Sabatolimab
VEGFR, EGFR, RET		Vandetanib		
VEGFR, FGFR, RET, PDGFR, KIT		**Axtinib, Lenvatinib**		

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3.2. Stratification of Patients by Metastatic Status

Our previous research on gene expressions associated with kidney cancer and medulloblastoma aggressiveness revealed a potential reversal in the impact on OS depending on metastatic status (non-metastatic, M0, versus metastatic, M1). Notably, the prognostic significance of Vascular Endothelial Growth Factor C (VEGFC), a key gene in lymphatic vessel development, displayed opposing trends in M0 and M1 contexts [24,25]. Therefore, we reiterate our analysis considering this important parameter. Approximately 700 curves were produced, which are presented in **Supplementary Figure S2**. Based on this analysis, **Table 4** summarizes the raw and Bonferroni-corrected P-values for each gene across the molecular subgroups of medulloblastoma and the metastatic status, M0/M1 (WNT, SHH, Group 3, and Group 4).

Table 4. Association Between Targeted Genes and Patient Survival Across Medulloblastoma Subgroups Considering Metastatic Status (M0, M1). This table explores the association of genes targeted by the therapies listed in Table 1 with overall survival (OS) in medulloblastoma patients, stratified by metastatic status (M0: non-metastatic, M1: metastatic). The analyzed genes or gene families are presented alongside their respective P-values, calculated using the R2 platform based on the optimal cutoff approach. Two P-values are reported for each gene: the raw significance value and the Bonferroni-corrected significance value. Genes are visually categorized using background colors to reflect their prognostic impact: White background: Genes associated with shorter OS; Black background: Genes associated with longer OS; Dark grey background with enlarged text: Genes associated with a poor prognosis, indicated by both raw and Bonferroni-corrected P-values < 0.05; Light grey background: Non-significant (NS) genes with no discernible impact on OS. This visual classification highlights the survival implications of specific genes across medulloblastoma subgroups while considering the patients' metastatic status, providing valuable insights into prognostic and therapeutic considerations.

	ALK	BCL2	BCL2L1	BCL2L2	BTK	CD3D	CD19	CD20	CD25	CD33	CD52	CDK		DDR2	EPCAM	FGFR			FLT3
	ALK	BCL2	BCL2L1	BCL2L2	BTK	CD3D	CD19	CD20	CD25	CD33	CD52	CDK4	CDK6	DDR2	EPCAM	FGFR1	FGFR2	FGFR3	FLT3
WNT M0	NS	NS	NS	NS	5.3e-3/NS	0.05/NS	0.01/NS	0.02/NS	NS	NS	NS	0.05/NS	NS	NS	NS	NS	5.9e-3/NS	NS	NS
WNT M1	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
SHH M0	NS	NS	NS	NS	1e-2/NS	1e-3/NS	NS	1e-6/1e-4	0.01/NS	3e-3/NS	6e-9/7e-7	3e-3/NS	NS	3e-3/NS	NS	NS	0.04/NS	7.8e-7/9e-5	NS
SHH M1	NS	NS	NS	NS	NS	NS	0.03/NS	NS	NS	0.05/NS	0.02/NS	7.8e-4/0.01	0.02/NS	NS	NS	NS	NS	0.075/NS	2e-3/0.08
GR4 M0	0.04/NS	2e-3/NS	0.03/NS	0.076/NS	NS	NS	2e-3/NS	9e-6/1e-3	NS	0.02/NS	5e-3/NS	0.03/NS	0.04/NS	0.03/NS	NS	NS	0.04/NS	1.4e-7/2e-5	0.04/NS
GR4 M1	2e-4/1.7e-3	8e-3/NS	0.02/NS	2.5e-3/NS	NS	1e-4/8.5e-3	0.02/NS	NS	NS	NS	0.02/NS	NS	6e-3/NS	0.02/NS	NS	NS	0.04/NS	0.071/NS	0.03/NS
GR3 M0	0.02/NS	2.5e-3/NS	3.7e-3/NS	0.02/NS	NS	0.06/NS	9e-3/NS	NS	0.04/NS	0.06/NS	5.5e-3/NS	0.02/NS	NS	2e-3/NS	0.04/NS	0.02/NS	NS	NS	NS
GR3 M1	3e-3/NS	0.05/NS	0.056/NS	0.02/NS	0.03/NS	0.07/NS	5e-3/NS	NS	2e-3/0.075	0.04/NS	NS	1e-3/0.04	NS	NS	NS	NS	NS	9e-3/NS	0.05/NS

	HER				Immune checkpoints							IDH1	JAK			MAPK		
	EGFR/HER1	ERBB2/HER2	ERBB3/HER3	ERBB4/HER4	PD1	PD2	PDL1	PDL2	CTLA4	TIM3	LAG3	IDH1	JAK1	JAK2	JAK3	MAP2K2	MAPK1	MAPK3
WNT M0	0.02/NS	0.02/NS	NS	NS	NS	NS	NS	NS	NS	0.05/NS	NS	NS	NS	NS	NS	NS	0.03/NS	NS
WNT M1	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
SHH M0	0.04/NS	NS	2e-5/4e-4	NS	7e-4/0.08	0.056/NS	0.02/NS	0.03/NS	NS	2e-3/NS	4e-4/0.046	0.07/NS	0.04/NS	3.9e-3/NS	NS	6e-3/NS	NS	NS
SHH M1	0.05/NS	NS	8.5e-4/NS	7e-3/NS	NS	NS	NS	NS	NS	0.01/NS	0.04/NS	NS	NS	0.04/NS	NS	NS	NS	NS
GR4 M0	0.05/NS	2.8e-4/0.04	0.056/NS	0.04/NS	0.064/NS	4e-3/NS	0.06/NS	NS	NS	0.02/NS	0.03/NS	NS	NS	0.04/NS	0.074/NS	NS	0.01/NS	0.04/NS
GR4 M1	0.02/NS	NS	4.7e-3/NS	0.05/NS	NS	0.04/NS	0.02/NS	NS	NS	NS	0.047/NS	NS	0.03/NS	0.015/NS	NS	NS	NS	0.04/NS
GR3 M0	0.05/NS	2.9e-3/NS	0.05/NS	NS	0.02/NS	NS	0.07/NS	0.035/NS	0.03/NS	NS	NS	0.02/NS	NS	NS	NS	7.5e-3/NS	0.02/NS	0.059/NS
GR3 M1	2e-4/7e-3	NS	NS	NS	1e-2/NS	0.04/NS	NS	NS	0.01/NS	NS	0.03/NS	4.5e-3/NS	NS	0.05/NS	NS	NS	NS	9e-4/0.03

	MET	MTOR	NTRK			PARP1	PDGFR				PIK3G							
	MET	MTOR	NTRK1	NTRK2	NTRK3	PARP1	PDGFRA	PDGFRB	FIP1L1	KIT	PIK3CA	PIK3CB	PIK3CD	PIK3G	PIK3C2A	PIK3C2B	PIK3C2G	PIK3C3
WNT M0	NS	NS	NS	7.5e-4/0.03	NS	NS	NS	NS	0.05/NS	NS	NS	NS	0.03/NS	NS	NS	3.6e-3/NS	0.01/NS	NS
WNT M1	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
SHH M0	0.05/NS	NS	2e-7/2e-5	NS	1.7e-3/NS	3e-3/NS	NS	NS	NS	NS	0.03/NS	NS	NS	5.7e-3/NS	0.04/NS	0.03/NS	4.8e-5/5.7e-3	NS
SHH M1	0.01/NS	NS	NS	2e-5/4e-4	0.03/NS	NS	NS	1.5e-3/0.03	NS	NS	NS	NS	0.04/NS	4.6e-3/NS	NS	0.01/NS	2e-4/3.3e-3	NS
GR4 M0	NS	NS	NS	NS	3e-7/4e-5	0.02/NS	0.035/NS	0.05/NS	0.02/NS	8.8e-3/NS	NS	0.02/NS	0.01/NS	0.03/NS	NS	1.2e-3/NS	5e-3/NS	0.03/NS
GR4 M1	NS	NS	0.046/NS	NS	0.02/NS	NS	0.025/NS	NS	NS	NS	NS	NS	0.06/NS	9e-3/NS	NS	NS	0.03/NS	1.2e-6/1e-4
GR3 M0	0.04/NS	0.04/NS	3e-3/NS	0.046/NS	0.05/NS	7.8e-3/NS	1.5e-3/0.09	0.09/NS	0.07/NS	0.06/NS	0.03/NS	NS	NS	0.02/NS	0.05/NS	NS	0.05/NS	0.06/NS
GR3 M1	0.045/NS	0.015/NS	NS	0.03/NS	NS	0.04/NS	NS	1.5e-3/0.03	0.03/NS	0.02/NS	NS	NS	NS	0.04/NS	7e-3/NS	NS	1.6e-4/6e-3	1.8e-3/0.07

	PKC				RAF			RET	ROS1	SMO	SRC					VEGFR		
	ITPKC	PRKCA	PRKCB	PRKCD	ARAF	BRAF	RAF1	RET	ROS1	SMO	ABL1	SRC	FYN	YES	LYN	FLT1	KDR	FLT4
WNT M0	NS	NS	NS	1.4e-5/5e-4	NS	NS	NS	NS	NS	2.3e-3/0.087	NS	0.03/NS	NS	NS	0.01/NS	NS	NS	NS
WNT M1	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
SHH M0	0.06/NS	NS	0.055/NS	0.01/NS	NS	7.7e-3/NS	5.8e-3/0.03	0.04/NS	7e-3/NS	0.05/NS	2e-3/NS	0.02/NS	1.4e-3/NS	0.05/NS	NS	6.8e-3/NS	6.6e-3/NS	0.045/NS
SHH M1	0.02/NS	NS	NS	0.03/NS	NS	0.03/NS	NS	NS	NS	7.5e-4/0.01	NS	NS	0.098/NS	0.05/NS	NS	4.8e-3/0.08	NS	0.07/NS
GR4 M0	NS	0.02/NS	0.015/NS	1.9e-4/0.03	NS	2.8e-3/NS	NS	0.03/NS	NS	0.02/NS	NS	NS	0.014/NS	0.02/NS	NS	0.03/NS	0.03/NS	NS
GR4 M1	NS	NS	0.04/NS	0.04/NS	4.7e-3/NS	NS	0.014/NS	NS	0.03/NS	NS	NS	0.02/NS	2.6e-3/NS	NS	0.014/NS	NS	NS	NS
GR3 M0	0.03/NS	0.02/NS	0.05/NS	NS	NS	NS	0.02/NS	NS	0.03/NS	NS	NS	NS	NS	0.05/NS	NS	NS	NS	NS
GR3 M1	7.7e-3/NS	NS	NS	0.02/NS	NS	1.5e-3/0.03	0.05/NS	NS	0.01/NS	NS	NS	NS	4.6e-4/0.02	0.085/NS	0.05/NS	0.03/NS	0.03/NS	0.04/NS

From **Table 4**, several genes emerged as relevant therapeutic targets, but their prognostic significance for OS varied depending on metastatic status. For example, **BCL2L1** was associated with poor prognosis in non-metastatic (M0) Group 3 patients but exhibited a favorable prognosis in metastatic (M1) Group 3 patients. Similarly, genes such as **CDK4**, **HER1**, and **SMO** showed differing prognostic roles between M0 and M1 patients in the SHH subgroup, while **HER1**, **MET**, and **ITPKC** displayed similar contrasting behavior in Group 3 patients. Additionally, **FLT3** and **PD2** were poor prognostic markers for Group 4 M0 patients but indicated good prognosis in Group 4 M1 patients.

Conversely, certain genes exhibited reversed prognostic associations between M0 and M1 stages. For example, **BCL2L2**, **HER4**, **LAG3**, **JAK2**, and **MAPK3** were linked to favorable prognosis

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in M0 Group 4 patients but poor prognosis in M1 Group 4 patients. Similarly, **CTLA4** was a favorable prognostic marker in M0 Group 3 patients but indicated poor prognosis in M1 Group 3 patients.

These results highlight that the prognostic behavior of certain genes depends significantly on tumor stage, reinforcing the importance of metastatic status in defining their clinical relevance. However, most genes demonstrate consistent prognostic behavior across both stages.

Genes associated with good prognosis were identified as being more significant in different patient groups based on metastatic status. In M0 patients, the genes **BTK, CD3D, CD19, CD20, CD33, DDR2, FGFR1, HER1, HER2, HER3, HER4, PD1, PDL1, PDL2, TIM3, LAG3, IDH1, JAK1, JAK2, MAPK1, NTRK1, NTRK3, PIK3CA, PIK3CD, PIK3C2A, PIK3C2G, PRKCB, PRKCD, RAF1, ROS1, LYN, KDR, and FLT4** demonstrated greater significance. Meanwhile, in M1 patients, genes such as **CD19, CD25, CDK6, FGFR3, PD1, MET, MTOR, NTRK2, PDGFRB, FIP1L1, PIK3C3, BRAF, ROS1, FYN, LYN, and FLT4** were identified as more significant.

Conversely, genes associated with poor **prognosis** also showed variation in significance based on metastatic status. In M0 patients, the genes **BCL2, BTK, CD3D, CD25, CD33, CD52, CDK4, DDR2, EPCAM, FGFR2, FGFR3, HER3, PD1, PD2, PDL2, TIM3, JAK3, MAP2K2, MAPK1, NTRK1, PARP1, PDGFRA, PDGFRB, FIP1L1, KIT, PIK3G, PIK3C2B, PRKCA, PRKCD, BRAF, RAF1, RET, SMO, ABL1, SRC, FYN, and KDR** were more significant. In contrast, in M1 patients, the genes **BTK, CD3D, CD19, CDK4, CDK6, DDR2, FLT3, HER1, HER4, PD2, PDL1, JAK1, MAPK3, NTRK1, NTRK2, PDGFRA, KIT, PIK3G, PIK3C2A, PIK3C2B, PIK3C2G, ITPKC, PRKCD, ARAF, RAF1, ROS1, FYN, FLT1, and KDR** showed higher significance.

These findings underscore the critical role of metastatic status in determining the prognostic significance and therapeutic prioritization of target genes. This distinction is vital for guiding gene-specific treatment strategies and optimizing therapeutic outcomes in medulloblastoma.

Through the deconvolution of genes associated with aggressiveness, we identified targeted therapies tailored to each genetic subgroup and their corresponding metastatic status (**Table 5**).

This updated table incorporates considerations for both genetic subgroups and tumor stages, in contrast to the previous table, which focused solely on genetic subgroups without accounting for tumor metastatic status. For the WNT subgroup, several therapies showed promise for M0 patients, who represented most of the cohort. These included Abemaciclib, Ribociclib, and Palbociclib (CDK inhibitors), Pemigaptinib (FGFR inhibitor), and, unexpectedly, Sonidegib (SMO inhibitor), which was originally designed for SHH patients. However, targeting HER2 was not beneficial for M0 patients in this subgroup.

In the SHH subgroup, Venetoclax (**BCL2 inhibitor**), Ipilimumab (**CTLA4 checkpoint inhibitor**), and Alpelisib (**PIK3CA inhibitor**) were found to be irrelevant for both M0 and M1 patients. Conversely, therapies such as Gilteritinib (**FLT3 inhibitor**), Sunitinib, Pazopanib, and Axitinib (**targeting VEGFR, PDGFR, KIT, and FLT3**) demonstrated potential greater effectiveness.

For Group 4, therapies such as Asciminib (**ABL1 inhibitor**), Gemtuzumab (**CD33-directed agent**), Ipilimumab (**CTLA4 inhibitor**), and Cobimetinib, Trametinib, and Selumetinib (**MAP2K2 inhibitors**), and Sabatolimab (**TIM3**), were no longer relevant for either M0 or M1 patients. However, potential treatments included Gilteritinib (**FLT3 inhibitor**), Gefitinib, Erlotinib, Afatinib, and Cetuximab (**EGFR-targeting agents**), as well as Regorafenib (**targeting KIT, RET, and RAF**), Nivolumab and Pembrolizumab (**PD1 inhibitors**), and Idelalisib (**PIK3CA inhibitor**).

For Group 3, Sabatolimab (**TIM3**) was suspected to have no effect for both M0 and M1 patients. In contrast, promising drugs included Abemaciclib, Ribociclib, and Palbociclib (**CDK inhibitors**), Gefitinib, Erlotinib, Dacomitinib, and Cetuximab (EGFR-targeting), along with Ivosidenib (**IDH1 inhibitor**), Regorafenib (**targeting KIT, RET, and RAF**), and Cabozantinib (**targeting VEGFR, MET, and RET**).These findings underscore the importance of considering differences in tumor stages—localized (M0) versus metastatic (M1)—when repositioning treatments. The choice of therapy should be informed by these distinctions, particularly at diagnosis, relapse, or based on whether the tumor is localized or has spread.

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Table 5. Alignment of Targeted Therapies with Gene-Survival Associations Across Medulloblastoma Subgroups Considering M0 and M1 Status. This table aligns targeted therapies with the survival impact of their corresponding genes across medulloblastoma subgroups, considering the metastatic status (M0: non-metastatic; M1: metastatic). The therapies are categorized based on the statistical significance of the association between the targeted gene and overall survival (OS), as determined by the lowest P-value. The significance levels are represented using text size: Small characters: Indicate a trend toward significance (suggestive but not statistically confirmed); Medium characters: Denote a statistically significant association based on raw P-values; Large characters: Represent statistically significant associations confirmed by both raw and Bonferroni-corrected P-values. This framework identifies the most promising therapies for each subgroup, offering a nuanced understanding of therapeutic relevance in the context of metastatic status and gene-survival dynamics.

TARGET	WNT M0	WNT M1	SHH M0	SHH M1	GR4 M0	GR4 M1	GR3 M0	GR3 M1
ABL1			Asciminib, Nilotinib					
BCR-ABL, FILP1, PDGFR, KIT			Imatinib		Imatinib	Imatinib		
BCL2					Venetoclax	Venetoclax	Venetoclax	Venetoclax
BTK			Acalabrutinib					Acalabrutinib
CD19/CD3			Blinatumomab	Blinatumomab				
CD25			Basiliximab					
CD33			Gemtuzumab	Gemtuzumab			Gemtuzumab	
CD52			**Alemtuzumab**	Alemtuzumab	Alemtuzumab	Alemtuzumab	**Alemtuzumab**	
CDK4/6	Abemaciclib, Ribociclib, Palbociclib		Abemaciclib, Ribociclib, Palbociclib		Abemaciclib, Ribociclib, Palbociclib	Abemaciclib, Ribociclib, Palbociclib	Abemaciclib, Ribociclib, Palbociclib	**Abemaciclib, Ribociclib, Palbociclib**
CTLA4								Ipilimumab
EPCAM							Adecatumumab	
FGFR	Pemigatinib		**Pemigatinib**		**Pemigatinib**	Pemigatinib		
FLT3				Gilteritinib	Gilteritinib			Gilteritinib
HER1			Gefitinib, Erlotinib, Afatinib, Cetuximab		Gefitinib, Erlotinib, Cetuximab	Gefitinib, Erlotinib,Afatinib, Cetuximab	Gefitinib, Erlotinib, Dacomitinib, Cetuximab	
HER2							Trastuzumab, Pertuzumab, Lapatinib, Afitinib	
IDH1								Ivosidenib
JAK1, 2, 3					Tofacitinib	Tofacitinib, Baricitinib		
Kit, RET, RAF					Regorafenib	Regorafenib	Regorafenib	
MEK			Cobimetinib, Trametinib, Selumetinib				Cobimetinib, Trametinib, Selumetinib	
MET							Cabozantinib, Crizotinib	
PARP			Olaparib, Rucaparib, Talazoparib		Olaparib, Rucaparib, Talazoparib		Olaparib, Rucaparib, Talazoparib	Olaparib, Rucaparib, Talazoparib
PD1					Nivolumab, Pembrolizumab			
PDL1					Atezolizumab, Avelumab, Durvalumab	Atezolizumab, Avelumab, Durvalumab		
PDGFR, KIT					Avapritinib	Avapritinib		
PIK3CA							Idelalisib	Idelalisib
SMO	**Sonidegib**		Sonidegib		Sonidegib			
TIM3			Sabatolimab	Sabatolimab				
VEGFR, EGFR, RET			Vandetanib					
VEGFR, FGFR, RET, PDGFR, KIT			Lenvatinib					
VEGFR, PDGFR, KIT, FLT3			Sunitinib, Pazopanib, Axitinib	Sunitinib, Pazopanib, Axitinib				

3.3. Analysis of Targetable Mutations in Medulloblastoma Cohorts

Table 1 highlights treatments applicable when specific mutations are present, such as **BRAFV600E**. To explore actionable targets, we analyzed medulloblastoma cohorts from the TCGA database, focusing on mutations in targetable genes. Across six available cohorts comprising 828 patients, we identified specific mutation frequencies as follows: 54 patients (6.5%) carried mutations in **CTNNB1**, 42 patients (5.1%) in **PTCH1**, 21 patients (2.5%) in **SMO**, 14 patients (1.7%) in **SUFU**, 13 patients (1.6%) in **PTEN**, 5 patients (0.6%) in **PI3KCA**, 3 patients (0.36%) in **PIK3R1**, and 2 patients (0.24%) in **FGFR1**. Additionally, mutations were identified in each single patient (0.12%) for **ATM**, **CDKN2A**, **ERBB4**, **FGFR2**, **IDH1**, and **NRAS**.

Given these mutation profiles, conventional treatments listed in **Table 1** may not be effective. The specific mutations identified in these cohorts and their clinical implications are detailed in **Table 6**.

To address this, we propose alternative therapies tailored to mutation-specific cases. For mutations in the **CTNNB1** pathway, inhibitors of GSK3 such as Elraglusib and Tideglusib [26,27] which target CTNNB1 activation, may be effective. In the **PI3K/AKT** pathway, several inhibitors could be utilized, including Capivasertib, used for metastatic breast cancer with at least one alteration on PIK3CA/AKT1/PTEN [28], and RLY-2608, a PIK3CA inhibitor [29]. Additionally, PI3Kβ inhibitors such as GSK2636771 and AZD8186 are potential options [30,31]. For mutations in the **FGFR** pathway, inhibitors like Erdafitinib and Fexagratinib may offer therapeutic [32,33]. In cases with EGFR mutations that heterodimerize with ERBB4, the inhibitor Dacomitinib could be considered [34].

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Mutations associated with resistance to SHH pathway inhibitors (e.g., Sonidegib and Vismodegib) were also identified, underscoring their role as predictive markers of treatment inefficacy.

Table 6. Alignment of Targeted Therapies with Specific Gene Mutations This table presents the alignment of targeted therapies with specific mutations that are not addressable by conventional therapies. It includes the names of patient cohorts from the TCGA, the specific genes and mutations identified, their associated expected phenotypes, and the names of treatments tailored to these mutations.

Cohort Name	Mutation (Number of case)	Phenotype	Treatment
PCGP Medulloblastoma Nature 2012 37 patients			
CTNNB1 (beta Cat) 2 patients 5%.	Mutations S33F (1), G34R (1)	Likely Oncogenic	Etraglusib, Tideglusib
PI3KCA 1 patient 2.7 %	Mutation Q546K (1)	Oncogenic	Capivasertib
PTCH1 1 patient 2.7 %	Mutation S861Mfs*2 (1)	Likely oncogenic truncating mutation	Sonidegib Vismodegib
Medulloblastoma Broad Nature 2012 92 Samples			
CTNNB1 (beta Cat) 6 Patients 6.5 %	Mutation D32G (1), Mutation S33F (1), S33Y (1) G34R (2), S37P (1)	Likely Oncogenic	
PTCH1 5 Patients 6.5 %	Mutation X406 Splice (1), I1055Sfs*3 (1), Q242Vfs*9 (1) Q889Afs*7 (1), n V439Qfs*59 (1)	Likely oncogenic truncating mutations Likely oncogenic truncating mutation	Sonidegib Vismodegib Sonidegib Vismodegib
FGFR1 2 Patients 2.2 %	Mutation N577K (1), K687E (1)	Likely Oncogenic	Erdafitinib, Fexagratinib
SMO 1 Patient 1.1 %	Mutation L412F (1)	Likely Oncogenic	Resistance to Vismodegib
PTEN 1 Patient 1.1 %	Mutation G165E (1)	Oncogenic	Capivasertib, GSK2636771, AZD8186
PIK3CA 1 Patient 1.1 %	Mutation H1047L (1)	Oncogenic	Alpelisib Capivasertib RLY-2608
SUFU 1 Patient 1.1 %	Mutation X386_Splice (1)	Likely Oncogenic	Resistance to Vismodegib
Medulloblastoma DKFZ Nature 2017 491 Samples			
PTCH1 25 Patients 5.1 %	Mutation C92* (1), W129* (1), Q177* (1), E374* (1), F583* (1) R602* (1), C618* (1), Q839* (1), C1093* (1), E1183* (1) Mutation V169Pfs*82 (1), Q242Vfs*9 (1), C226Ffs*2 (1) Mutation D301fs*23 (1), X406_splice (1), L448Nfs*9 (1) L450Pfs*5 (1), A451Pfs*5 (1), C462Wfs*27 (1) F495Nfs*50 (1), X750_splice (1), Y797Sfs*24 (1) L819Tfs*10 (1), I1055Sfs*3 (1), X1150_splice (1)	Likely oncogenic truncating mutations	Sonidegig Vismodegib
CTNNB1 (beta Cat) 25 Patients 5.1 %	Mutation D32Y (2), S33C (2), S33F (6), S33Y (4), G34E (1) G34R (4), G34V (1), S37C (1), S37F (1), S37P (1) S37Y (1), T41A (1)	Likely Oncogenic	Etraglusib, Tideglusib
ERBB4 1 Patient 0.2 %	Fusion ERBB4-LCLAT1 (1)	Likely Oncogenic	Lapatinib Dacomitinib
SMO1 11 Patients 2.2 %	Mutation L412F (8), W535L (3)	Likely Oncogenic	Resistance to Vismodegib
SUFU 11 Patients 2.2 %	Mutation I291* (1), E437* (1), P12Rfs*90 (1), A25Gfs*23 (1) Y147Vfs*21 (1), F149Sfs*20 (1), T190Nfs*25, T261Gfs*8 (1) P341Rfs*20 (1), X386_splice (1), SUFU-CYP17A1-AS1 Fusion (1)	Likely Oncogenic	Resistance to Vismodegib
IDH1 1 Patient 0.2 %	Mutation R132C	Oncogenic	Ivosidenib Vorasidenib
PTEN 9 Patients 1.83 %	Mutation W111R (1), G132V (1), G165E (1), D324Y (1), M134del (1) T319fs*2 (1), K322Rfs*23 (1), PTEN-NR2F1-AS1 Fusion (1) Mutation PTEN-THAP9 Fusion (1)	Oncogenic	Capivasertib GSK2636771 AZD8186
PIK3R1 3 Patients 0.61 %	X582_splice (1), Y452_N453ins* (1), D68Gfs*38 (1)	Likely Oncogenic	Capivasertib
Medulloblastoma ICGC Nature 2012 125 Samples			
CTNNB1 (beta Cat) 15 Patients 12 %	Mutation D32A (2), D32Y (3), S33C (4), S33F (2) G34R (2), S37F (1), S37Y (1)	Likely Oncogenic	Etraglusib, Tideglusib
PTCH1 6 Patients 4.8 %	Mutation E374* (1), Y1009* (1), F495Efs*50 (1) D773Rfs*16 (1), Y804Cfs*3 (1), L819Tfs*10 (1)	Likely oncogenic truncating mutations	Sonidegig Vismodegib
PIK3CA 2 Patients 1.6 %	Mutation H1047L (1), C420R (1)	Oncogenic	Alpelisib Capivasertib RLY-2608
NRAS 1 Patient 0.8 %	Mutation G13V	Oncogenic	Binimetinib Cobimetinib Trametinib
CDKN2A 1 Patient 0.8 %	Mutation D84N	Likely oncogenic truncating mutation	Palbociclib Ribociclib Abemaciclib
SMO 8 Patient 6.4 %	Mutation L412F	Likely Oncogenic	Resistance to Vismodegib
PTEN 1 Patient 0.8 %	Mutation H93Y	Oncogenic	Capivasertib GSK2636771 AZD8186
PIK3R1 1 Patient 0.8 %	Mutation X582_splice	Likely Oncogenic	Capivasertib
ATM 1 Patient 0.8 %	Mutation Y1915*	Likely Oncogenic	Olaparib Talazoparib + Enzalutamide
FGFR2 1 Patient 0.8 %	Mutation K659E	Likely Oncogenic	Erdafitinib RLY-4008 AZD4547
Medulloblastoma PCGP Nature 2012 37 Samples			
CTNNB1 (beta Cat) 4 Patients 10.8 %	Mutation D32G (1), S33F (1), S33Y (1), G34R (1)	Likely Oncogenic	Etraglusib, Tideglusib
PIK3CA 1 Patient 2.7 %	Mutation Q546K	Oncogenic	Capivasertib + Fulvestrant RLY-2608
SUFU 2 Patients 5.4 %	Mutation T261Gfs*8 (1), V148Sfs*30 (1)	Likely Oncogenic	Resistance to Vismodegib
Medulloblastoma Sickkids Nature 2016 46 Samples			
PTCH1 4 Patients 8.7 %	Mutation E675* (1), V442Gfs*54 (1), S444Afs*11 (1), Y452Lfs*4 (1)	Likely oncogenic truncating mutation	Sonidegig Vismodegib
PTEN 2 Patients 4.3 %	Mutation A126T (1), G132V (1)	Oncogenic	Capivasertib GSK2636771 AZD8186
CTNNB1 (beta Cat) 2 Patients 4.3 %	Mutation D32V (1), G34R (1)	Likely Oncogenic	Etraglusib, Tideglusib
SMO 1 Patient 2.2 %	Mutation L412F	Likely Oncogenic	Resistance to Vismodegib

This analysis provides valuable insights into potential repurposing of drugs approved for other tumors to address specific subsets of medulloblastoma, enhancing treatment precision.

3.4. Experimental Validation of In Silico-Identified Therapies in Medulloblastoma Cell Lines

Based on Table 5, several unexpected treatments emerged as potentially relevant for medulloblastoma, including Venetoclax, a BCL2-targeted therapy traditionally used for hematological malignancies and seldom applied to solid tumors. [35]. Our analysis indicated that this therapy showed the greatest efficacy in Group 3 and Group 4 tumors, with a lesser effect on SHH

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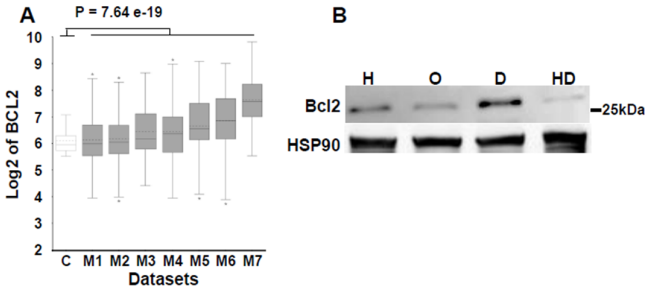
tumors. To validate this, we compared BCL2 expression in normal cerebellum and different datasets of medulloblastoma in the R2 database. This analysis reveals a global upregulation of BCL2 across several datasets of medulloblastoma compared to healthy cerebellum (Figure 1A). Then, we assessed BCL2 protein levels in normal microglial cells (HMC3) and in the medulloblastoma cell lines ONS76 (SHH), DAOY (SHH with a P53 mutation mimicking Group 3 tumor outcomes), and HDMB03 (Group 3 tumor). BCL2 expression, as assessed by immunoblot analysis, was highest in DAOY cells, intermediate in ONS76 and HMC3 cells, and low in HDMB03 cells (Figure 1B). Then, we compared the effect of Venetoclax in normal cells based on their neural origin and tumor cells. The IC50 of Venetoclax was determined on these normal cells and medulloblastoma cell lines (Figure 1 C-F). Except in normal cells, dose-response experiments demonstrated a direct correlation between BCL2 expression levels and Venetoclax efficacy (Figure 1C-G). subsequently calculated the specificity index for venetoclax (Figure 1G) [36]. The specificity index was defined as the ratio of the IC50 in HMC3 (normal) cells and the IC50 in medulloblastoma cell lines, with values greater than 1 indicating preferential activity in tumor cells. Although a specificity index above 5 is generally considered indicative of therapeutic relevance with low toxicity [36], Venetoclax has already demonstrated both efficacy and manageable toxicity in a pediatric cohort of patients with newly diagnosed acute myeloid leukemia [37]. These clinical findings support Venetoclax as a viable treatment option in children. Taken together with our data, these results suggest that Venetoclax warrants further preclinical evaluation as a potential therapy for medulloblastoma.



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	IC50 (µM)	Specificity Index
HMC3	17.02	1
ONS-76	8.74	1.95
DAOY	10.69	1.59
HDMB03	8.97	1.90

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Figure 1. Relevance of targeting BCL2 for the treatment of medulloblastoma. A) Box-dot plot showing mRNA expression level of BCL2 (R2: Genomics Analysis and Visualization Platform (http://r2.amc.nl) in normal cerebellum (C) (n = 9 retrieved from Roth database), and medulloblastoma patients (M1–M7); M1: (n = 76) from Gilbertson database, M2: (n = 57) from Delattre database, M3: (n = 62) from Kool database, M4: (n = 223) from Pfister1 database, M5: (n = 51) from den Boer database, M6: (n = 31) from Hsieh database and M7: (n = 73) from Pfister2 database. Statistical analysis (One-way analysis of variance (ANOVA)) is shown, P = 7.64 e-19. B) Immunoblot analysis of BCL2 expression in HMC3 (H) ONS76 cells (O), DAOY cells (D) and HDMB03 cells (HD). GAPDH is shown as loading control. C-F) Dose dependent inhibition of viability of the four cells lines by increasing concentrations of venetoclax. *: $P < 0.05$; **: $P < 0.01$; ***: $p < 0.001$: **** $P < 0.0001$. G) IC_{50} and specificity index of venetoclax for the different cell lines.

4. Discussion

The treatment of medulloblastoma remains a significant challenge, whether in the first line setting— aiming to limit the side effects of intensive therapies—or following relapse, which often represents a therapeutic dead end. The development of new drugs is particularly complex and time-intensive, often taking years to reach clinical application. In this context, drug repositioning offers a promising alternative, bypassing extensive preclinical toxicology studies in animals, though still requiring clinical trials to assess toxic effects in children, who are no longer viewed as "small adults."

Through comprehensive analysis of available patient cohorts, we identified potential opportunities for therapy repositioning using drugs with established safety profiles in adults. **Table 7** highlights several targeted therapies previously tested in early-phase clinical trials for pediatric brain tumors. Some demonstrated promising effects, though confirmation in phase III trials is still required. Notably, therapies relevant to specific genetic subgroups of patients in our analysis were often found ineffective when metastatic status was considered, underscoring a potential source of failure in some clinical trials. Additionally, the presence of mutations in specific genes may act as confounding factors in therapeutic outcomes.

Among the repositioned therapies, treatments for hematological cancers such as **Imatinib** and **Venetoclax** emerged as particularly intriguing. **Venetoclax** showed significant specificity in medulloblastoma model cell lines, further supporting its potential relevance considering that BCL2 expression correlated to the most aggressive form of medulloblastoma [38]. Moreover, using a completely different approach, Garancher, A. et al. demonstrated the efficacy of the pan-inhibitor of BCL family members, TW37 [39]. However, based on our study, the use of a pan-BCL family inhibitor is not recommended, as the overexpression of certain BCL family members appears to have a beneficial effect for reasons that remain unclear. Instead, **Venetoclax** is strongly recommended due to its selective targeting and its ability to penetrate the blood-brain barrier [40].

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Table 7. Overview of treatments that have been approved for clinical use or previously described in the literature. Potentially repositionable treatments were extensively reviewed to evaluate their relevance for medulloblastoma or other brain tumors. The table also indicates whether each treatment can cross the blood-brain barrier (BBB) and provides the corresponding PubMed ID (PMID) for reference.

TREATMENT	Clinical application				Research (in vitro/vivo)					
	Used in MB	Reference(s)	Other brain tumor	Reference(s)	Used in MB	Reference(s)	Other brain tumor	Reference(s)	Cross the BBB	Reference(s)
Abemaciclib	No		No		No		Glioblastoma	PMID: 38999983	Yes (low)	PMID: 38999983
Acalabrutinib	No		Leptomeninges/CNS	PMID: 35732356	No		Glioblastoma Neuroblastoma (+in vivo)	PMID: 34577576 PMID: 32705581		
Afatinib	No		No		No		No			
Alemtuzumab	No		CD4+ / Tcells in brain Tcells / CNS	PMID: 36362454 PMID: 32802528	No		No		Yes	PMID: 36362454 PMID: 33728194
Alpelisib	No		No		Yes (+in vivo)	PMID: 31492956	Neuroblastoma (+in vivo) Glioblastoma	PMID: 33491755 PMID: 33318517 PMID: 27120806		
Asciminib	No		No		Yes (+in vivo)	PMID: 37781087	No			
Atezolizumab	No		Glioblastoma	PMID: 30073642	No		No			PMID: 37122727
Avapritinib	No		No		No		No		Yes	PMID: 38167404
Avelumab	No		No		No		No			
Axitinib	Yes	PMID: 38778441	No		No	PMID: 35008234 PMID: 34234256 PMID: 29377550 PMID: 31035676	No		Yes	PMID: 35008234 PMID: 31035676
Baricitinib	No		No		No		No			
Basiliximab	No		No		No		No			
Blinatumomab	No		No		No		No			
Cetuximab	Yes	PMID: 23426003 PMID: 24092425	No							
Cobimetinib	No		No		No		No			
Dacomitinib	No		No		Yes (+in vivo)	PMID: 29574250	Glioblastoma & Pineoblastoma (+in vivo)	PMID: 29574250		
Durvalumab	No		No		non		No			
Erlotinib	Yes	PMID: 29778738	Glioblastoma	PMID: 32550606						
Gefitinib	No		No		Yes Yes (+in vivo)	PMID: 21726539 PMID: 19033425 PMID: 18829483	Glioblastoma Glioma	PMID: 21726539 PMID: 18829483		
Gemtuzumab	No		No		No		No			
Gilteritinib	No		No		No		No			
Idelalisib	No		No		No		No			
Imatinib	No		No		Yes	PMID: 37367713 PMID: 13417143	Glioblastoma	PMID: 37367713		
Ipilimumab	Yes	PMID: 36808285	Glioblastoma	PMID: 36808285						
Nilotinib	No		No		Yes	PMID: 31539380	No			
Nivolumab	Yes	PMID: 36808285 PMID: 30681550	Glioblastoma	PMID: 36808285 PMID: 30681550						
Olaparib	No		No		Yes Yes (+in vivo) Yes (+in vivo) Yes	PMID: 37783879 PMID: 35001340 PMID: 34508175 PMID: 22184287	neuroblastoma (+in vivo) Glioblastoma High grade glioma and Ependymoma	PMID: 34508175 PMID: 35001340 PMID: 22184287		
Palbociclib					Yes (+in vivo) Yes (+in vivo) Yes Yes (+in vivo)	PMID: 39055517 PMID: 37333134 PMID: 37127652 PMID: 35080986	No			
Pembrolizumab	non		No		No		No			
Pemigatinib	non		No		No		No			
Pertuzumab	non		No		No		No			
Ribociclib	non		No		Bioinformatic study Yes (+in vivo) Yes (+in vivo)	PMID: 37783879 PMID: 36318650 PMID: 35709750	No			
Rucaparib	No		No		Yes	PMID: 20978505	No			
Sabatolimab	No		No		No		No			
Selumetinib	No		No		Yes (+in vivo) Yes (+in vivo)	PMID: 35835837 PMID: 29330101	No			
Sonidegib										
Sunitinib	No		No		Yes (+in vivo) Yes Yes	PMID: 35008234 PMID: 20524040 PMID: 20053726	No		Yes	PMID: 35008234 PMID: 20524040
Talazoparib	No		No		Yes (+in vivo) Yes (+in vivo)	PMID: 37910601 PMID: 25263539	No		No	PMID: 37910601
Tofacitinib	No		No		Yes	PMID: 30332965	No			
Trametinib	No		No		Yes	PMID: 37726268	No			
Trastuzumab	No		No		No		No			
Venetoclax	No		No		Yes Yes (+in vivo) Yes	PMID: 35056150 PMID: 32855528 PMID: 26394044	No			

5. Conclusions

Although our findings represent an initial step in treatment repositioning for pediatric brain tumors, they provide a foundation for exploring therapies previously overlooked for medulloblastoma, with the goal of improving outcomes in this challenging context.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1: Kaplan-Meier analysis of the relationship between targetable genes and survival in different medulloblastoma subgroups; Figure S2: Kaplan-Meier analysis of the relationship between targetable genes and survival in different medulloblastoma subgroups considering the non-metastatic (M0) and metastatic (M1) patients.

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Informed Consent Statement: Since the information we used for our manuscript came from publicly available databases, informed consent was obtained from all subjects involved in the study.

Data Availability Statement: the data were from publicly available databases including the R2 Genomics Analysis and Visualization Platform https://hgserver1.amc.nl/cgi-bin/r2/main.cgi?open_page=login and the TCGA databases from the cbioportal visualization platform https://www.cbioportal.org/.

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Abbreviations

The following abbreviations are used in this manuscript:

ABL	Abelson Tyrosine-Protein Kinase 1
ALK	Anaplastic Lymphoma Kinase
AXL	Tyrosine-protein kinase receptor UFO
BCL2	B Cell Lymphoma 2
BCR	Breakpoint Cluster Region protein
BRAF	B-Raf protein, serine/threonine kinase
BTK	Bruton Kinase
CDK	Cyclin Dependent Kinase
CTLA4	Cytotoxic T-Lymphocyte Associated Protein 4
DDR2	Discoidin Domain Receptor Tyrosine Kinase 2
DFS	Disease Free Survival
EGFR/HER1	Epithelial Growth Factor Receptor
EPCAM	Epithelial Cell Adhesion Molecule
FDA	Food and Drug Administration
FGF	Fibroblast growth factors
FILP1	Filamin A Interacting Protein 1
FLT3	Fms Related Receptor Tyrosine Kinase 3
HGFR/MET	Hepatocyte Growth Factor Receptor
HRP	Horse Radish Peroxidase
KIT	KIT proto-oncogene, receptor tyrosine kinase
IDH1	Isocitrate dehydrogenase
JAK	Janus Kinase
LAG 3	Lymphocyte Activating 3
LYN	Protein tyrosine kinase Src family
MAPK	Mitogen-activated protein kinase
MEK	Mitogen Activated Protein Kinase Kinase
mTOR	Mammalian target of rapamycin
OS	Overall Survival
PARP	Poly ADP Ribose Polymerase
PD1/PDL1	Programmed Cell Death Protein 1/PD1 Ligand
PDGFR	Platelet Derived Growth Factor Receptor
PFS	Progression Free Survival
PKC	Protein Kinase C
PI	Propidium Iodide

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PI3K	Phosphoinositide 3-kinase
PVDF	Polyvinylidene Fluoride
RAF	Rapidly Accelerated Fibrosarcoma
RET	Rearranged during transfection tyrosine kinase receptor
ROS	ROS Proto-Oncogene 1, Receptor Tyrosine Kinase
SMO	Smoothened protein
TIM3	T-cell immunoglobulin and mucin-domain containing-3
TRK	Tropomyosin Receptor Kinase
VEGFR	Vascular Endothelial Growth Factor Receptor

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