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The rationale for targeted therapies in medulloblastoma

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Medulloblastoma (MB) is the most frequent malignant brain tumor in children. Patients with MB who are classified as having high-risk disease or those with recurrent disease respond poorly to current therapies and have an increased risk of MB-related mortality. Preclinical studies and molecular profiling of MB tumors have revealed upregulation or activation of several key signaling pathways such as the sonic hedgehog and WNT pathways. Although the exact mechanisms underlying MB tumorigenesis remain poorly understood, inhibiting these key pathways with molecularly targeted therapies represents an important approach to improving MB outcomes. Several molecularly targeted therapies are already under clinical investigation in MB patients. We discuss current preclinical and clinical data, as well as data from clinical trials of targeted therapies that are either ongoing or in development for MB.

Keywords: hedgehog, medulloblastoma, oncogenic signaling, smoothened, targeted therapy.

urrent treatments can cure a majority of patients diagnosed with medulloblastoma (MB). However, these therapies are associated with significant long-term toxicities. Furthermore, patients with high-risk disease or recurrent tumor face a paucity of effective therapies. Preclinical studies have revealed the potential for treatment of MB with molecularly targeted therapies. This review synthesizes the preclinical and clinical data to date that support the use of targeted therapies as a novel treatment strategy in patients with high-risk or recurrent MB.

MB is a tumor of still-uncertain etiology that arises in the posterior fossa.[1] It is the most common malignant brain tumor in children aged <4 years, and comprises approximately 12% of all childhood brain and central nervous system (CNS) tumors.[2] According to the World Health Organization (WHO), there are 4 major histologic variants of MB: classic, desmoplastic/nodular, MB with extensive nodularity, and anaplastic/large-cell. Each is associated with a distinct morphology, age of onset, and prognosis. Other histologic features present in multiple variants can include MB with myogenic differentiation and MB with melanotic differentiation.[3,4] More recent data suggest that MBs are comprised of at least 4 distinct subgroups based on gene expression.[5]

The current standard of care for patients with MB aged ≥3 years involves surgery followed by craniospinal radiation and chemotherapy.[6,7] Various combination chemotherapy regimens, administered with or following treatment with craniospinal radiotherapy, have proven effective in patients with newly diagnosed MB.[1] In the recurrent setting, a combination of surgery, reirradiation, and/or chemotherapy with or without autologous stem-cell rescue have demonstrated efficacy.[6] Treatment regimens for recurrent disease include high-dose chemotherapy, bevacizumab, irinotecan, temozolomide (TMZ), and/or etoposide, metronomic chemotherapy, and molecularly targeted agents (reviewed in Aguilera et al.[8]).

In infants and young children, radiation therapy is rarely used because of the risk of long-term neurocognitive deficits, the severity of which inversely correlates with patient age at the time of treatment.[7] Postoperative multiagent chemotherapy followed by intraventricular methotrexate has proven effective in children aged <3 years[9] and <4 years,[10] particularly in patients with non-metastatic disease and in patients with desmoplastic/nodular MB.[9,10] Furthermore, neurocognitive function appeared to be less affected in children treated with this chemotherapy regimen, compared with children treated with radiotherapy following standard chemotherapy (ie, without intraventricular methotrexate).[9,11] Radiotherapy is used as a salvage regimen in patients who relapse following chemotherapy.[9,10]

Five-year event-free survival rates for patients with high-risk MB are >60% and can be >80% in patients with standard-risk disease.[1,2] However, patients at a high risk of recurrence (aged <3 years, with significant residual disease following surgery, large-cell/anaplastic MB, or metastatic disease) have lower survival rates.[1,12–14] In addition, long-term control in patients with recurrent disease is difficult to achieve.[1,12] Neurocognitive sequelae in MB survivors is one of the most devastating side effects of current treatments. This is most significant in young patients who are treated with craniospinal radiation.[1,7] Considering the

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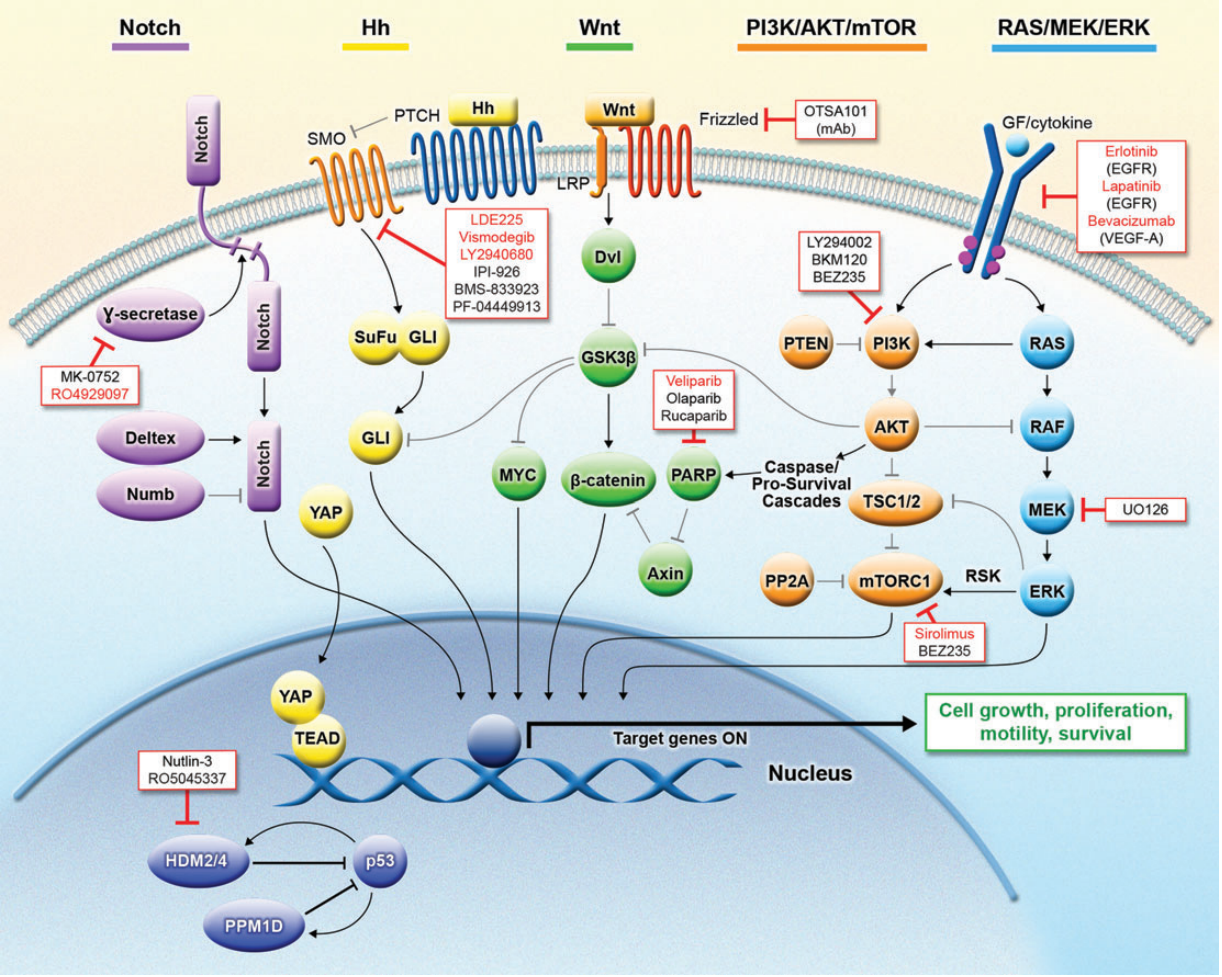

Fig. 1. Molecular signaling pathways implicated in MB and targeted therapies under investigation for the treatment of MB. Several key signaling pathways—including Notch, Hh, WNT, PI3K/AKT/mTOR, RAS/MEK/ERK, and p53—have been implicated in the tumorigenesis and/or maintenance of MB. Numerous agents that target these pathways are being developed and investigated in clinical trials. A subset of these agents (shown in red) is currently being investigated in clinical studies of MB. Abbreviations: AKT, Ak mouse thymoma; Dvl, disheveled; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GF, growth factor; Gli, glioma-associated oncogene; GSK3b, glycogen synthase kinase 3 beta; Hh, hedgehog; mAb, monoclonal antibody; MB, medulloblastoma; HDM2/4, p53 E3 ubiquitin protein ligase (human homologue of MDM2/4); MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; MYC, v-myc myelocytomatosis viral oncogene homolog (avian); PARP, poly (ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; PP2A, protein phosphatase 2A; PPM1D, p53-induced protein phosphatase, Mg^{2+}/Mn^{2+} dependent, 1D; PTCH, patched; PTEN, phosphatase and tensin homolog; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RSK, ribosomal protein S6 kinase; SMO, smoothened; SuFu, suppressor of fused; TEAD, transcription enhancer and activator domain; TSC1/2, tuberous sclerosis 1/2; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Wnt, Wingless and int; YAP, Yes-associated protein.

lack of a salvage therapy that is clearly effective and durable for patients with recurrent disease, it is clear that novel therapies are needed for patients with MB.

Signaling Pathways in MB

Based on data from numerous transcriptional profiling studies,[15–18] a consensus was determined that described at least 4 distinct molecular subgroups of MB.[5] The 4 groups: WNT [group 1], sonic hedgehog [Hh; group 2], group 3, and group 4, are distinguished by demographics, histology, DNA copy-number aberrations, and outcome.[5] Molecular profiling and independent studies have identified the hedgehog (Hh) and WNT pathways, among others, as potential molecular targets in MB[19,20] (Fig. 1) and have sparked numerous preclinical studies of molecularly targeted therapies in models of MB (Table 1). The molecular pathogenesis of groups 3 and 4 MBs is not well understood. Further studies are required to elucidate the key signaling pathways involved in their pathogenesis.

Hh/Smoothened

The Hh pathway is critical for cell proliferation, differentiation, and patterning during early embryonic development and for tissue homeostasis in adults.[21,22] Together with insulin-like growth factor

Table 1. Preclinical evidence for inhibition of key signaling pathways implicated in medulloblastoma

Signaling Pathway	Neoplastic Effects in MB	Inhibitor (target)	Preclinical Effects of Signaling Inhibition in MB	References
Hedgehog/SMO	• Maintenance of MB tumor growth in vitro • Overexpressed in group 2 MB tumors	HhAntag (SMO); GDC-0449 (SMO); LDE225 (SMO); IPI-926 (SMO); PF-5274857 (SMO)	• Significant tumor growth reduction and increased survival in MB mouse models	5,24-29
WNT/β-catenin/ PARP	• Wnt/β-catenin expression associated with classical MB and favorable prognosis • Increased PARP in MB is associated with poor prognosis • Role in tumor growth and survival in vitro	Rucaparib (PARP)	• Enhanced TMZ-induced tumor growth delay in MB xenografts	35–37,40
PI3K/AKT/mTOR	• Involved in functions such as cell growth, motility, survival, and angiogenesis • Several isoforms (including p110α and p110γ) are overexpressed in MB cell lines and in tumors from patients with MB • Increased PI3K/mTOR signaling in a mouse model of MB displaying resistance to SMO inhibitors	LY294002 (PI3K); YM024 (PI3K p110α); PIK-75 (PI3K p110α); AS-252424 (PI3K p110γ)	• Significantly reduced growth of MB cell lines • Reduced cell proliferation and sensitized MB cells to chemotherapy • Slowed proliferation of several MB cell lines and enhanced cisplatin cytotoxicity	46 43 44
mTOR	• ERK- and PI3K-dependent mTOR activity upregulated in MB	BEZ235 (PI3K-mTOR); BKM120 (PI3K); RAD001 (mTOR);	• Inhibited MB cell proliferation, clonogenicity, and tumor growth in vitro • Significantly delayed SMO-mediated resistance in vivo	27,51,54
		Sorafenib (multitargeted inhibitor of mTOR) + valproate or vorinostat (HDAC inhibitors);	• Induced MB cell apoptosis and enhanced radiation-induced apoptosis	107
		Rapamycin (mTOR); PP242 (mTORC1/2);	• Suppressed MB cell proliferation and fibronectin-stimulated MB cell migration	108
		OSU-03012 (PDK1) alone or in combination with temsirolimus (mTOR);	• OSU-03012 alone induced apoptosis and enhanced chemotherapy-induced cytotoxicity • OSU-03012 + temsirolimus slowed growth of MB tumors	109
		OSU-03012 (PDK1) ± LY294002 (PI3K)	• Reduced c-MYC and CCND1 in a β-catenin–dependent manner	109
RAS/MEK/ERK	• Upregulated in patient MBs • ERK upregulation associated with favorable prognosis	U0126 (MEK)	• Inhibited PDGFA/MEK-induced cell migration • Reduced PAK1 activation and MB cell migration	60, 61
PDGFR	• Upregulated in tumors from patients with metastatic MB	Imatinib (PDGFR);	• Inhibited ERK and AKT signaling, cell proliferation, survival, migration and invasion, and blocked EGFR transactivation by PDGF-BB	110
		Sunitinib (PDGFR);	• Inhibited PDGF/PDGFR-mediated MB cell migration • Sunitinib pretreatment reduced cell migration but not cell survival	111
		Tandutinib (PDGFRA)	• Induced MB cell apoptosis in vitro and slowed Shh-dependent tumor growth in vivo	112

Continued

Table 1. *Continued*

Signaling Pathway	Neoplastic Effects in MB	Inhibitor (target)	Preclinical Effects of Signaling Inhibition in MB	References
IGF-1R	• Upregulated in tumors resistant to SMO antagonists	NVP-ADW742 (IGF-1R) + TMZ	• Induced apoptosis and cell-cycle arrest	113
EGFR/HER2	• HER2/neu overexpression in human MBs correlates with poor patient survival	AEE788 (HER1/2 and VEGFR1/2);	• Inhibited MB cell proliferation in vitro and MB tumor growth in vitro (in both chemosensitive and chemoresistant models of MB)	114
		Gefitinib (EGFR)	• Induced cell-cycle arrest of MB cell lines and primary MB cells in vitro and inhibited MB tumor growth in vivo	115
VEGF/VEGFR	• Overexpressed in MB cell lines and in human MBs	Commercially available inhibitor VEGF V1 (VEGF-dependent angiogenesis via NRP-1 inhibition)	• Treatment with a VEGFR2 inhibitor reduced VEGF-dependent MB cell proliferation in vitro	116
p53/PPM1D/ HDM2	• *PPM1D* is overexpressed in human MBs • *PPM1D* expression enhances proliferation and decreases survival in MB xenograft models • HDM2 promotes PPM1D-mediated growth of MB cells	Nutlin-3a (HDM2); CCT007093 (PPM1D)	• Nutlin-3a treatment inhibits growth of MB cells with increased *PPM1D* expression • CCT007093 treatment reduces HDM2 expression and growth of MB cells with high expression of *PPM1D* • Combined inhibition of HDM2 and PPM1D more effectively blocks growth of MB cells	71
Notch	• Overexpressed in human MBs	γ-secretase inhibitor (Notch)	• Stimulated cell-cycle exit, apoptosis of stem-like cells, and neuronal differentiation of MB cells in vitro	74,75
COX-2	• Expression is elevated in CD133-positive versus CD133-negative MB cells	Celecoxib (COX-2)	• Inhibited CD133-positive MB cellular proliferation and colony formation; enhanced ionizing radiotherapy-induced apoptosis • Reduced expression of angiogenesis- and stemness-related genes in vivo	82,83

Abbreviations: CCND1, cyclin D1; COX-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; HDAC, histone deacetylase; HDM2/4, p53 E3 ubiquitin protein ligase (human homologue of MDM2/4); HER2, human epidermal growth factor receptor 2; IGF-1R, insulin-like growth factor 1 receptor; MB, medulloblastoma; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; NRP-1, neuropilin-1; PAK1, p21-activated kinase 1; PARP, poly(ADP-ribose) polymerase; PDGFR, platelet-derived growth factor receptor; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphoinositide 3-kinase; PPM1D, p53-induced protein phosphatase, Mg2+/Mn2+ dependent, 1D; SMO, smoothened; TMZ, temozolomide; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

signaling, Hh signaling can drive formation of MBs in vivo.[23] Several Hh pathway inhibitors that target the transmembrane receptor smoothened (SMO) have demonstrated antitumor activity in MB in vivo. The SMO inhibitors HhAntag, vismodegib (GDC-0449), LDE225, IPI-926, and PF-5274857 each reduced tumor growth significantly and increased survival in several mouse models of MB,[24–29] suggesting that the Hh pathway is required for maintenance of MB tumor growth.

Recent work suggests that components of the Hh signaling pathway may cross talk with other pathways, such as Hippo, to promote MB growth and/or treatment resistance.[30,31] The Hippo pathway plays an important role in the control of organ development.[32] Its downstream effector, Yes-associated protein (YAP), is an oncoprotein, which is normally inactivated by Hippo signaling.[33] Conversely, Hh signaling promotes expression and activation of YAP. In fact, in the absence of Hh, ectopic YAP promotes proliferation of cerebellar granule neuron precursors, one of the cells of origin of MB. Furthermore, expression of YAP was shown to be amplified in 3% of human MB samples.[30] Evidence from mouse models further suggests that YAP promotes resistance to radiation therapy.[31] This suggests an important mechanism of treatment resistance in YAP high-expressing, Hh-activated MBs.

WNT/β-Catenin

The WNT/β-catenin pathway is involved in cell proliferation, differentiation, cell polarity, and migration during embryogenesis and in tissue homeostasis in adults.[34] WNT pathway genes and β-catenin, the main effector of the WNT pathway, are overexpressed in MB and are associated with favorable patient prognosis.[35,36] Similarly, expression of the poly (ADP-ribose) polymerase (PARP) enzyme has been observed in tumor samples from patients with MB compared with those with normal brain tissue; however, PARP expression is associated with poor prognosis.[37] Thus, the majority of WNT pathway inhibitors developed to date target PARP and lead to the destruction of β-catenin.[38,39] The PARP inhibitor rucaparib (AG-014699) enhanced TMZ-induced tumor growth delay in human MB xenografts.[40] Dickkopf homolog 1 (*DKK1*), which negatively regulates the WNT pathway, was found to be downregulated in MB patient samples and primary MB cell cultures. In vitro expression of *DKK1* in MB cells suppressed tumor growth and induced apoptosis. In addition, *DKK1* upregulation was observed following treatment with a histone deacetylase (HDAC) inhibitor,[41] suggesting that *DKK1* is silenced during MB tumorigenesis.

PI3K/AKT/mTOR

The phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is involved in functions such as cell growth, motility, survival, and angiogenesis,[42] and several PI3K isoforms are upregulated in MB tumors.[43–45] Mutations and allelic loss in phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K pathway, have been identified in MBs; reduced PTEN expression (sometimes associated with promoter hypermethylation) is common in MB cell lines, mouse models of MB, and tumor samples.[46–48] In addition, activation of receptor tyrosine kinases such as insulin-like growth factor 1 receptor and human epidermal growth factor receptor 2 (HER2)/ERBB2, which both lie upstream of and activate PI3K, has been observed in MB.[49]

Treatment with LY294002, a PI3K small-molecule inhibitor, caused a significant reduction in cell growth of MB cell lines, which was reversed upon expression of a constitutively activated form of AKT.[46] Similarly, RNA interference–mediated downregulation of p110α reduced growth, increased apoptosis, and inhibited migration of MB cells.[43] In addition to its role in driving neoplastic growth in vitro, PI3K signaling is upregulated in MB tumors resistant to SMO inhibitors in vivo. In a mouse model of MB, inhibition of PI3K signaling with the PI3K inhibitor BKM120 or the dual PI3K/mTOR inhibitor BEZ235 led to a significant delay in development of resistance to SMO inhibition,[27] suggesting that dual inhibition of PI3K and SMO could circumvent or delay MB tumor resistance. Consistent with these findings, PI3K activation drove the survival of MB stem cells following radiation in vivo.[48]

In addition to canonical signaling, signaling through common downstream targets between pathways appears to play an important neoplastic role in MB. The PI3K/AKT/mTOR, WNT, and Hh pathways can each inactivate glycogen synthase kinase 3 beta (GSK-3β), which in turn induces MYC upregulation and protein stabilization.[49,50] Data suggest that any of the PI3K/AKT/mTOR, WNT, or Hh pathways can inactivate GSK-3β, an important negative regulator of MYC, resulting in upregulation and stabilization of MYC protein. Consistent with the neoplastic role of MYC, data from a recent report demonstrated that cerebellar cells overexpressing MYC together with a dominant-negative form of p53 had a similar molecular profile to that of human MB and that these tumors were dependent on PI3K signaling.[51] The hepatocyte growth factor (HGF)/scatter factor-c-MET pathway also signals through activation of MYC.[52] HGF and its receptor c-MET are strongly expressed in MB, particularly the large-cell MB subtype, and are associated with poor prognosis.[53] HGF/c-MET-stimulated MYC signaling is mediated in part by mitogen-activated protein kinase kinase (MEK) and PI3K and results in cell cycle progression and proliferation.[52] Together, these data demonstrate that multiple oncogenic signaling pathways can converge on common intracellular molecular effectors, which are excellent candidates for inhibition using molecularly targeted therapies.

RAS/MEK/ERK

Growth factor stimulation of the RAS/MEK/extracellular signal-regulated kinase (ERK) pathway has been observed in MBs, particularly classical MBs. Moreover, expression of ERK is associated with a favorable prognosis.[54,55] Activation of ERK was shown to activate mTOR and downregulate protein phosphatase 2A.[54,56] Data thus far suggest that ERK is a common downstream target of epidermal growth factor receptor (EGFR), RAF, and the chemokine receptor CXCR4,[54,56] which is upregulated in the SHH group of MB tumors.[57] In addition, the EGFR family member HER2/neu was found to be overexpressed in a subset of tumors from patients with MB, which has been correlated with poor patient outcome.[58,59]

Increased ERK and platelet-derived growth factor receptor alpha (PDGFR-α) signaling have been observed in tumor samples from patients with metastatic MB.[60] PDGF-dependent MB cell migration was shown to be dependent on ERK-mediated activation of p21-activated kinase 1 (PAK1). Tissue microarray analysis of MB samples demonstrated that PAK1 is overexpressed in over 50% of MB tumor samples and is associated with unfavorable outcomes. Treatment of MB cells with the MEK/ERK inhibitor U0126

abolished PAK1 activation and PAK1-dependent cell migration,[61] suggesting a role for ERK in migration of MB cells.

p53

One-third of MBs exhibit gain of the long arm of chromosome 17 (17q) and isochromosome 17q.[62,63] *p53*, on 17p13, is the most frequently inactivated gene in human cancers. However, it is only mutated in approximately 10% of MBs, and its impact on survival is controversial.[64–68] Evidence suggests that p53 signaling is abnormal, especially in aggressive histologic subtypes of MB. A recent study identified focal amplification of the p53-inactivating genes *PPM1D* and *MDM4* in SHH MBs.[69] We have previously demonstrated increased expression of *PPM1D* in non-WNT MBs.[70,71] Recent publications demonstrate evidence of cross-talk between PPM1D and Hh pathways and suggest a role for targeting PPM1D in Hh-active tumors.[72,73]

Additional Pathways and Processes

The Notch signaling pathway, which is important for the specification, proliferation, and survival of neural precursors, has also been implicated in MB tumorigenesis.[74] In MB cell lines, inhibition of the Notch pathway with γ-secretase inhibitors led to cell cycle exit, apoptosis of stem-like cells, and neuronal differentiation.[75] γ-secretase inhibition may also be an effective therapy for patients with MB with spinal metastasis. Inhibition of γ-secretase blocked the proteolytic processing of the p75 neurotrophin receptor, which in turn reduced MB cell migration and invasion in vitro and in vivo.[76]

Targeting global cellular processes may be another approach for the treatment of MB. For example, because many tumor suppressor genes are epigenetically silenced in MB,[77,78] HDAC inhibitors have become an area of interest in MB research.[79] In addition, the proteasome inhibitor bortezomib is being evaluated and has demonstrated promising activity in vitro and in vivo.[80,81]

Therapies using an antiangiogenic approach are currently in various stages of development. Angiogenic targets include vascular endothelial growth factor receptor (VEGFR), PDGFR, and the Notch protein. Similarly, the cyclooxygenase 2 (COX-2) protein is overexpressed in MB and constitutes a potentially valuable therapeutic target, as COX-2 inhibition demonstrates activity against human MB xenograft tumors in vivo.[82,83]

Clinical Investigation of Targeted Therapies in MB

Hh/SMO

Multiple ongoing clinical trials are evaluating molecularly targeted agents in patients with MB (Table 2), including several trials with SMO inhibitors. To date, data from clinical trials in MB are only available for vismodegib and LDE225. Vismodegib is currently under evaluation in 5 clinical trials in patients with MB, either as monotherapy (NCT01239316, NCT00939484, NCT00822458) or in combination with TMZ (NCT01601184) or maintenance chemotherapy (NCT01878617). Preliminary data from a phase 1 study in pediatric patients with recurrent or refractory MB demonstrated that vismodegib was well tolerated, with 1 grade 3 elevation of γ-glutamyl transpeptidase (GGT) at a vismodegib dose of 170 mg/m^2 and no grade 4 toxicities. Efficacy data from this trial are not yet publicly available. However, among 13 patients with treatment-refractory MB and confirmed Hh pathway activation, 1 patient progressed after 6 months of therapy with oral vismodegib. Another patient remained on study and was progression-free after 391 days of follow-up.[84] In a phase 1 study of vismodegib in adults with advanced solid tumors, one patient with metastatic MB achieved a partial response (PR), but relapsed after approximately 3 months.[85,86]

LDE225 is currently under investigation as a monotherapy in pediatric and adult patients with recurrent or refractory MB, or other tumors (NCT01125800). LDE225 was well tolerated and showed antitumor activity (complete responses) in 2 of 24 pediatric patients with MB.[87] In a phase 1 study of LDE225 in adults with advanced solid tumors, tumor responses were observed in 2 patients with MB (1 PR, 1 metabolic PR).[88] All patients from the pediatric and adult studies who responded (complete or partial response) to LDE225 treatment were found to have Hh pathway–activated tumors as determined by a 5-gene Hh signature assay.[89] Several additional trials are currently ongoing, including a phase 3 trial of LDE225 in patients with Hh-activated, relapsed MB (NCT01708174) and a phase 1 trial of the SMO inhibitor LEQ506 in adult patients with advanced solid tumors, including MB (NCT01106508).

Resistance to SMO-dependent Hh pathway inhibitors through acquired mutations in *SMO*, or amplification of the Hh pathway transcription factor glioma-associated oncogene homologue 2 (*Gli2*) and the Hh target gene *CCND1*, has been observed in preclinical mouse MB models and was determined to be the cause of relapse in the patient with MB described above who initially responded to vismodegib treatment.[27,90,91] The frequency and clinical relevance of this resistance will be realized as results from ongoing trials become available. Several preclinical studies have identified potential mechanisms to overcome this resistance, including combination with PI3K/mTOR inhibitors or arsenic and itraconazole.[27,92,93] A phase 1 trial testing the combination of LDE225 and BKM120 in patients with advanced solid tumors is currently recruiting (NCT01576666).

WNT/β-Catenin

Several agents targeting the WNT pathway in pediatric patients with CNS tumors are being evaluated in clinical trials, including the PARP5/tankyrase inhibitors olaparib and veliparib (ABT-888). Veliparib plus TMZ is being evaluated in a phase 1 study in pediatric patients with recurrent or refractory CNS tumors (NCT00946335). A phase 1 study of veliparib plus radiation therapy in adult patients with brain metastasis is currently ongoing (NCT00649207). A phase 1 study of olaparib with TMZ in patients with relapsed glioblastoma is currently recruiting (NCT01390571). Agents targeting additional members of the WNT pathway include the porcupine inhibitor LGK974 (phase 1 trial in patients with WNT ligand–dependent malignancies, NCT01351103) and a radiolabeled monoclonal antibody against frizzled (phase 1 trial in patients with synovial sarcoma, NCT01469975).

Table 2. Ongoing clinical trials of targeted agents in MB

Agent	Target(s)	Phase: Status[a]	Study Population ($N_{planned}$)	Regimen	NCT ID
GDC-0449 (vismodegib)	SMO	2: ANR	Adult pts with R/R MB ($n = 50$)	GDC-0449	NCT00939484
		2: CR	Pts aged 3–21 years with R/R MB ($n = 50$)	GDC-0449	NCT01239316
		1/2: CR	Adult pts with MB with activated SHH ($n = 38$)	TMZ ± GDC-0449	NCT01601184
		1: ANR	Pts aged 3–21 years with R/R MB ($n = 30$)	GDC-0449	NCT00822458
		2: CR	Pts aged 3–21 years with newly diagnosed MB stratified based on clinical risk and molecular subgroup (WNT, SHH, non-WNT/non-SHH) ($n = 350$)	For SHH group: craniospinal radiation and chemotherapy (cisplatin, vincristine, cyclophosphamide) followed by GDC-0449 + maintenance chemotherapy	NCT01878617
LDE225	SMO	3: CR	Pediatric or adult pts with Hh-activated, relapsed MB ($n = 109$)	LDE225 or TMZ	NCT01708174
		1/2: CR	Pediatric or adult pts with R/R MB ($n = 91$)	LDE225	NCT01125800
		1: ANR	Adult pts with advanced solid tumors, including MB ($n = 100$)	LDE225	NCT00880308
		1: CR	East Asian adult pts with advanced solid tumors, including MB ($n = 44$)	LDE225	NCT01208831
LEQ506	SMO	1: ANR	Adult pts with advanced solid tumors, including R/R MB ($n = 71$)	LEQ506	NCT01106508
Veliparib	PARP	1: ANR	Pts aged ≤ 21 years with R/R CNS tumors, including MB ($n = 24$)	ABT-888 + TMZ	NCT00946335
Sirolimus	mTOR	1: CR	Pediatric or adult pts aged ≤30 years with R/R solid tumors, including MB ($n = 24$)	Sirolimus + daily celecoxib, plus low-dose etoposide alternating with cyclophosphamide	NCT01331135
Antiangiogenic agents, including bevacizumab	VEGF, VEGFR	2: CR	Pts aged ≤21 years with R/R MB or CNS primitive neuroectodermal tumors ($n = 108$)	TMZ + irinotecan hydrochloride ± BEV	NCT01217437
		2: ANR	Pts aged ≤21 years with R/R or progressive malignant gliomas, diffuse/intrinsic brainstem gliomas, MB, ependymomas, or low-grade gliomas ($n = 140$)	BEV + irinotecan	NCT00381797
		2: CR	Pediatric pts with recurrent or progressive MB ($n = 40$)	BEV + intrathecal etoposide and cytarabine + thalidomide, celecoxib, and fenofibric acid, with alternating cycles of daily low-dose etoposide and cyclophosphamide	NCT01356290
		1: CR	Pts aged 18 months to 23 years with R/R CNS tumors, including MB ($n = 30$)	BEV + irinotecan + TMZ	NCT00876993
Vorinostat	HDAC	1: CR	Pediatric pts aged ≤ 4 years treated with surgery for embryonal CNS tumors, including MB ($n = 62$)	Vorinostat, isotretinoin + combination chemotherapy	NCT00867178

Abbreviations: ANR, active, not recruiting; BEV, bevacizumab; CNS, central nervous system; CR, currently recruiting; GD2, ganglioside G2; HDAC, histone deacetylase; Hh, hedgehog; ID, identifier; mAb, monoclonal antibody; MB, medulloblastoma; mTOR, mammalian target of rapamycin; NCT, national clinical trial; PARP, poly(ADP-ribose) polymerase; pts, patients; R/R, recurrent/refractory; SHH, sonic hedgehog; SMO, smoothened; TMZ, temozolomide; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
[a]Current status of each trial based on a search of ClinicalTrials.gov conducted on July 26, 2013.

PI3K/AKT/mTOR and RAS/MEK/ERK

Although inhibitors of PI3K and MEK are being tested in patients with CNS tumors, no clinical trials are currently evaluating these agents in patients with MB. In contrast, the mTOR inhibitor sirolimus is being evaluated in a phase 1 study in combination with celecoxib plus low-dose etoposide, alternating with cyclophosphamide in patients with relapsed or refractory solid tumors including MB (NCT01331135). Data from this trial have not yet been reported. A second mTOR inhibitor, everolimus, was well tolerated in a phase 1 study in pediatric patients with recurrent or refractory solid tumors; however, no objective responses were observed.[94]

EGFR

The EGFR inhibitors erlotinib and lapatinib are being investigated in trials in children with CNS tumors, but few results have been published to date. Ongoing trials are testing erlotinib in combination with chemotherapy in young patients with embryonal brain tumors, choroid plexus carcinoma, high-grade glioma, or ependymoma (NCT00602667). Erlotinib is also being tested in combination with radiation in young patients with refractory or relapsed CNS tumors, or in newly diagnosed brainstem glioma (NCT00360854). Data from a phase 1 study demonstrated that erlotinib, followed by combined erlotinib/TMZ, was well tolerated in children with recurrent or refractory solid tumors (NCT00077454).[95] Similarly, data from a phase 2 study demonstrated the tolerability of single-agent lapatinib in pediatric patients with refractory/recurrent CNS tumors (NCT00095940). Although no objective responses were reported, disease stabilization was observed in 13 patients, including 1 patient with MB.[96]

Antiangiogenic Approaches

Angiogenesis inhibitors blocking VEGF or PDGF are also being tested in combination with chemotherapy or other targeted agents in patients with MB. Data from a recent study of patients ($n = 16$) with recurrent embryonal brain tumors, including MB ($n = 7$), who were treated with bevacizumab, thalidomide, celecoxib, fenofibrate, etoposide, and cyclophosphamide (NCT01356290) demonstrated favorable rates of event-free survival for patients with MB: 6-month, 12-month, and 24-month event-free survival rates were 100%, 85.7%, and 68.6%, respectively.[97] Of the 5 patients with MB with long-term survival (> 12 months), 2 patients received radiotherapy following surgery ($n = 1$) or in combination with PEI chemotherapy (cisplatin, etoposide, ifosfamide; $n = 1$) for their most recent relapse before switching to the antiangiogenic regimen described above. Similarly, data from a phase 1 trial of pediatric patients and young adults with refractory solid tumors and leukemia ($n = 19$) treated with combined bevacizumab, sorafenib, and low-dose cyclophosphamide (NCT00665990) demonstrated that 5 of the 17 patients evaluable for tumor response achieved a PR (including 1 patient with MB), and 9 of 17 achieved stable disease (SD).[98]

Combined bevacizumab and irinotecan, a topoisomerase I inhibitor, was evaluated in a phase 2 study in young patients with recurrent, progressive, or refractory glioma, MB, ependymoma, or low-grade glioma (NCT00381797). This combination was well tolerated, but no MB efficacy data were reported.[99] Early data from 2 patients in a phase 1 study of patients with relapsed/refractory CNS tumors (including MB) treated with bevacizumab plus TMZ and irinotecan (NCT00876993) demonstrated that this combination was well tolerated and was associated with favorable clinical activity: one patient achieved SD > 30 months (ongoing at the time of the report), and the other patient had a near-complete response lasting 18 months.[100] A recently published follow-up study reported results in 9 patients treated with bevacizumab and irinotecan with or without TMZ. Six months after the start of salvage therapy, objective response rate was 55%, with 2 patients achieving PR and 3 achieving complete response. Additionally, 1 patient had SD, and 3 had PD. Two patients remain alive and progression-free at 15 and 55 months, and another is alive with stable disease at 20 months.[8] Together, these data suggest that antiangiogenic agents such as bevacizumab, in combination with cytotoxic therapies, may provide marked clinical benefit in patients with MB, including patients with recurrent or refractory MB.

Targeting angiogenesis through the Notch pathway via γ-secretase inhibition is under evaluation in pediatric patients with CNS tumors, but limited efficacy data have been reported to date. Safety data from a dose-escalation study of the γ-secretase inhibitor MK-0752 in pediatric patients with refractory or recurrent CNS malignancies ($n = 17$), including MB ($n = 2$), demonstrated that although MK-0752 was well tolerated, it was associated with only modest efficacy.[101,102] Future clinical development of this agent in MB remains uncertain. A study evaluating the γ-secretase inhibitor RO4929097 in young patients with relapsed/refractory solid tumors, CNS tumors (including MB), lymphoma, or T-cell leukemia is no longer recruiting (NCT01088763). Results have not yet been reported. Several additional trials using antiangiogenic regimens are currently ongoing.

Additional Pathways and Processes

Celecoxib, a COX-2 inhibitor, has demonstrated efficacy when combined with chemotherapy in pediatric patients with MB. In a pilot study of pediatric patients with relapsed MB ($n = 4$), celecoxib monotherapy or in combination with TMZ was associated with clinically stable disease or better in all 4 patients. One patient (who received the combination regimen) achieved an objective response, as confirmed by magnetic resonance imaging.[103] Currently, celecoxib is being tested in combination with antiangiogenic agents in patients with recurrent or progressive MB (NCT01356290).[97]

The HDAC inhibitor vorinostat has been tested in several clinical trials in children with relapsed/refractory solid tumors. Vorinostat was generally well tolerated, both as a single agent and in combination with isotretinoin, in pediatric patients with recurrent/refractory solid tumors (including MB), lymphoma, or leukemia (NCT00217412).[104] Data from 2 phase 1 studies in pediatric patients with relapsed/refractory CNS or solid tumors demonstrated that vorinostat was well tolerated when combined with either TMZ (NCT01076530; $n = 19$, 2 patients with MB)[105] or bortezomib (NCT00994500; $n = 23$, 1 patient with MB).[106] A phase 1 study testing the combination of vorinostat, isotretinoin, and chemotherapy in young patients with previous surgeries for an embryonal tumor is currently recruiting (NCT00867178).

Conclusions

For a subset of patients with MB, particularly the very young and those with recurrent disease, a significant need exists for novel

therapies that provide improved clinical benefit with reduced toxicity, compared with existing treatments. Identifying risk status soon after diagnosis may help identify these patients and drive therapeutic decisions.[36] Molecular profiling studies of primary tumor samples and preclinical studies using models of MB have identified several key signaling pathways that appear to be involved in the clinical development and maintenance of MB clinically. Inhibitors of these pathways have demonstrated antitumor activity in vitro and in vivo, and several are now being investigated in clinical trials in patients with MB or other CNS tumors. Although only a handful of studies have reported efficacy data in patients with MB, promising clinical activity has been observed with Hh inhibitor monotherapy and with combined antiangiogenic/chemotherapy regimens.

The identification of MB molecular subgroups and advances in molecular profiling techniques have incited a new era in the treatment of MB in which preselection of patients who may derive benefit from a particular targeted therapy is likely possible. Preselection of patients is critical given the toxicities associated with current therapies and potential toxicities associated with novel targeted therapies. Although this new era brings great promise, there are still many hurdles to overcome. In particular, due to the limited number of patients with MB, it may be challenging to conduct prospective studies that are sufficiently powered to determine if molecular profiling data can be used in clinical practice. Nevertheless, the potential for treating MB in the upfront and relapsed settings, using targeted agents based on molecular profiling, is encouraging. Thus, although the molecular mechanisms contributing to the pathogenesis of MB in pediatric and adult patients are not completely known, emerging clinical data from trials investigating these novel targeted agents will help improve the future landscape of available therapies for patients with high-risk and recurrent MB.

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