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Mechanistic Insights into Medulloblastoma Relapse

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ABSTRACT

Pediatric brain tumors are the leading cause of cancer-related deaths in children, with medulloblastoma (MB) being the most common type. A better understanding of these malignancies has led to their classification into four major molecular subgroups. This classification not only facilitates the stratification of clinical trials, but also the development of more effective therapies. Despite recent progress, approximately 30% of children diagnosed with MB experience tumor relapse. Recurrent disease in MB is often metastatic and responds poorly to current therapies. As a result, only a small subset of patients with recurrent MB survive beyond one year. Due to its dismal prognosis, novel therapeutic strategies aimed at preventing or managing recurrent disease are urgently needed. In this review, we summarize recent advances in our understanding of the molecular mechanisms behind treatment failure in MB, as well as those characterizing recurrent cases. We also propose avenues for how these findings can be used to better inform personalized medicine approaches for the treatment of newly diagnosed and recurrent MB. Lastly, we discuss the treatments currently being evaluated for MB patients, with special emphasis on those targeting MB by subgroup at diagnosis and relapse.

Key Words: Pediatric Brain Tumors, Medulloblastoma, Recurrence, Relapse, Resistance, Stem Cells, Targeted Therapeutics, Personalized Medicine.

Abbreviations: 131I, iodine-131; ABC, ATP-binding cassette; ALK, Anaplastic lymphoma kinase; Amp, Amplification; APC, Adenomatous Polyposis Coli; APCs, astrocyte progenitor cells; B7-H3, B7 homolog 3; BET, Bromodomain and extra-terminal domain; BMPs, bone morphogenetic proteins; BPIFB4, BPI Fold Containing Family B Member 4; BRCA2, Breast Cancer Gene 2; BTK, Bruton tyrosine kinase; C7R, Constitutively active IL-7 cytokine receptor; CAR, Chimeric antigen receptor; CD133, Cluster of differentiation 133; CD15, Cluster of differentiation 15; CD40, Cluster of differentiation 40; CDK14, Cyclin dependent kinase 14; CDK4/6, Cyclin dependent kinase 4/6; CDK6, Cyclin Dependent Kinase 6; CDKN2A, Cyclin dependent kinase inhibitor 2A; CHD7, Chromodomain helicase DNA binding protein 7; Chemo, Chemotherapy; ChIP, Chromatin immunoprecipitation; CHK1, Checkpoint kinase 1; Chr, Chromosome; CK1α, Casein kinase 1α; CK2, Casein kinase 2; ClpP, Caseinolytic peptidase; c-MET, MET proto-oncogene; COX-1, Cyclooxygenase 1; CRBN, Cereblon; CREB, CAMP-Response Element Binding Protein; CREBBP, CREB binding protein; CSF, Cerebrospinal fluid; CSI, Craniospinal irradiation; CTNNB1, β-Catenin; DDX31, DEAD-box polypeptide 3; DDX3X, DEAD-box helicase 3 X-linked; DFMO, Difluoromethylornithine; DHFR, Dihydrofolate reductase; DNMT, DNA methyltransferase; DRD2, Dopamine receptor D2; DST, Dystonin; EGF, Endothelial growth factor; EGFR, Epidermal growth factor receptor; EPHA7, Ephrin A receptor 7; ERK, Extracellular signal-regulated kinase; EudraCT, European Union drug regulating authorities clinical trials; EZH2, Enhancer of zeste 2 polycomb repressive complex 2 subunit; FDA, Food and drug administration; FGFR, Fibroblast growth factor receptor; FOXO1, Forkhead box O1; FTD, Fast-track designation; FZD, Frizzled; G3, Group 3; G4, Group 4; GD2, Ganglioside; GFAP, Glial fibrillary acidic protein; GFI1A, Growth factor independent 1 transcriptional repressor; GFI1B, Growth factor independent 1B transcriptional repressor; GLI, Glioma associated oncogene; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GPCs, Granular precursor cells; GTF3C, General transcription factor IIIC; GTF3C, General transcription factor IIIC subunit 1; H3K27, Histone 3 in lysine 27; HDAC2, Histone deacetylase 2; HDACs, Histone deacetylases; HER2, Human epidermal growth factor receptor; HSV, Herpes simplex virus; i17q, isochromosome 17q; IDH1, Isocitrate dehydrogenase 1; IDO1, Indoleamine 2,3-dioxygenase-1; IgG1κ, Immunoglobulin G, subclass 1, κ light chain; IL13Ralpha2, Interleukin 13 receptor subunit alpha 2; KDM3B, Histone lysine demethylase 3B; KDM6A, Lysine Demethylase 6A; lnc-HLX-2-7, long coding RNA HLX-2-7; mAb, Monoclonal Antibodies; MAPK, Mitogen activated protein kinase; MB, Medulloblastoma; MEK, MAPK kinase; mTORC1, Mammalian target of rapamycin complex 1; MYCN, MYCN proto-oncogene; NCI, National cancer institute; NCT, National clinical trial; NEB, Nebulin; NGF, Nerve growth factor; ODC, Ornithine decarboxylase; ODD, Orphan disease designation; OLIG2, Oligodendrocyte transcription factor 2; OPCs, oligodendrocyte progenitor cells; OTX2, Orthodenticle homeobox 2; PARP, Poly(ADP-Ribose) polymerase; PD-1, Programmed cell death protein 1; PDGFRβ, Platelet-derived growth factor receptor beta; PDK1, Pyruvate dehydrogenase kinase 1; PD-L1,

Programmed cell death ligand 1; PEP-CMV, Peptide-cytomegalovirus; PI3K, Phosphoinositide 3-kinase; PORCN, Porcupine; PPARa, Peroxisome proliferator activated receptor alpha; PTCH1, Patched-1; PTCH2, Patched-2; PTEN, Phosphatase and Tensin Homolog; RAS, Rat sarcoma; RB, Retinoblastoma; RET, Ret proto-oncogene; RNAseq, RNA sequencing; ROS1, ROS proto-oncogene 1; SHH, Sonic hedgehog; SMARCA4, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, Member 4; SMO, Smoothened; SNCAIP, Synuclein alpha interacting protein; SnoN, Ski-related novel protein N; SOX2, SRY-box 2; SOX9, SRY-box 9; SST2A, Somatostatin receptor subtype 2A; STAT3, Signal transducer and activator of transcription 3; SUFU, Suppressor of Fused Homolog; TCA, Tricarboxylic acid; TCF/LEF, T-cell factor/lymphoid enhancer factor; TERT, Telomerase reverse transcriptase; TGF-β, Transforming growth factor-Beta; TIS21, 12-O-tetradecanoyl phorbol-13-acetate-inducible sequence 21; TNKS, Tankyrase; TOPO, Topoisomerase; TP53/P53, Tumor Protein P53; TRK, Tropomyosin receptor kinase; USH2A, Usherin; VEGF, Vascular endothelial growth factor; VEGFR2, Vascular endothelial growth factor receptor 2; WGS, Whole-genome sequencing; WNT, Wingless and Int-1; YAP1, Yes-associated protein 1; ZFHX3, Zinc finger homeobox 3.

1. MEDULLOBLASTOMA

Tumors in the central nervous system have recently surpassed leukemia as the leading cause of cancer-related deaths in children (Curtin et al., 2016). This shift is primarily attributed to the recent advancements in the clinical management of hematological malignancies. Amongst the pediatric brain malignancies, medulloblastoma (MB) is the most common, representing ~20% of all pediatric brain tumors (Louis et al., 2016). Although rarer, MB can also be observed in adults, where it constitutes less than 1% of all adult brain malignancies (Bloom and Bessell, 1990). This neuroectodermal tumor originates in the cerebellum, the region of the brain responsible for controlling intricate motor functions such as balance, coordination, and speech (Jimsheleishvili and Dididze, 2023). In addition to the disruption of these functions, patients with MB frequently experience increased intracranial pressure due to the inadequate circulation of the cerebrospinal fluid (CSF) (Packer et al., 1999), leading to hydrocephalus. This condition is accompanied by headaches, vomiting, and lethargy (Packer et al., 1999, Nejat et al., 2008). Additionally, MB can manifest with signs of cerebellar herniation, such as ataxia and tilting of the head (Nejat et al., 2008).

Upon inclusion of radiation to standard of care protocols in the 1950s (Paterson and Farr, 1953) and chemotherapy in the 1970s (Crist et al., 1976), the average survival rate for children with MB transitioned to the current ~70% (Smoll, 2012, Ostrom et al., 2018). Unfortunately, the survival outcomes have not improved since then, with 30% of MB patients eventually succumbing to the disease (Smoll, 2012, Ostrom et al., 2018, Bowers et al., 2007). Most of these deaths, with the rare exception of those associated with treatment-related toxicities, are attributed to tumor relapse (Sabel et al., 2016, Bowers et al., 2007). MB cells can disseminate from the primary tumor, located in the posterior fossa, into the ventricles, subarachnoid spaces, and nerve roots via the CSF in a process known as seeding (Jenkin et al., 2000, Bowers et al., 2007). While metastasis can occur in newly diagnosed patients, it is far more frequent in those with recurrent MB (Li et al., 2021, Bowers et al., 2007). Similar to other cancers, the likelihood of treatment failure in MB patients is significantly greater when metastatic lesions are present (Ramaswamy et al., 2016). Unfortunately, children with metastatic relapsed MB rarely survive beyond one year (Modha et al., 2000). These statistics highlight the urgent and unmet clinical need for treatments that can either prevent MB relapse or effectively manage recurrent cases. A major challenge in developing such treatments lies in the limited understanding of the fundamental mechanisms that underlie treatment failure and promote the growth of recurrent MB, which will be reviewed herein.

1.1. MB Treatment

Studies have demonstrated that complete resection of the tumor improves survival rates in patients with localized MB (Nejat et al., 2008). As a result, the primary treatment for MB involves surgical intervention aimed at maximizing tumor removal while minimizing damage to healthy brain tissue (Packer et al., 1999, Brandes et al., 1999). Following tumor resection, patients typically receive craniospinal irradiation (CSI) and chemotherapy to further enhance outcomes (Thomas and Noel, 2019). Moreover, some patients may qualify for participation in ongoing clinical trials exploring the efficacy of optimized radiation protocols and novel chemotherapy- or immunotherapy-based therapeutic strategies (Cooney et al., 2023).

Risk stratification is crucial in the treatment of patients with MB, as it dictates the type and intensity of the radiation and chemotherapy protocol to be administered (**Table 1**). Risk stratification is determined by various factors, including the patient's age, the extent of the disease, and the molecular and histological characteristics of the tumor (Ramaswamy et al., 2016). High-risk patients may require more aggressive therapeutic approaches, including irradiation of the entire craniospinal axis. One of the most frequently used chemotherapy protocols for low-risk MB includes the administration of vincristine, cisplatin, and lomustine (Thompson et al., 2020, Martin et al., 2014). For average-risk patients, cyclophosphamide is generally added to this combination (Gottardo and Gajjar, 2008, Packer and Vezina, 2008). In high-risk cases, additional therapies include administration of etoposide and carboplatin (Sirachainan et al., 2018). Due to the aggressive nature of the treatment in high-risk MB cases, stem cell transplantation to restore the bone marrow is often considered (Cheuk et al., 2008). When these approaches fail, second-line chemotherapeutic agents include the topoisomerase (TOPO) I inhibitor irinotecan and the alkylator/crosslinker agent temozolomide (Bautista et al., 2017).

While most children respond to these treatment protocols, they often experience long-term treatment-induced morbidities (Crawford et al., 2007, Merchant, 2013). Examples of such sequelae include neurological and cognitive impairments, endocrine dysfunctions, hearing loss, mutism, cardiovascular defects (Packer et al., 1999), and an increased risk of developing secondary malignancies (Neglia et al., 2006, Goldstein et al., 1997, Duffner et al., 1998). Strategies to reduce sequelae in MB patients include the use of proton radiation therapy, which spares healthy tissue and reduces long-term toxicity by targeting tumors more precisely than conventional photon radiation (Mohan and Grosshans, 2017). The possibility of substituting chemotherapy for radiation is particularly emphasized for younger aged patients, where radiation-linked neurocognitive sequelae can be especially detrimental (Pazzaglia et al., 2020). Another strategy to mitigate treatment-associated toxicity involves the use of targeted therapies. These strategies aim to specifically target tumor drivers rather than indiscriminately affecting all proliferating cells. As later reviewed herein, the current classification of MB into molecular subgroups (Cavalli et al., 2017) has led to the development of personalized therapeutic strategies that are, a priori, less toxic to MB patients. These strategies are based on disease risk factors and tumor drivers specific to each subgroup.

1.2. MB Etiology

The underlying cause of MB remains largely unknown, and as a result most cases are considered sporadic. Nevertheless, some reports have suggested a link with maternal diet (Bunin et al., 2005) and with certain viral infections in early childhood (Baryawno et al., 2011, Krynska et al., 1999). Additionally, there are a few rare genetic syndromes that have been associated with an increased risk of developing MB. One of these is Turcot syndrome (Hamilton et al., 1995). Patients with this syndrome harbor germline mutations in key regulators of the Wingless and Int-1 (WNT) pathway (**Figure 1**), including the tumor suppressor gene *Adenomatous Polyposis Coli* (*APC*) or the gene that encodes for β-Catenin (*CTNNB1*). Another condition associated with an increased risk of MB is Gorlin syndrome, typically linked to germline mutations in the tumor suppressor gene *PATCHED-1* (*PTCH1*) (Evans et al., 1991, Garre et al., 2009). Additionally, associations are observed with mutations in the genes codifying for Patched-2 (PTCH2) (Fan et al., 2008) or Smoothened (SMO) (Pastorino et al., 2009). As shown in **Figure 2** these three proteins play crucial roles in regulating the Sonic Hedgehog (SHH) pathway (Robbins et al., 2012). Mutations in their corresponding genes result in the constitutive activation of SHH signaling, thereby increasing the risk for the development of MB (Teglund and Toftgard, 2010). Conversely, individuals with Li-Fraumeni syndrome harbor mutations in the *Tumor Protein P53* (*TP53*) suppressor gene (Sorrell et al., 2013). Loss of P53 predisposes these patients to a wide range of cancers, including MB (Carta et al., 2020). In addition, patients with Fanconi anemia harbor germline mutations in *Breast cancer gene 2* (*BRCA2*) and are also at risk for MB (Woodward and Meyer, 2021). Finally, patients with Rubinstein-Taybi syndrome have germline deletions in the gene codifying for CAMP-Response Element Binding Protein (CREB) binding protein (CREBBP) and are similarly at risk of MB (Bourdeaut et al., 2014). Interestingly, all these syndromes result in tumors driven by specific signaling mechanisms, highlighting the intertumoral heterogeneity which led to the classification of MB into distinct molecular subgroups.

1.3. MB Classification

Before the era of genetic testing paved the way for MB classification into molecularly distinct subgroups, histological differences between tumors were already apparent. These differences led to the histological classification of MB into five subgroups (Orr, 2020). Classic MB, the most prevalent subtype, has an intermediate prognosis with small, densely packed cells forming circular arrangements called Homer Wright rosettes (Orr, 2020). Desmoplastic/nodular MB features prominent nodules and generally exhibits a better prognosis (Siegfried et al., 2016). Extensive nodularity MB, defined by numerous well-defined nodules, is associated with a more favorable outcome (Korshunov et al., 2018). Large cell MB, comprising larger, more differentiated cells, is linked to a more aggressive disease and an increased risk of metastasis, while anaplastic MB typically presents the least favorable outcome (Orr, 2020).

Following the histology-based classification, the utilization of deep sequencing methods, along with transcriptomic and methylation analyses, has resulted in the classification of MB into four molecular subgroups: WNT, SHH, Group 3 (G3), and Group 4 (G4) (Louis et al., 2014, Louis et al., 2016, Taylor et al.,

2012). These subgroups are characterized by unique driver mutations, gene signatures, outcomes, and age distributions, and are further refined by integrating histological features that identify the predominant histology within each subgroup. By employing similarity network fusion and integrative clustering computation methods, recent studies have fine-tuned this four subgroup based classification into a more precise system with twelve subtypes (Cavalli et al., 2017). These analyses were done across over 700 primary MB samples and led to the identification of two WNT subtypes (WNTα and WNTβ), four SHH subtypes (SHHα, SHHβ, SHHγ and SHHδ), and three G3 (G3α, G3β and G3γ) and G4 (G4α, G4β and G4γ) subtypes (Cavalli et al., 2017). Understanding the distinctions among these subgroups/subtypes, not only in terms of prognosis but also of molecular profile, is crucial in stratifying clinical trials and developing tailored therapeutics. Importantly, a number of clinical trials, which will be reviewed later in this manuscript, already take into consideration MB diversity, marking the beginning of a new era of more effective and less toxic therapeutics for these children.

The characteristics of each MB subgroup/subtype have been reviewed extensively (Juraschka and Taylor, 2019, Northcott et al., 2019, Ramaswamy and Taylor, 2017, Northcott et al., 2012b). Hence, only a concise summary of the main features for each subgroup (**Table 2**), alongside an overview of ongoing clinical assessments of subgroup-based therapies and potential additional targeted strategies, will be discussed.

1.3.1. WNT MB

WNT MB typically manifests in the cerebella peduncle or pontine angle of older children and adolescents (Stock et al., 2019). These tumors are characterized by the activation of WNT/β-Catenin signaling pathway and frequently present with classic histology (Cavalli et al., 2017). Genetic hallmarks of this subgroup include mutations in *CTNNB1* or its regulator, the tumor suppressor *APC* (**Table 2**). These mutations stabilize β-Catenin (**Figure 1**), in turn allowing it to translocate to the nucleus and associate with T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors to promote the expression of WNT target genes (Saito-Diaz et al., 2013). Patients within this subgroup are divided in two subtypes: WNTα and WNTβ. WNTα, commonly found in pediatric patients, is characterized by monosomy on chromosome 6. Meanwhile WNTβ, more prevalent in adults, exhibits diploidy on chromosome 6 and is associated with a better prognosis compared to WNTα (100% versus 97% 5-year survival) (Cavalli et al., 2017).

Several strategies have demonstrated efficacy in blocking WNT signaling and therefore WNT-driven tumor growth (**Figure 1**). Inhibitory strategies acting upstream on the pathway include the use of Porcupine (PORCN) inhibitors which affect WNT ligand processing (Shah et al., 2021), and monoclonal antibodies (mAb) that prevent WNT ligands from binding to the receptor Frizzled (FZD) (Zeng et al., 2018). At the level of the β-Catenin destruction complex, compounds acting on Tankyrase (TNKS), that induce APC degradation (Kamal et al., 2014), and Casein kinase 1α (CK1α) agonists, that increase β-Catenin phosphorylation resulting in its degradation (Li et al., 2017, Li et al., 2014b, Thorne et al., 2010), have similarly shown efficacy. Finally, attenuation of β-Catenin dependent transcription by using inhibitors of TCF/LEF (Koelman et al., 2022) and of CREBBP (Jung and Park, 2020) have recently emerged as candidate therapeutics for WNT-driven malignancies. While these interventions hold promise for blocking WNT-dependent tumor growth, activation of WNT signaling at the level of β-Catenin renders many of them likely ineffective for WNT MB patients. Moreover, dose-limiting toxicities associated with the use of WNT-targeting approaches have hindered their broader utilization in cancer treatment (Kahn, 2014), including WNT MB. Given that WNT inhibition is currently not a viable therapeutic option, clinical studies for WNT MB patients at diagnosis predominantly focus on improving neurocognitive outcomes, leveraging their generally favorable prognosis. Consequently, the effectiveness of de-escalation protocols, previously demonstrated to be advantageous in average-risk MB patients (Michalski et al., 2021), is under investigation in clinical settings for WNT MB patients (**Table 3**).

1.3.2. SHH MB

Tumors in the SHH subgroup are typically located in the cerebellar hemisphere and exhibit constitutive activation of the SHH pathway (Tan et al., 2018). This subgroup is more prevalent in infants and adults, constituting approximately one-third of all MB cases (Taylor et al., 2012). SHH MB displays diverse histological features, including classic, desmoplastic/nodular, and extensive nodularity patterns (Orr, 2020). These tumors often harbor mutations in key components of the SHH pathway (**Figure 2**), such as *PTCH1*,

SMO, *Suppressor of Fused Homolog* (*SUFU*), or amplifications in the Glioma associated oncogene 2 (*GLI2*) (Cavalli et al., 2017, Orr, 2020, Taylor et al., 2012). Additionally, mutations or amplifications may occur in *TP53*, *Yes-associated protein 1* (*YAP1*), and *MYCN proto-oncogene* (*MYCN*), all of which contribute to an increased activation of SHH signaling (Fernandez et al., 2009, Stecca and Ruiz i Altaba, 2009, Hatton et al., 2006). The overall prognosis within this subgroup is significantly influenced by *TP53* status, with *TP53* mutant SHH MB (SHHα) patients showing poorer outcomes (Cavalli et al., 2017, Orr, 2020, Ray et al., 2021, Zhukova et al., 2013). In addition to *TP53* defects, SHHα tumors present amplifications in *MYCN*, *GLI2 and YAP1*, and are prevalent in children and adolescents. Similar to SHHα, prognosis in infants with SHH MB harboring *Phosphatase and Tensin Homolog* (*PTEN*) mutations (SHHβ) is poor due to its propensity to metastasize (Cavalli et al., 2017), while infants with SHHγ and SHHδ tumors tend to have better outcomes (~88%). This last subgroup (SHHδ), which occurs mainly in adults, is characterized by the presence of mutations in the *Telomerase reverse transcriptase* (*TERT*) promoter (Cavalli et al., 2017).

Due to its druggability and pivotal role in regulating SHH signaling (**Figure 2**), SMO inhibitors have emerged as a viable therapeutic option for SHH-driven malignancies. The effectiveness of this class of inhibitors in cancer (Tang et al., 2012, Rodon et al., 2014) led to the Food and drug administration (FDA) approval of vismodegib (Axelson et al., 2013) and sonidegib (Kish and Corry, 2016) for the treatment of basal cell carcinoma, as well as the approval of glasdegib for acute myeloid leukemia (Norsworthy et al., 2019). The efficacy of similar compounds in MB patients is currently under clinical evaluation (**Table 3**). Despite their promising value, treatment resistance and relapse are often observed in cancer patients treated with SMO inhibitors (Rudin et al., 2009, Yauch et al., 2009). Most of these relapses may be attributed to either the clonal of expansion of cells harboring mutations in *SMO* or in which SHH activation occurs downstream of SMO (Sharpe et al., 2015, Atwood et al., 2015). Taken together, these findings support the premise that compounds acting downstream of this transmembrane protein may provide clinical benefit (**Figure 2**). Accordingly, compounds targeting either GLI directly by using Arsenic Trioxide (Beauchamp et al., 2011), or its transcriptional activity by inhibiting epigenetic regulators such as Bromodomain and extra-terminal domain (BET) proteins (Swiderska-Syn et al., 2022, Tang et al., 2014, Long et al., 2014), Histone deacetylases (HDACs) (Pak et al., 2019) or DNA methyltransferases (DNMTs) (Yang et al., 2022) are promising in bypassing these resistance mechanisms, and therefore their efficacy in combination with SMO inhibitors should be determined. Additionally, clinical trials for compounds affecting GLI stability by acting on CK1α (Li et al., 2014a, Rodriguez-Blanco et al., 2019) or on Casein kinase 2 (CK2) (Purzner et al., 2018), in combination with compounds acting on SMO, should be considered. In line with these GLI-targeting approaches, although still as a single agent, the efficacy of the CK2 inhibitor silmitasertib (CX-4945) in recurrent SHH MB patients is currently being tested (NCT03904862). On the other hand, compounds blocking Aurora-A have been shown to destabilize N-MYC by disrupting the Aurora-A/N-MYC complex, thereby attenuating neuroblastoma growth (Brockmann et al., 2013). Given the role of N-MYC as a SHH target gene (Robbins et al., 2012), and the proven efficacy of Aurora-A inhibitors in SHH MB models (Hill et al., 2015, Markant et al., 2013), these compounds could be similarly utilized to improve response to SMO inhibitors. Alternatively, resistance to SMO inhibition may involve the Rat sarcoma (RAS)/Mitogen activated protein kinase (MAPK) pathway, whose activation may either facilitate SHH signaling activation downstream of SMO (Frohlich et al., 2015, Brechbiel et al., 2014) or bypass SHH pathway dependency to promote tumor growth (Zhao et al., 2015). Therefore, it remains possible that the emergence of this resistance mechanism could be prevented by combining SMO inhibitors with those acting on RAS/MAPK, such as the MAPK kinase (MEK) inhibitor selumetinib, whose efficacy in attenuating SHH MB growth was previously described (Zagozewski et al., 2022). Additionally, strategies to increase the efficacy of the SMO inhibitor vismodegib include the use of nanoparticles to improve brain penetrance. These approaches include utilizing polyoxazoline block copolymer micelles (Hwang et al., 2021), as well as nanocarriers targeting endothelial P-selectin to induce caveolin-1-dependent transcytosis in response to radiation (Tylawsky et al., 2023). Alternatively, SMO inhibitors could be combined with therapies acting on the proliferation of the granular precursor cells (GPCs) of the cerebellum in a SHH independent fashion, by for instance targeting the homeodomain Orthodenticle Homeobox 2 (OTX2) transcription factor (El Nagar et al., 2018), the transcriptional regulator Ski-related novel protein N (SnoN) (Chen et al., 2019) or the Nerve growth factor (NGF)-inducible protein 12-O-tetradecanoyl

phorbol-13-acetate-inducible sequence 21 (TIS21) by using *TIS21* expressing adenovirus (Presutti et al., 2018).

1.3.3. G3 MB

G3 MB is more frequently observed in the midline of the cerebellum of younger children (Millard and De Braganca, 2016). It often manifests with classic, large cell or anaplastic histology (Orr, 2020). Amplifications in the proto-oncogene *MYC* represent one of the most prevalent genetic hallmarks in these tumors, followed by *TP53* mutations, copy gain of the transcription factor *OTX2*, loss of the helicase *DEAD-box polypeptide 3* (*DDX31*) (Cavalli et al., 2017), and alterations in components of the Transforming growth factor-Beta (TGF-β) pathway (Northcott et al., 2017, Northcott et al., 2012d). Unlike SHH MB, *TP53* mutations do not serve as a prognosis indicator in G3 MB (Zhukova et al., 2013, Cavalli et al., 2017). Conversely, patients with G3 MB harboring *MYC* amplifications (G3γ) are often metastatic at diagnosis and therefore face an extremely poor prognosis (Cavalli et al., 2017). Similar to G3γ, G3α tumors are frequently metastatic. However, the outcome for these patients is more favorable, with an overall survival of 66%. Additionally, G3α tumors demonstrate more frequent chromosome loss and gains compared to other subtypes. G3β, occurring in older children and adolescents, exhibits marked *OTX2* gain, *DDX31* loss, and frequent activation of the Growth factor independent transcriptional repressors *GFI1A* and *GFI1B* (Cavalli et al., 2017).

Frequent *MYC* amplifications (Cavalli et al., 2017), have brought this oncogene into focus for the development of targeted therapeutics for G3 MB. Despite its poor druggability, recent studies have proved the efficacy of drugs blocking MYC transcriptional activity in G3 MB (**Figure 3**). One example is the brain permeable BET inhibitor, JQ1, which was efficacious in increasing the overall survival of mice harboring *MYC* amplified G3 MB (Bandopadhayay et al., 2014). Unfortunately, the translational promise of these results may be hindered due to the short half-life of JQ1 (Jonchere et al., 2023). Another epigenetic regulator, Histone deacetylase 2 (HDAC2), is overexpressed in G3 MB tissues (Ecker et al., 2013), and the ability of HDAC inhibitors to attenuate the growth of these tumors accordingly described (Ecker et al., 2015). Importantly, this subset of drugs also synergized with Phosphoinositide 3-kinase (PI3K) inhibitors, resulting in the activation of Forkhead box O1 (FOXO1) and a subsequent suppression of G3 MB growth (Pei et al., 2016).

Advances in the development of Cyclin dependent kinases 4/6 (CDK4/6) inhibitors have shown promise in various human cancers (Fassl et al., 2022). Given that the Retinoblastoma (RB) pathway is functional in G3 MB (Jonchere et al., 2023), it is reasonable to speculate that inhibiting CDK4/6 could effectively suppress the growth of this particular tumor subset. In support of this premise, preclinical studies have shown the efficacy of drugs acting on CDK4/6, ribociclib and palbociclib, in attenuating G3 MB growth (Cook Sangar et al., 2017, Pribnow et al., 2022, Jonchere et al., 2023, Raleigh et al., 2018). Despite their promising efficacy, the translation of CDK4/6 inhibitors for the treatment of G3 MB may be affected by dose-limiting toxicities already observed in glioblastoma trials (Taylor et al., 2018), as well as its limited brain permeability (Raub et al., 2015). To circumvent the latter limitation, current studies are investigating the potential of using polyoxazoline micelles, akin to the approach with vismodegib (Hwang et al., 2021), to encapsulate the CDK4/6 inhibitor palbociclib and improve its pharmacokinetics (Lim et al., 2022). Additionally, combination strategies that enhance CDK4/6 inhibitor efficacy may lead to dosing regimens that would bypass toxicities previously observed. Such strategies include the concurrent use of inhibitors of CDK4/6 and of those acting on Mammalian target of rapamycin complex 1 (mTORC1) or on BET proteins (Lim et al., 2022, Jonchere et al., 2023, Bandopadhayay et al., 2019). Furthermore, efficacy of CDK4/6 inhibitors could be increased by their combination with the antimetabolite drug gemcitabine (Pribnow et al., 2022), which interferes with DNA synthesis. Due to the expression of the long coding RNA *HLX-2-7* (*lnc-HLX-2-7*) in G3 MB (Katsushima et al., 2021) and its role in recruiting factors to the *MYC* promoter, the use of oligonucleotides targeting *lnc-HLX-2-7* could be also considered a candidate therapeutic strategy for G3 MB. Accordingly, nanoparticles coated with antisense oligonucleotides targeting this non-coding RNA have been successful in attenuating G3 MB growth in pre-clinical models (Katsushima et al., 2024).

Despite the promise of these candidate targeted approaches, none of them are currently undergoing clinical evaluation for newly diagnosed G3 MB patients (**Table 3**). Consequently, current clinical trials for this subset

of patients, often grouped with those classified as G4 MB, are focusing on testing the effectiveness of various combination protocols involving non-targeted chemotherapy agents alongside CSI.

1.3.4. G4 MB

G4 MB often exhibits classic histology and is typically found in midline structures of the cerebellum (Millard and De Braganca, 2016). These tumors are the most common, comprising approximately 35% of all cases, and are more prevalent in mid-childhood (Cavalli et al., 2017). This subgroup of MB is associated with an intermediate prognosis (Taylor et al., 2012). Unlike other MB subgroups, most of these tumors lack well-defined genetic hallmarks. *MYCN* and *CDK6* amplifications, as well as frequent isochromosome 17q (i17q), chromosome 8p loss, and 7q gain, are observed in G4α. G4β is characterized by *Synuclein alpha interacting protein* (*SNCAIP*) duplication and alike G4α are enriched for i17q. G4γ, similar to G4α, features 8p loss and 7q gain along with *CDK6* amplifications, but lacks *MYCN* amplification.

Frequent *CDK6* amplifications (Slika et al., 2023, Khatua et al., 2018, Northcott et al., 2012c) suggest potential benefits for G4 MB patients through the use of CDK4/6 targeting compounds (**Figure 4**). While the efficacy of these inhibitors has only been tested in pre-clinical models of G3 and SHH MB (Cook Sangar et al., 2017, Pribnow et al., 2022, Jonchere et al., 2023, Raleigh et al., 2018), clinical trials for CDK4/6 inhibitors in progressive/refractory brain tumors, including MB, are ongoing (Van Mater et al., 2021). Mutations in *Lysine demethylase 6A* (*KDM6A*) are also prevalent in G4 MB (Gajjar and Robinson, 2014, Northcott et al., 2012a, Northcott et al., 2012d). Due to the role of this enzyme in promoting gene transcription via the demethylation of the Histone 3 in lysine 27 (H3K27) (Tran et al., 2020), the efficacy of HDAC inhibitors in attenuating G4 MB growth is warranted (**Figure 4**). Lastly, similar to the case of SHH MB, *MYCN* amplified G4 MB may also benefit from the use of inhibitors of Aurora-A/N-MYC binding (Brockmann et al., 2013) such as alisertib (**Figure 4**). Similar to the situation with G3 MB, none of these strategies are currently undergoing clinical evaluation for G4 MB patients at the time of diagnosis (**Table 3**).

2. TREATMENT FAILURE IN MB

Despite the overall efficacy of currently approved treatments, ~30% of patients with MB will eventually recur (Smoll, 2012, Ostrom et al., 2018, Bowers et al., 2007). Treatment failure and MB relapse have traditionally been associated with a rare pool of undifferentiated progenitor cells with tumor-initiating capabilities. These tumor cells retain some stem-like features characteristic of neuronal stem cells, including the ability to undergo asymmetric division (Dirks, 2008). During asymmetric division, one daughter cell retains its stem-like properties and self-renewal capacity, while the other may exhibit varying degrees of differentiation (Gomez-Lopez et al., 2014). As shown in **Figure 5**, these stem-like and partially committed progenitor MB cells resemble the different stages of the neural lineage observed during brain development (Manoranjan et al., 2012).

The extensive but somewhat controversial literature regarding MB progenitor cells is fueled by their ability to master a wide range of strategies that facilitate treatment resistance (Lee et al., 2020, Phi et al., 2018). Like any other stem cell, MB progenitor cells may enter a latent or quiescent state in fully-developed malignancies, which enables them to evade certain standard-of-care therapies aimed at eliminating highly proliferative tumor cells (Basu et al., 2022, Lee et al., 2020, Fan and Eberhart, 2008). Resembling bacteria (Reygaert, 2018), stem-like cancer cells may express drug pumps such as ATP-binding cassette (ABC) transporters (Begicevic and Falasca, 2017), alter the drug target (Ajmeera and Ajumeera, 2024), exhibit reduced susceptibility to undergo apoptosis (Phi et al., 2018), and demonstrate an increased ability to repair damaged DNA (Cree and Charlton, 2017). Additionally, as their drivers are unlikely to be the same as those found in the bulk tumor (Suter et al., 2020), stem-like MB progenitor cells are also likely to evade targeted approaches based on the molecular classification of tumors. Due to their persistence in tumor tissues, cancer stem cells also have an increased likelihood of accumulating mutations (Iseghohi, 2016), which may contribute to the genetic disparities observed at tumor recurrence.

2.1. MB Progenitor Cell Markers and Drivers

The likely impact of stem-like progenitor MB cells on treatment failure and disease relapse has brought them to the forefront. Initial efforts to characterize these cells pointed to undifferentiated and self-renewing cells positive for the Cluster of differentiation 133 (CD133) antigen and resembling neuro-epithelial cells at the top of the neuronal hierarchy (Singh et al., 2003, Singh et al., 2004). In SHH MB tumors, these cells demonstrated an enhanced ability to grow neurospheres *ex vivo* (Singh et al., 2003*)* and to engraft *in vivo*, forming tumors that fully recapitulate the original disease (Singh et al., 2004). Similarly, in G3 MB, CD133 was identified as a marker of an aggressive population of MB progenitor cells, in which both MYC and phosphorylated Signal transducer and activator of transcription 3 (STAT3) were upregulated (Garg et al., 2017). Given its role in promoting brain tumor growth and its extracellular localization, CD133 is an appealing target for Chimeric antigen receptor (CAR) T cell therapies. Initial studies have already suggested the potential of this therapeutic strategy in glioblastoma models (Vora et al., 2020). However, other studies have failed to observe the increased ability of $CD133^+$ cells to form tumors, but rather pointed to a small pool of cells positive for the Cluster of differentiation 15 (CD15) (Read et al., 2009). $CD15^+$ cells have been demonstrated to be required for MB initiation and progression (Huang et al., 2016, Read et al., 2009), and found to be resistant to standard-of-care chemotherapies (Lee et al., 2020). Notably, microarray analyses have suggested a role for Aurora kinase and Polo like kinases in the self-renewal of these cells, which may provide a therapeutic vulnerability by targeting $CD15^+$ cells in MB (Read et al., 2009). Additional studies suggest that treatment failure in SHH MB is facilitated by a subset of $CD15^+$ cells expressing the pivotal stemness regulator SRY-box 2 (SOX2) (Vanner et al., 2014). $SOX2^+$ cells were shown to drive the growth of MB by giving rise to a more differentiated progeny of GPCs that comprises the bulk of the SHH driven tumor (Ahlfeld et al., 2013, Selvadurai et al., 2020, Vanner et al., 2014). Suggesting their key role in sustaining tumor growth, treatment with mithramycin, a compound with the ability to attenuate the propagation of $SOX2^+$ cells, led to smaller tumors *in vivo* (Vanner et al., 2014).

In addition to these highly undifferentiated cells, recent single-cell RNA sequencing analyses have begun to identify populations of partially committed MB cells that may also contribute to treatment failure. Among these, the role of astrocyte progenitor cells (APCs) in MB relapse has been explored. On one hand, relapse upon radiation seems to be facilitated by the trans-differentiation of tumor cells into astrocytes (Guo et al., 2021). This trans-differentiation is dependent on the phosphorylation of SRY-box 9 (SOX9) by bone morphogenetic proteins (BMPs), whose inhibition suppress MB relapse (Guo et al., 2021). An alternative study showed that the role of APCs in promoting MB relapse extends beyond radiation, and suggested their resistance to targeted therapeutics acting on SMO (Swiderska-Syn et al., 2022). Single cell transcriptomic analysis uncovered APCs dependence on GLI to propagate and supported the use of compounds blocking its transcriptional activity in reducing SHH MB relapse. Due to its likely role in treatment failure, an alternative glia committed cell population, oligodendrocyte precursor cells (OPCs), positive for previously described stemness markers such as CD133, SOX2 and Nestin, along with the oligodendrocyte transcription factor Oligodendrocyte transcription factor 2 (OLIG2), has recently gained increased attention (Zhang et al., 2019, Ocasio et al., 2019). Similar to what was previously described for $SOX2^+$ cells (Selvadurai et al., 2020), proliferative $OLIG2^+$ cells were found in high numbers during early stages of neoplasia, yet reduce their presence and acquire a quiescent state once disease is fully established. Due to their quiescent properties, these cells have been demonstrated to exhibit resistance to standard-of-care therapeutics (Zhang et al., 2019), as well as to compounds acting on SMO (Ocasio et al., 2019). Subsequent studies suggesting OPCs involvement in treatment failure paradoxically highlight the possibility of targeting OLIG2 as a novel therapeutic strategy (Li et al., 2023). Unfortunately, the premise of targeting OLIG2 to improve therapeutic response faces a major hurdle in that OLIG2 is also expressed in healthy brain tissues (Ligon et al., 2006). Therefore, identifying the specific drivers of tumor-associated OPCs may provide additional therapeutic vulnerabilities in MB. Accordingly, Chromatin Immunoprecipitation (ChIP)-sequencing analyses for OLIG2 regulated promoters in MB tissues identified HIPPO and AURORA-A/N-MYC as OPC drivers (Zhang et al., 2019). Follow-up studies should assess the effectiveness of targeting these signaling mechanisms in enhancing the response to chemotherapy.

Despite the growing understanding of how cells with varying degrees of differentiation contribute to treatment failure, further studies are needed to not only narrow down their markers but also to elucidate their tumor-

specific drivers. A more comprehensive understanding of these cells could offer a feasible approach to ensuring a sustained tumor remission.

3. MB RELAPSE

Due to the aggressiveness of recurrent disease, preventing relapse emerges as the most viable option for the long-term benefit of patients with MB. Unfortunately, strategies aimed at preventing treatment failure have not yet yielded successful outcomes. This has led to a shift toward the development of therapeutic regimens specifically tailored for recurrent MB. This form of the disease is predominantly metastatic at the time of diagnosis and exhibits poor responsiveness to salvage therapies following the failure of current standard-of-care. As a result of this limited response, the average survival for children with recurrent MB is ~10 months (Koschmann et al., 2016). A deeper understanding of the mechanisms driving relapsed MB growth may reveal novel therapeutic vulnerabilities, in turn facilitating the development of more effective treatment options. In addition to true relapses, children with MB also face the challenge of misdiagnoses involving secondary malignant neoplasms. The factors driving secondary malignancies, identified in 4-5% of MB patients (Packer et al., 2013), are likely distinct from those facilitating the growth of true relapsed MB. Thus, it is crucial to histologically differentiate between recurrent MB and secondary malignancies to tailor therapies accordingly.

3.1. MB Relapse by Subgroups

Differences between primary and recurrent disease in terms of location and treatment response suggest that there may be a substantial difference in their DNA methylation pattern. However, paired biopsies of newly diagnosed and recurrent disease showed no change in subgroups (Morrissy et al., 2016, Richardson et al., 2022), and therefore, their overall transcriptome persists. In line with these findings, other studies have shown that 60% of the genetic events found in primary MB are maintained at relapse (Richardson et al., 2022). In contrast to this subgroup steady state, there are reports suggesting that due to their common embryological origin (Smith et al., 2022), G3 and G4 tumors have the ability to switch subgroups at relapse (Hill et al., 2020).

Despite this overall transcriptomic stability, the acquisition of unique genetic alterations at relapse, including mutations and copy number alterations that might lead to enhanced aggressiveness and poor treatment response, has been described (Hill et al., 2015, Morrissy et al., 2016, Hill et al., 2020, Richardson et al., 2022). Moreover, recent RNA sequencing analyses comparing MB at diagnosis and relapse have revealed changes in gene signatures that might similarly contribute to the poor prognosis of recurrent patients (Okonechnikov et al., 2023). Importantly, various features including time to relapse, recurrence patterns, genetic events and transcriptomic changes, often undergo alterations in a subgroup-dependent manner (**Table 2**).

3.1.1. WNT MB Relapse

In line with the excellent prognosis of this subgroup, the relapse of WNT MB is relatively uncommon. Notably, the number of relapsed WNT MB patients has recently increased due to the ongoing radiation dosing de-escalation trials (Nobre et al., 2020), highlighting the need to review these protocols. When relapses occur in WNT MB, they frequently present with metastasis in the lateral ventricles and have very limited therapeutic options. Time to relapse in WNT MB is approximately 18 months (Huybrechts et al., 2020). Most of the genetic alterations found in primary tumors, such as mutations in the gene codifying for β-Catenin and monosomies of chromosome 6, normally persist in the WNT recurrent disease. Moreover, acquisition of new genetic alterations is common in relapsed WNT MB (Richardson et al., 2022). The most enriched genetic event in relapsed WNT MB is mutations in *TP53*, detected in about 80% of relapsed cases compared to roughly 15% in the primary tumor (Richardson et al., 2022). These mutations may occur in combination with *MYC* amplifications (Hill et al., 2020). Moreover, chromosome 9q, 9p, and 11q loss were also found to be enriched at recurrence (Richardson et al., 2022). Due to its low frequency, limited effort has been devoted to uncovering the mechanisms facilitating WNT MB relapse. However, treatment de-escalation studies suggested that extended cyclophosphamide treatment is effective in preventing relapse for this MB subgroup (Nobre et al., 2020).

3.1.2. SHH MB Relapse

SHH MB tends to exhibit metastatic recurrence, with the rate increasing from 20% at the initial diagnosis to 65% at relapse (Hill et al., 2020). Time to relapse in SHH MB is about 15 months (Huybrechts et al., 2020). In recurrent SHH MB, mutations in the components of the SHH pathway are commonly retained from primary to relapsed disease. However, there is an enrichment in copy number variations at relapse, and this varies depending on patient age (Richardson et al., 2022). In infant cohorts, genetic events such as chromosome 15 gain is enriched by both maintenance and acquisition, while in non-infant cohorts a significant enrichment in acquired chromosome 4p and 4q gain and 10p loss are observed. Interestingly, enrichments in copy number variations in non-infants correlate with tumors harboring *TP53* mutations (Richardson et al., 2022). In regard to putative driver gene mutations, most studies describe an enrichment in *TP53* mutations or in genes controlling P53 signaling (Hill et al., 2015, Morrissy et al., 2016), while amplification on *MYCN* was only found in some cohorts (Hill et al., 2020, Morrissy et al., 2016). Interestingly, even though the MYC family member normally found amplified in SHH MB is *MYCN*, a relapsed case in which a *TP53* mutation came along with a *MYC* amplification was previously described (Hill et al., 2015, Hill et al., 2020). Enrichment in *MYCN* amplifications suggests the likely vulnerability of recurrent SHH MB to therapies targeting N-MYC. For instance, the inhibitor Aurora-A/N-MYC Alisertib (MLN8237) has previously demonstrated efficacy in mice harboring *MYCN* and *TP53* mutant MB (Hill et al., 2015). At the transcriptome level, an enrichment in gene signatures characterizing undifferentiated progenitor cells, along with a decrease in those associated with differentiated neuron-like cells, was observed when comparing SHH MB at diagnosis and relapse (Okonechnikov et al., 2023). This enrichment in genes characterizing poorly committed progenitor cells highlights their role in tumor relapse, as previously outlined in this review article.

3.1.3. G3 MB Relapse

Relapse of G3 MB has a marked impact on the rates of metastasis. Specifically, the metastatic frequency increases from 38% of distant disease at diagnosis to 92% at relapse (Hill et al., 2020). With an average relapse time of just 8 months, the time to relapse from diagnosis for G3 MB is the shortest among all MB subgroups (Huybrechts et al., 2020). Importantly, patients who were previously treated with radiation and chemotherapy (Hill et al., 2020) show relapse-specific loss of the *Cyclin dependent kinase inhibitor 2A* (*CDKN2A*) gene, which encodes regulatory proteins within the P53 pathway (Stott et al., 1998), and the amplification of *MYC*. These concurrent genetic alterations are not observed upon initial diagnosis of G3 MB. In addition to *TP53* and *MYC* defects, recurrent G3 MB also shows enrichment of chromosome 2q gain and chromosome 15 loss (Richardson et al., 2022). As described above, recent evidence suggests that compounds targeting epigenetic regulators, such as BET (Bandopadhayay et al., 2014) or HDAC (Ecker et al., 2015, Pei et al., 2016) proteins, are efficacious in blocking MYC transcriptional activity and attenuating the growth of *MYC* amplified G3 MB. Therefore, the translation of these approaches for the treatment of recurrent G3 MB should be considered. Similar to SHH MB, transcriptomic analyses comparing G3/G4 MB at diagnosis and relapse showed a decrease in neuronal differentiation gene signatures (Okonechnikov et al., 2023), while an increase in cell cycle activity, likely underlying the aggressiveness of recurrent disease, was observed.

3.1.4. G4 MB Relapse

In contrast to other subgroups, G4 MB recurrence is diagnosed significantly later (median time of 2.08 years) (Huybrechts et al., 2020), suggesting the need for a prolonged surveillance period for these patients. Like other subgroups, recurrence in G4 MB has high rates of metastasis, increasing from 34% at initial diagnosis to 90% metastasis in relapsed disease (Hill et al., 2020). G4 MB constitutes the subgroup that acquires the most genetic differences compared to the tumor at initial diagnosis (Richardson et al., 2022). Despite no significant alterations reported in previous chromosomal analyses of recurrent G4 tumors (Kumar et al., 2021), an increase in acquired loss of 9p, 10p, 20p, and 20q at relapse has been demonstrated in G4 MB (Richardson et al., 2022). Additionally, the loss of 17p and 11p was increased at G4 MB relapse but was also present at diagnosis (Richardson et al., 2022). In addition to these chromosome arm losses, concurrent *TP53* mutations and *MYCN* amplification were also observed (Hill et al., 2015). This observation contrasts with analyses from other cohorts reporting *TP53* mutation enrichment with no significant increase in *MYCN*

amplification (Richardson et al., 2022). In addition to *TP53* mutations and *MYCN* amplifications, an enrichment on Cyclin dependent kinase co-amplifications, *CDK6* and Cyclin dependent kinase 14 (*CDK14*), was found to be more prevalent in relapsed G4 MB than in their primary diagnostic counterparts (Richardson et al., 2022). Additionally, G4 relapsed MB showed enrichment in mutations commonly found at diagnosis, including *DEAD-box helicase 3 X-linked* (*DDX3X*)*, Chromodomain helicase DNA binding protein 7* (*CHD7*)*, Nebulin* (*NEB*)*, Ephrin A receptor 7* (*EPHA7*)*, General transcription factor IIIC (GTF3C*), as well as de novo mutations in the *Usherin* (*USH2A*) gene (Richardson et al., 2022), which encodes for a component of basement membranes in the inner ear and retina. Enrichment in *MYCN* amplifications suggests that, similar to SHH MB (Hill et al., 2015, Hill et al., 2020), Aurora-A kinase inhibitors may be used for the clinical management of recurrent G4 MB. Furthermore, the observed enrichment in *CDK6* amplifications in relapsed G4 MB (Richardson et al., 2022) suggests that therapies targeting RB signaling, such as CDK4/6 inhibitors, could be a viable approach not only for primary, but also for recurrent cases.

3.2. Animal Models of Relapsed MB

In addition to therapeutic predictions based on sequencing data obtained from biopsied recurrent MB, several laboratories have gathered additional information on relapsed MB by developing elegant *in vivo* models aimed at recapitulating treatment failure and MB relapse. One such study employed a transposon-driven functional genomic mouse model of SHH MB (Morrissy et al., 2016). In these animals, tumors were resected before being subjected to radiation and allowed to relapse. Results revealed a limited overlap between primary and relapsed tumor samples, which was hypothesized to result from the expansion of dormant clones after therapy. A similar approach involving chemotherapy and radiotherapy in mice harboring human derived G3 MB led to the identification of new candidate targets for relapsed G3 MB. One notable candidate driver was *BPI Fold Containing Family B Member 4* (*BPIFB4*), whose expression was not only enriched in relapsed G3 MB, but also needed for its growth (Bakhshinyan et al., 2021). Subsequent studies using a similar MB model followed by a high-throughput drug screening predicted the response of relapsed G3 MB to kinase inhibitors acting on Checkpoint Kinase 1 (CHK1) and Platelet-Derived Growth Factor Receptor Beta (PDGFRβ), which were shown to be efficacious *ex vivo* (Adile et al., 2023). These studies collectively underscore the significance of mouse models in gaining a better understanding of the drivers of recurrent MB.

3.3. Trials for Recurrent MB Patients

Relapsed MB poses a complex challenge due to its resistance to conventional therapies. This overall lack of response has driven the initiation of numerous clinical trials focused on evaluating the safety and efficacy of novel protocols in recurrent and refractory MB patients. Among these, ongoing trials will be outlined in this section based on two major subtypes: (1) chemotherapy-based and (2) immunotherapy-based trials.

3.3.1. Chemotherapy-based Trials for Recurrent MB Patients

Recent advancements in the molecular classification of MB have just started to impact the design of clinical trials for recurrent MB patients. Consequently, as summarized in **Table 4**, most ongoing chemotherapy-based trials are not yet tailored to target specific MB subgroups. Many of these trials focus on targeting well-known cancer drivers, such as Fibroblast growth factor receptor (FGFR), RAS, PI3K, Ret proto-oncogene (RET), MEK, Vascular endothelial growth factor (VEGF), Cereblon (CRBN), CDK4/6, Poly(ADP-Ribose) polymerase (PARP), MET proto-oncogene (c-MET) or mTOR. Some other trials concentrate on epigenetic regulators like Enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) or HDACs, while several include TOPO inhibitors and DNA alkylating agents. Additionally, a few agents targeting metabolism are under clinical evaluation, including ONC206, which has been shown to act as an antagonist of the Dopamine receptor D2 (DRD2) and an agonist of the mitochondrial serine protease Caseinolytic peptidase P (ClpP) to attenuate the growth of midline diffuse glioma (Purow, 2022). Tricarboxylic acid (TCA) cycle inhibitors such as ivosidenib, acting on Isocitrate dehydrogenase 1 (IDH1), and the recently FDA-approved inhibitor of the Polyamine biosynthetic pathway, Difluoromethylornithine (DFMO) (Tangella et al., 2023), are also being explored for recurrent MB patients. However, it is worth noting that the efficacy of most of these therapeutics in recurrent MB may be marginal due to the intertumoral heterogeneity that is not fully taken into consideration in their design.

Nevertheless, changes are underway, as evidenced by the emergence of several trials for recurrent MB patients considering the molecular drivers of the different MB subgroups. An example is the SJDAWN trial (NCT03434262) assessing the efficacy of double combination therapies for children with recurrent brain tumors. Patients are stratified by subgroup in this trial, with those classified as WNT or SHH MB receiving a CDK4/6 inhibitor (ribociclib) and a MEK inhibitor (trametinib). Within the SHH MB subgroup, ribociclib is combined with a SMO inhibitor (vismodegib) for patients who have not received a SMO inhibitor in at least 6 months, contingent upon the presence of 9q loss or mutations in *PTCH1*. Due to premature and irreversible growth plate fusion observed in children treated with SMO inhibitors (Robinson et al., 2017), patients in this group also need to be skeletally mature. A third MB patient group in this trial includes children with G3/G4 MB, for whom a CDK4/6 inhibitor is combined with a drug affecting DNA synthesis, gemcitabine, instead of a MEK inhibitor. In addition to the SJDAWN trial, two other trials specifically including SHH MB recurrent patients are underway. The PBTC-053 (NCT03904862) aims to assess the tolerability and efficacy of the CK2 inhibitor CX-4945, which blocks SHH signaling at the level of GLI (Purzner et al., 2018). The other trial, SJELIOT (NCT04023669), evaluates the checkpoint kinase CHK1 inhibitor, prexasertib. In this trial, prexasertib is combined with cyclophosphamide with the intention of blocking the repair of the DNA damage induced by this alkylating agent (Angius et al., 2020). G3/4 MB patients are also included in SJELIOT trial, where prexasertib is combined with either cyclophosphamide or gemcitabine. Although, not specifically designed for WNT MB, the NCI-COG Pediatric MATCH trial (NCT03213652) studies the efficacy of the Anaplastic Lymphoma Kinase (ALK) receptor tyrosine kinase inhibitor ensartinib in patients with *ALK* and *ROS proto-oncogene 1 (ROS1*) mutant tumors. Enrollment of WNT recurrent patients in this trial is expected due to the presence of ALK mutations in a subset of them (Yan et al., 2016). Another excellent example of the impact of the current understanding of MB inter-tumor heterogeneity is the PNOC027 trial (NCT05057702). In this trial, relapsed MB patients will receive individualized treatment based on the results from a high-throughput drug screening for FDA-approved compounds, along with whole-exome gene and RNA sequencing of tumors. Such an approach promises to demonstrate the efficacy that recurrent MB patients are in dire need of.

3.3.2. Immunotherapy-based Trials for Recurrent MB Patients

Immune-based therapies have demonstrated significant efficacy, not only in the treatment of hematological malignancies (Tang et al., 2023), but also, more recently, in the management of an expanding array of solid tumors (Khalil et al., 2016, Kantoff et al., 2010, Doroshow et al., 2019, Feld and Mitchell, 2018). Such efficacy has not been overlooked in the pediatric brain tumor field, leading to a surge in preclinical studies determining the effectiveness of similar immunotherapy-based approaches in MB (Kabir et al., 2020, Sayour and Mitchell, 2017). Several of these preclinical studies have yielded promising results (Nouri Rouzbahani et al., 2018, Kabir et al., 2020), laying the groundwork for the inclusion of recurrent MB patients in a number of immunotherapy-based clinical trials summarized in **Table 5**. Among the most promising immune-based therapies for MB, special consideration should be given to the use of CAR technology, which has greatly expedited the generation of antigen-specific CAR T cells (Waldman et al., 2020). In the case of MB, CAR T cell trials have been fueled by studies showing expression of candidate CAR targets such as Interleukin 13 receptor subunit alpha 2 (IL13Ralpha2) (Stastny et al., 2007), Ganglioside (GD2) (Ciccone et al., 2024) and B7 homolog 3 (B7-H3) (Castriconi et al., 2007, Gregorio et al., 2008, Purvis et al., 2020, Majzner et al., 2019) in MB tissues. In addition to these possible CAR targets, involvement of the Endothelial growth factor (EGF) pathway in MB progression (Rico-Varela et al., 2015) supported the inclusion of MB patients in trials testing the efficacy of CAR T cells engineered to target EGF receptor (EGFR) family members, including the Human epidermal growth factor receptor 2 (HER2) (Bodey et al., 2005).

Similar to CAR T-based cell therapies, the efficacy of checkpoint inhibitors in other malignancies (Robert, 2020), along with the expression of Programmed cell death ligand 1 (PD-L1) in MB tissues (Martin et al., 2018), laid the groundwork for determining the efficacy of blocking PD-L1 in pre-clinical MB models (Pham et al., 2016). Encouraging results from these studies have prompted trials in recurrent MB patients investigating the efficacy of the anti-PD-1 mAbs pembrolizumab and nivolumab, with the latter also being tested in combination with the HDAC inhibitor entinostat to enhance T cell efficacy (Truong et al., 2021). Unfortunately, the efficacy of checkpoint inhibitors in pediatric solid malignancies might be limited by the poor

immunogenicity of pediatric cancers compared to those in adulthood (Eisemann and Wechsler-Reya, 2022). A way to increase their efficacy, as well as that of chemo and radiotherapy, includes the use of immunomodulators to turn hot the hostile immune MB environment (Terry et al., 2020). Among these strategies, pre-clinical studies supported the translation of an inhibitor of the enzyme Indoleamine 2,3-dioxygenase-1 (IDO1), indoximod, alone or in combination with a Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, to prevent cancer-driven immunosuppression (Prendergast et al., 2018, Fox et al., 2018, Sharma et al., 2021). Another approach under evaluation for immune response stimulation involves the use of a humanized Immunoglobulin G, subclass 1, κ light chain (IgG1κ) mAb targeting Cluster differentiation 40 (CD40), a transmembrane receptor present in both antigen-presenting cells and cancer cells (Elgueta et al., 2009). Activation of CD40 triggers immune response and cytokine production, while also inducing apoptosis in tumor cells.

Approaches based on oncolytic viruses, which utilize a virus that selectively infects and destroys cancer cells while eliciting immune responses, represent another promising immunotherapeutic avenue for managing recurrent MB. While the efficacy of a number of oncolytic viruses including poliovirus (Thompson et al., 2018), measles (Aref et al., 2016, Studebaker et al., 2010), as well as reovirus (Figova et al., 2006, Yang et al., 2003) has been demonstrated in pre-clinical MB models, currently only two oncolytic viruses are undergoing clinical evaluation. One of these trials consists of the use of the neurotropic and genetically engineered herpes simplex virus type 1 HSV G207 (Bernstock et al., 2020), while the other uses bone marrow-derived allogenic mesenchymal stem cells infected with the oncolytic adenovirus ICOVIR-5. Somehow overlapping with these oncolytic virus-based strategies, vaccines are being tested for treating recurrent MB. One of these vaccines consists of the administration of the cytomegalovirus antigen pp65 which is ubiquitously expressed in brain tumors (Libard et al., 2014) including MB (Baryawno et al., 2011). This vaccine activates the immune system against pp65 expressing cells. Another strategy consists of the vaccination with dendritic cells loaded with total tumor RNA along with an autologous lymphocyte transfer to direct immune activity against the tumor (Flores et al., 2019). Finally, the peptide vaccine conjugate SurVaxM has been demonstrated to stimulate the immune system by targeting survivin, a protein whose expression is mostly found in tumor cells including MB (Brun et al., 2015). Another immunotherapy-based approach is radioimmunotherapy, which consists of antibodies linked to radioactive isotopes that bind to cancer cells. Once the antibody binds to the cancer cell, radiation damages their DNA and therefore triggers tumor cell death with minimal off-target effects to healthy tissues. Antibodies used in trials for MB patients target either B7-H3 (Purvis et al., 2019) or GD2 (Kramer et al., 2018, Longee et al., 1991) whose reactivity against MB cells was proved in pre-clinical MB models.

Like most studies on chemotherapeutic agents, ongoing clinical trials for immune-based therapies fail to specify the MB subgroup. This lack of specificity may lead to conflicting and incomparable data. For instance, variations in cytokine composition within the tumor microenvironment have been noted among MB subgroups (Low et al., 2020), indicating that not all immune-based treatments may be equally effective across subgroups. Hence, it is crucial to gain a deeper understanding of the tumor microenvironment characterizing MB subgroups, in order to guide future subgroup-specific immunotherapy trials.

4. CONCLUDING REMARKS

MB remains the most common type of malignant brain cancer in children with varying responses to therapy that are dependent on both pathological and molecular characteristics. Furthermore, the intrinsic heterogeneity of MB increases the complexity of treating not only primary, but recurrent MB. Given its inherent resistance to salvage therapies, a focus on prevention emerges as the most promising strategy when addressing relapsed MB. Unfortunately, despite decades of research aimed at identifying markers and drivers of the stem-like MB progenitor cells underlying treatment failure, translating these discoveries into clinical applications has fallen short. As a result, the field is slowly shifting towards the development of therapeutic approaches demonstrating efficacy in pre-clinical MB models that faithfully replicate key features of relapsed disease. The development of these research tools has become feasible, in part, due to the increasing accessibility to biopsies from recurrent tumors. Despite recent advancements in our understanding of recurrent MB, it remains crucial to conduct additional analyses of the genomics and proteomics of these tumors. Acquiring a deeper understanding of the mechanisms facilitating the propagation of recurrent MB will

lead to the development of clinical strategies that improve outcomes for these children—an outcome that has not changed in the last half century.

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TABLE LEGENDS

Table 1: Disease-risk based therapies for newly diagnosed MB. Current treatment protocols for newly diagnosed MB patients vary depending on their risk-stratification (Gajjar et al., 2006, Jakacki et al., 2012, von Bueren et al., 2016). Abbreviations: Amp: amplification, TP53: Tumor protein P53, Chr: chromosome, Chemo: chemotherapy.

	WNT	**SHH**		**G3**		**G4**		
		Metastatic *MYCN* amp *TP53* mutation	**Non-Metastatic *MYCN* amp *TP53* mutation**	**Metastatic *MYC* amp**	**Non-Metastatic Non *MYC* amp**	**Metastatic**	**Non-Metastatic No Chr11 loss**	**Non-Metastatic Chr11 loss**
Risk	Low	High	Average	High	Average	High	Average	Low
Radiation Dose	Reduced	Maximum	Lower	Maximum	Lower	Maximum	Lower	Reduced
Radiation Site	Posterior fossa	Posterior Fossa + Metastatic Sites	Posterior fossa	Posterior Fossa + Metastatic Sites	Posterior fossa	Posterior Fossa + Metastatic Sites	Posterior fossa	Posterior fossa
Adjuvant Chemo	Vincristine Cisplatin Lomustine	Vincristine Cisplatin Lomustine Cyclophosphamide Etoposide Carboplatin	Vincristine Cisplatin Lomustine Cyclophosphamide	Vincristine Cisplatin Lomustine Cyclophosphamide Etoposide Carboplatin	Vincristine Cisplatin Lomustine Cyclophosphamide	Vincristine Cisplatin Lomustine Cyclophosphamide Etoposide Carboplatin	Vincristine Cisplatin Lomustine Cyclophosphamide	Vincristine Cisplatin Lomustine

Table 2: Disease pattern and genetic events of MB at diagnosis and relapse. As outlined in this table, several key cancer features differ between newly diagnosed and recurrent MB. This indicates that therapies effective at diagnosis may fall short in treating recurrent cases (Hill et al., 2015, Hill et al., 2020, Huybrechts et al., 2020, Richardson et al., 2022, Morrissy et al., 2016, Cavalli et al., 2017). Abbreviations: CTNNB1:

Catenin Beta 1, APC: Adenomatous polyposis coli, TP53: Tumor protein P53, DDX3X: DEAD-box helicase 3 X-linked, SMARCA4: SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, Member 4; PTCH1: Patched 1, SMO: Smoothened, SUFU: Suppressor of fused homolog, GLI2: Glioma-associated oncogene 2, YAP1: Yes1 associated transcriptional regulator, ZFHX3: Zinc finger homeobox 3, KDM3B: Histone lysine demethylase 3B, TERT: Telomerase reverse transcriptase, DST: Dystonin, OTX2: Orthodenticle homeobox 2; DDX31: DEAD-box helicase 31, TGF-β: Transforming growth factor Beta 1, BPIFB4: BPI fold containing family B member 4, CDKN2A: Cyclin dependent kinase inhibitor 2A, CDK6: Cyclin dependent kinase 6, SNCAIP: Synuclein alpha interacting protein, OTX2: Orthodenticle homeobox 2, CDK14: Cyclin dependent kinase 14, USH2A: Usherin, CHD7: Chromodomain helicase DNA binding protein 7, NEB: Nebulin, GTF3C: General transcription factor IIIC subunit 1, EPHA7: Ephrin A receptor 7.

		WNT	SHH	G3	G4
Diagnosis	Prevalence	10%	30%	25%	35%
	Age Distribution	Children, adults	Infants, adults	Infants, children	Children
	Prognosis	Excellent	Poor - *TP53* mutant Intermediate - *TP53* WT	Poor	Intermediate
	Metastasis	5-10%	20%	38%	34%
	Key Driver Gene Mutations	*CTNNB1, APC, TP53, DDX3X, SMARCA4*	*PTCH1, SMO, SUFU, GLI2, TP53, YAP1, MYCN*	*MYC, OTX2, TP53, DDX31, TGF-β*	*MYCN, CDK6, SNCAIP, OTX2*
	Chromosomal Alterations	6	3p, 9p/9q, 10q, 17p	1q, 7, 8, 10q, 11, 16q, i17q, 18,	7, 8, 11p, i17q, 18q, X
Relapse	Time to Relapse	1.53 years	1.29 years	0.66 years	2.08 years
	Metastasis	80%	65%	92%	90%
	Key Driver Gene Mutations	*CTNNB, APC, TP53, MYC*	*TP53, MYCN, ZFHX3, KDM3B,* TERT, DST	*BPIFB4, CDKN2A, MYC, TP53*	*CDK6, CDK14, USH2A, TP53, MYCN, DDX3X, CHD7, NEB, GTF3C, EPHA7*
	Chromosomal Alterations	9q, 9p, 11q	9q, 4p, 4q , 10p 15	2q, 15	9p, 10q, 11p, 16q, 17p, 19p 19q, 20p, 20q

Table 3: Clinical trials for newly diagnosed MB patients by subgroup. The ongoing clinical trials for newly diagnosed MB patients take into consideration the disease risk and molecular characteristics of the tumor to adjust therapies accordingly. From: Clinicaltrails.org. Abbreviations: CSI: Craniospinal irradiation, NCT: National clinical trial. Blue tumor: WNT MB, red tumor: SHH MB, yellow tumor: G3 MB and green tumor: G4 MB.

Intervention	Phase	Trial Identifier	Subgroup
Reduced CSI, Reduced Chemotherapy/CSI + Reduced Maintenance Chemotherapy	2	NCT02724579	
Reduced CSI + Reduced Cyclophosphamide	2	NCT01878617	

Low CSI + Focal CSI	N/A	NCT04474964	
Sonidegib + Reduced CSI	2	NCT04402073	
Chemotherapy + Vismodegib	2	NCT01878617	
Reduced Cyclophosphamide + Pemetrexed + Gemcitabine	2	NCT01878617	
Systemic Chemotherapy + Delayed Risk-Adapted CSI + Carboplatin	2	NCT05535166	
Tailored Induction Chemotherapy + Randomization Single Cycle or Three Tandem Cycles of Marrow-Ablative Chemotherapy	4	NCT02875314	
Prexasertib + Cyclophosphamide & Prexasertib + Gemcitabine	1	NCT04023669	

Table 4: Chemotherapy-based clinical trials for recurrent MB patients. While most ongoing trials for patients with relapsed MB do not consider the molecular classification of tumors, a new era of targeting approaches is emerging, and several trials for these patients are stratified according to the MB subgroup. From: Clinicaltrails.org. Abbreviations: ODD: Orphan disease designation, FTD: Fast-track designation, NCT: National clinical trial, DRD2: Dopamine receptor D2, ClpP: Caseinolytic protease proteolytic subunit, DHFR: Dihydrofolate reductase, TOPO: Topoisomerase, C-met: MET proto-oncogene receptor tyrosine kinase, HDAC: Histone deacetylase, PI3K: Phosphoinositide 3-kinase, SST2A: Somatostatin receptor subtype 2A CDK4/6: cyclin dependent kinase 4/6, GD2: Ganglioside, GM-CSF: Granulocyte-macrophage colony-stimulating factor, EZH2: Enhancer of zeste homolog 2, ERK: Extracellular signal-regulated kinase, ODC: Ornithine decarboxylase, IDH1: Isocitrate dehydrogenase 1, FGFR: Fibroblast growth factor receptor, PARP: Poly(ADP-ribose) polymerase-1, TRK: Tropomyosin receptor kinase, mTOR: mammalian Target of rapamycin, RET: RET proto-oncogene, VEGFR2: Vascular endothelial growth factor receptor 2, PDK1: Pyruvate dehydrogenase kinase 1, VEGF: Vascular endothelial growth factor, COX-1: Cyclooxygenase 1, PPARa: Peroxisome proliferator activated receptor alpha, SMO: Smoothened, MEK1/2: mitogen-activated protein kinase 1/2, CK2: Casein kinase 2, CHK1/2: Checkpoint kinase 1/2, ALK-TKR: Anaplastic lymphoma kinase tyrosine kinase receptor, WGS: Whole-genome sequencing, RNAseq: RNA sequencing. Blue tumor: WNT MB, red tumor: SHH MB, yellow tumor: G3 MB and green tumor: G4 MB.

Subgroup	NCT Number	Phase	Target Protein/Process	FDA Approval
N/A	NCT04541082	1	DRD2 & ClpP (ONC206)	Yes
N/A	NCT02905110	1	DHFR (Methotrexate), TOPOII (Etoposide)	Yes
N/A	NCT03598244	1	c-Met (Savolitinib)	Yes
N/A	NCT04337177	1	TOPOI (Irotecan), DNA alkylation (Temozolomide)	Yes
N/A	NCT04315064	1	HDAC (Panobinostat)	No, withdrawn
N/A	NCT03893487	1	PI3K (Fimepinostat)	No, FTD
N/A	NCT00638898	1	DNA alkylation (Busufaltan, Melphalan), TOPOI (Topotecan), Myelosuppression (Filgrastim)	Yes, except Melphalan

N/A	NCT05278208	1/2	SST2A (Lutathera)	Yes
N/A	NCT06161519	1/2	TOPOII (PLX038)	Yes
N/A	NCT04238819	1/2	CDK4/6 (Abemaciclib), TOPOI (Irotecan), DNA alkylation (Temozolomide), GD2 (Dinutuximab), granulocyte production (GM-CSF)	Yes
N/A	NCT03709680	1/2	CDK4/6 (Palbociclib), DNA alkylation (Temozolomide, Cyclophosphamide), TOPOI (Irotecan, Topotecan)	Yes
N/A	NCT03213665	2	EZH2 inhibitor (Tazemetostat)	Yes
N/A	NCT04284774	2	Farnesyltransferase-HRAS (Tipifarnib)	No, FTD
N/A	NCT03698994	2	ERK (Ulixertinib)	No, ODD
N/A	NCT04696029	2	ODC (Difluoromethylornithine-DFMO)	Yes
N/A	NCT04195555	2	IDH1 (Ivosidenib)	Yes
N/A	NCT03526250	2	CDK4/6 (Palbociclib)	Yes
N/A	NCT03210714	2	FGFR (Erdafitinib)	Yes
N/A	NCT03233204	2	PARP (Olarapib)	Yes
N/A	NCT03213704	2	TRK (Larotrectinib Sulfate)	Yes
N/A	NCT03213678	2	PI3K/mTOR (Samotolisib)	No
N/A	NCT04320888	2	RET (Selpercatinib)	Yes
N/A	NCT04501718	2	VEGFR2 (Apatinib), DNA alkylation (Temozolomide), TOPOII (Etoposide)	No
N/A	NCT02574728	2	mTOR (Sirolimus), PDK1 (Celecoxib),TOPOII (Etoposide), DNA alkylation (Cyclophosphamide)	Yes
N/A	NCT01356290	2	VEGF (Bevacizumab, Thalidomide), COX-1 (Celecoxib), *PPARα* (Fenofibric acid), *TOPOII (Etoposide), DNA al*kylation (Cyclophosphamide), DNA synthesis (Cytarabine)	Yes
	NCT03434262 (SJDAWN)	1	DNA synthesis (Gemcitabine), CDK4/6 (Ribociclib), SMO (Sonidegib), MEK1/2 (Trametinib)	Yes
	NCT03904862 (PBTC-053)	1/2	CK2 (CX-4945)	No, ODD
	NCT04023669 (SJELIOT)	1	CHK1/2 (Prexasertib) *DNA al*kylation (Cyclophosphamide) DNA synthesis (Gemcitabine)	Yes, except Prexasertib (FTD)
	NCT03213652 (NCI-COG Pediatric MATCH)	2	ALK-TKR (Ensartinib)	Yes
	NCT05057702 (PNOC027)	N/A	Varies depending on results on drug screen, WGS & RNAseq	Yes

Table 5: Immunotherapy-based clinical trials for recurrent MB. The efficacy of immunology-based therapies in other malignancies has led to a surge in trials testing similar approaches for recurrent MB patients. The currently ongoing trials for such approaches are listed in this table. From: Clinicaltrails.org. Abbreviations: ODD: Orphan disease designation, FTD: Fast-track designation, NCT: National clinical trial, mAb: monoclonal antibody, IL13Ra2: Interleukin 13 receptor alpha 2, CAR T: Chimeric antigen receptor T cells, GD2: Ganglioside, C7R: Constitutively active IL-7 cytokine receptor, B7-H3: B7 Homolog 3, EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, PD-1: Programmed cell death protein 1, EudraCT: European Union drug regulating authorities clinical trials, BTK: Bruton tyrosine kinase, IDO: Indoleamine 2,3-dioxygenase, CD40: Cluster of differentiation 40, HSV: Herpes simplex virus, PEP-CMV: Peptide-cytomegalovirus, 131I: iodine-131. Blue tumor: WNT MB, red tumor: SHH MB, yellow tumor G3 MB and green tumor G4 MB.

	Intervention	Phase	Trial Identifier	FDA Approval
Adoptive	Anti IL13Rα2 CAR T cell infusion	1	NCT04661384	No
	Anti GD-2 & C7R CAR T cell infusion	1	NCT04099797	No

	Anti GD-2 CAR T cell infusion	1	NCT05298995	No
	Anti B7-H3-CAR T cell locoregional delivery	1	NCT05835687	No
	Anti B7-H3 CAR T cell infusion	1	NCT04185038	No
	Anti EGFR CAR T cell infusion	1	NCT03638167	No
	Anti HER2 CAR T cell infusion	1	NCT03500991	No
Checkpoint Inhibitors	Anti-PD-1 mAb (Nivolumab)	2	NCT03173950	Yes
	Anti-PD-1 mAb (Pembrolizumab)	1	NCT02359565	Yes
	Anti-PD-1 mAb (Nivolumab) & HDAC inhibitor (Entinostat)	1/2	EudraCT 2018-000127-14	Yes, except Entinostat
Immuno-modulators	BTK (Ibrutinib)/IDO (Indoximod) inhibitors & chemo	1	NCT05106296	No, ODD
	IDO inhibitor (Indoximod) & radiation	2	NCT04049669	No, ODD
	Anti-CD40 Ab (APX005M)	1	NCT03389802	No, ODD
Oncolytic Viruses	Modified herpes virus (HSV G207)	1	NCT03911388	No
	AloCELYVIR: Allogenic bone-marrow mesenchymal stem cells infected with oncolytic adenovirus (ICOVIR-5)	1/2	NCT04758533	No
Vaccines	PEP-CMV	1 2	NCT03299309 NCT05096481	No
	Total tumor RNA-loaded dendritic cells	1/2	NCT01326104	No
	Synthetic oligopeptide derived from Survivin (SurVaxM)	1	NCT04978727	No, FDD
Radio-immunotherapy	131I-radiolabeled anti-B7-H3 mAb (131I-Omburtamab)	2	NCT04743661	No

Figure 1: Translational vulnerabilities of WNT MB. WNT signaling is activated upon binding of WNT ligands to the FZD receptor, resulting in DSH/DVL activation. DSH/DVL inhibits β-Catenin destruction complex comprised of AXIN, APC, GSK3β, and CK1α. These last two kinases phosphorylate β-Catenin to trigger its degradation. Upon WNT signaling activation, β-Catenin is released from this complex, translocates to the nucleus and initiates the transcription of WNT target genes controlling cell proliferation and survival. WNT signaling can be blocked at several points along the pathway, but many of these approaches act upstream of β-Catenin. Hence, they are unlikely to be effective in WNT MB, where WNT signaling is commonly triggered by mutations in the genes coding for either β-Catenin or APC.

Figure 2: Translational vulnerabilities of SHH MB. SHH MB is characterized by the constitutive activation of SHH signaling. A predominant mutation in this subgroup involves the loss of the SHH receptor PTCH, leading to the stimulation of SMO. This, in turn, causes the translocation of GLI family members to the nucleus, where they transcribe genes supporting cell proliferation. The diagram illustrates the actions of inhibitors targeting key SHH pathway regulators, including compounds acting on SMO, CK1α, CK2, GLI, DNMT, BET, and HDAC. The expression of the gene encoding the cell cycle regulator Cyclin-D1 is induced by GLI. Therefore, compounds targeting CDK4/6, the kinase regulated by Cyclin-D1, prove effective in controlling SHH MB growth. Another notable SHH target gene is *MYCN*. Inhibitors of Aurora-A kinase prevent the binding of N-MYC to Aurora-A, leading to N-MYC degradation and subsequent attenuation of SHH MB growth. RAS/MAPK signaling plays a dual role in SHH MB. It has been demonstrated to enhance SHH signaling at the level of GLI, and its inhibition results in the attenuation of SHH MB growth. Conversely, RAS/MAPK can also promote the growth of SHH MB independently of SHH signaling, potentially contributing to the failure of therapies targeting SMO.

Figure 3: Translational vulnerabilities of G3 MB. G3 MB frequently exhibits *MYC* amplifications. Consequently, compounds that inhibit MYC transcriptional activity, such as BET and HDAC inhibitors, effectively mitigate G3 MB growth. Similar to SHH MB, the growth of G3 MB can be suppressed through the use of CDK4/6 inhibitors. Additionally, compounds targeting the PI3K pathway synergize with those acting on HDAC to block G3 MB growth.

Figure 4: Translational vulnerabilities of G4 MB. Due to the frequent *CDK6* amplifications observed in these tumors, the use of CDK4/6 inhibitors is expected to attenuate the growth of G4 MB. Additionally, *MYCN* amplifications are commonly found in G4 MB, making Aurora-A kinase inhibition a candidate strategy to control the growth of these tumors. Lastly, G4 MB exhibits amplifications in *KDM6A*, resulting in a decrease in the repressor mark H3K27 trimethylation. The subsequent increase in the acetylation of this Histone suggests a potential responsiveness of these tumors to HDAC inhibitors.

Figure 5. Neuronal cell markers and their hierarchy. In healthy brain tissues, neuronal linage is led by neuro-epithelial stem cells expressing stemness markers such as Nestin, CD15, CD133, and SOX2. These undifferentiated cells segregate either into Doublecortin positive neuronal progenitor cells (NPCs), or into a glia-committed linage that includes astrocyte progenitor cells (APCs) expressing the Glial fibrillary acidic protein (GFAP) and oligodendrocyte progenitor cells (OPCs) expressing the Oligodendrocyte transcription factor OLIG2. Under normal physiological conditions, NPCs differentiate into post-mitotic neurons, while APCs differentiate into astrocytes with the ability to re-enter the cell cycle, and OPCs into myelinating oligodendrocytes.

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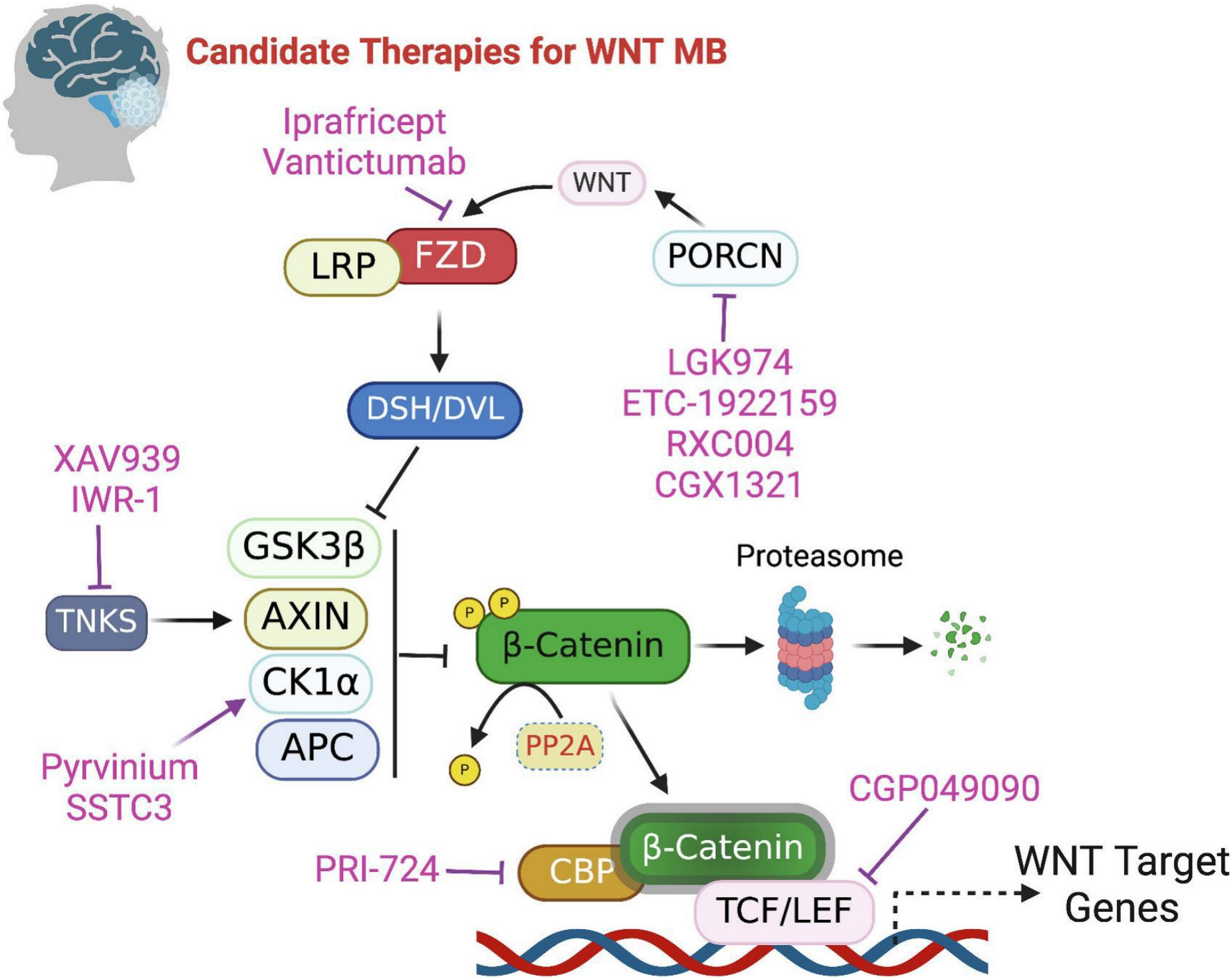
Candidate Therapies for WNT MB
Iprafricept
Vantictumab
WNT
LRP
FZD
PORCN
LGK974
ETC-1922159
RXC004
CGX1321
DSH/DVL
XAV939
IWR-1
GSK3β
TNKS
AXIN
CK1α
APC
Pyrvinium
SSTC3
Proteasome
P
P
β-Catenin
PP2A
P
CGP049090
PRI-724
CBP
β-Catenin
TCF/LEF
WNT Target
Genes

Figure 1

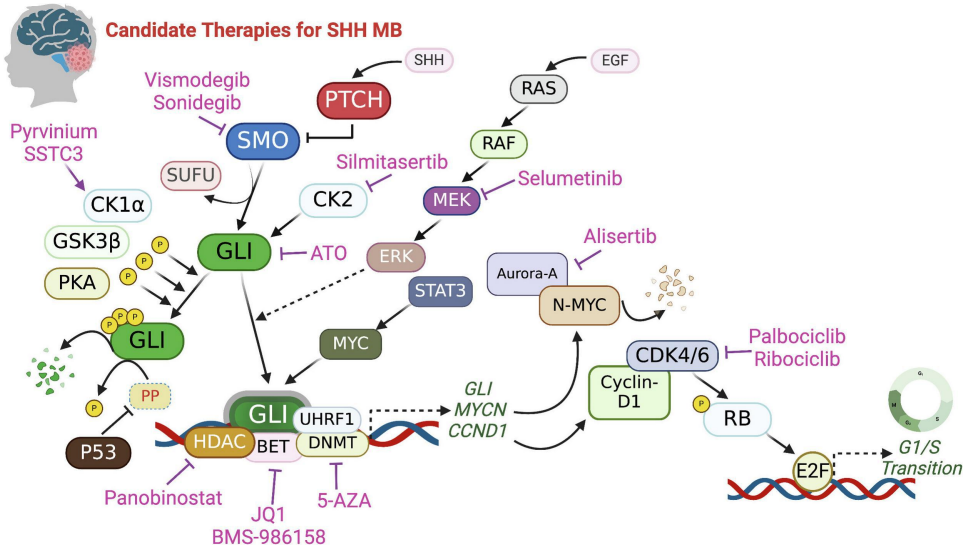
Candidate Therapies for SHH MB
SHH
EGF
Vismodegib
Sonidegib
PTCH
RAS
Pyrvinium
SSTC3
SMO
RAF
SUFU
Silmitasertib
Selumetinib
CK1α
CK2
MEK
GSK3β
GLI
ATO
ERK
Alisertib
PKA
Aurora-A
STAT3
N-MYC
GLI
MYC
CDK4/6
Palbociclib
Ribociclib
PP
GLI
UHRF1
GLI
MYCN
CCND1
Cyclin-
D1
P53
HDAC
BET
DNMT
RB
E2F
G1/S
Transition
Panobinostat
JQ1
BMS-986158
5-AZA

Figure 2

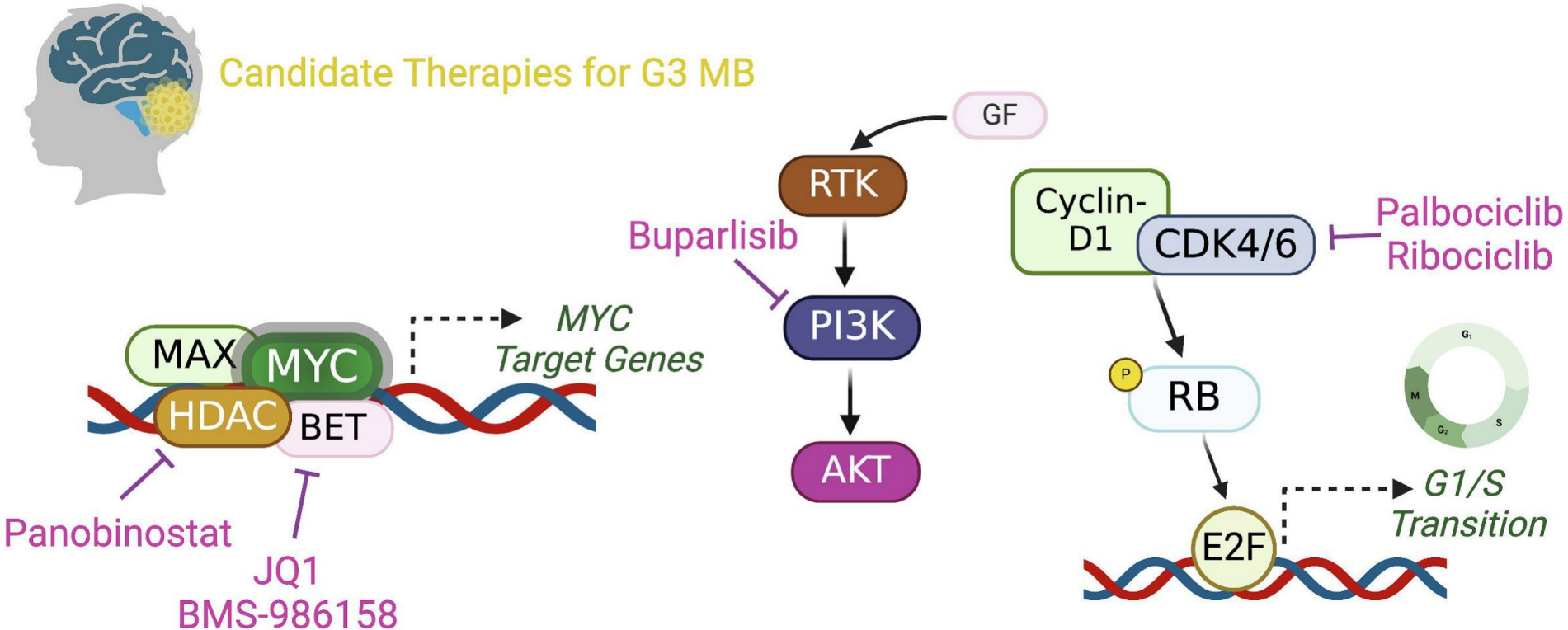
Candidate Therapies for G3 MB
GF
RTK
Buparlisib
PI3K
AKT
Cyclin-D1
CDK4/6
Palbociclib
Ribociclib
P
RB
E2F
G1/S Transition
MAX
MYC
HDAC
BET
MYC Target Genes
Panobinostat
JQ1
BMS-986158

Figure 3

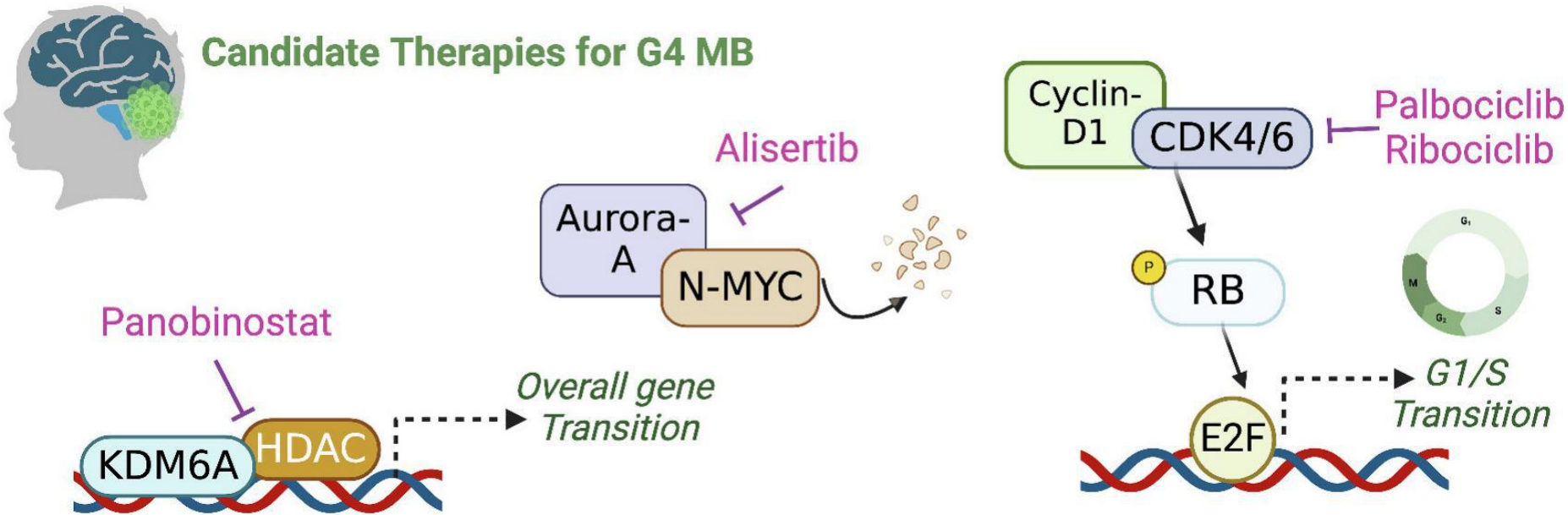
Candidate Therapies for G4 MB
Alisertib
Aurora-A
N-MYC
Panobinostat
KDM6A
HDAC
Overall gene Transition
Cyclin-D1
CDK4/6
Palbociclib
Ribociclib
P
RB
E2F
G1/S Transition

Figure 4

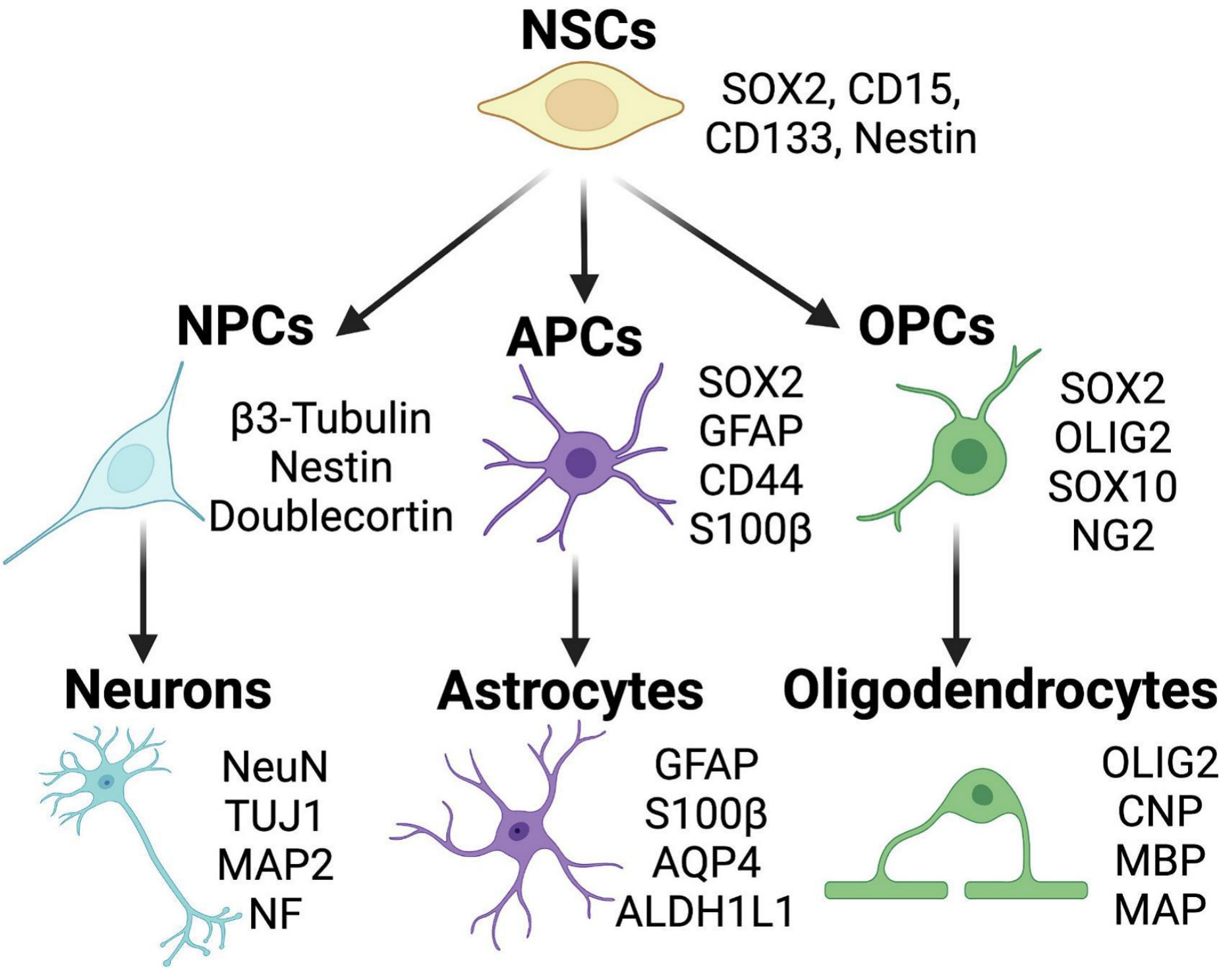
NSCs
SOX2, CD15,
CD133, Nestin
NPCs
β3-Tubulin
Nestin
Doublecortin
APCs
SOX2
GFAP
CD44
S100β
OPCs
SOX2
OLIG2
SOX10
NG2
Neurons
NeuN
TUJ1
MAP2
NF
Astrocytes
GFAP
S100β
AQP4
ALDH1L1
Oligodendrocytes
OLIG2
CNP
MBP
MAP

Figure 5