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Review

Molecular Genetics and Targeted Therapies for Paediatric High-grade Glioma

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Abstract. *Brain tumours are the leading cause of paediatric cancer-associated death worldwide. High-grade glioma (HGG) represents a main cause of paediatric brain tumours and is associated with poor prognosis despite surgical and chemoradiotherapeutic advances. The molecular genetics of paediatric HGG (pHGG) are distinct from those in adults, and therefore, adult clinical trial data cannot be extrapolated to children. Compared to adult HGG, pHGG is characterised by more frequent mutations in PDGFRA, TP53 and recurrent K27M and G34R/V mutations on histone H3. Ongoing trials are investigating novel targeted therapies in pHGG. Promising results have been achieved with BRAF/MEK and PI3K/mTOR inhibitors. Combination of PI3K/mTOR, EGFR, CDK4/6, and HDAC inhibitors are potentially viable options. Inhibitors targeting the UPS proteosome, ADAM10/17, IDO, and XPO1 are more novel and are being investigated in early-phase trials. Despite preclinical and clinical trials holding promise for the discovery of effective pHGG treatments, several issues persist. Inadequate blood-brain barrier penetration, unfavourable pharmacokinetics, dose-limiting toxicities, long-term adverse effects in the developing child, and short-lived duration of response due to relapse and resistance highlight the need for further improvement. Future pHGG management will largely depend on selecting combination therapies which work synergistically based on a sound knowledge of the underlying molecular target pathways. A systematic investigation of multimodal therapy with chemoradiotherapy, surgery, target agents and immunotherapy is paramount. This review provides a comprehensive overview of pHGG focusing on molecular genetics and novel targeted therapies. The diagnostics, genetic discrepancies with adults and their clinical implications, as well as conventional treatment approaches are discussed.*

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Intracranial and intraspinal tumours are the most common solid tumours in paediatrics (1). They are the second leading cause of cancer-associated death in children and adolescents under the age of 19 in the USA and Canada (1), with an average annual age-adjusted incidence of 6.06 per 100,000 in the USA between 2012 and 2016 (2). Brain tumours are now the leading cause of paediatric-cancer-associated death worldwide, surpassing deaths from childhood leukaemia (3). Gliomas represent the highest proportion of childhood brain tumours (4, 5) accounting for 60% of paediatric brain tumour cases (5, 6), of which approximately half are classified as high grade (6, 7).

Classification. Gliomas are brain tumours of neuroepithelial origin and are derived from glial cells which are responsible for neuronal support (5). The classification of gliomas into grades follows the histopathological criteria set out by the World Health Organisation (WHO) (8) (Table I).

Tumour behaviour, survival rates, and treatment strategies vary according to WHO grades I-IV. Generally, gliomas are divided into three categories: low-grade gliomas (LGG) (WHO grade I-II), high-grade gliomas (HGG) (WHO grade III-IV) and diffuse intrinsic pontine gliomas (DIPG) which is a unique HGG entity with peak incidence between 6 and 9 years of age (9). DIPG belongs to the category of malignant midline gliomas, also known as diffuse midline gliomas (DMGs), which occur in the thalamus, brainstem, or spine, in contrast to non-midline, hemispheric HGGs which include anaplastic astrocytoma and glioblastoma multiforme (GBM). While 5-year survival rates for paediatric LGG are as high as 95%, HGG prognosis remains poor with reports indicating only 15-35% 5-year survival rates and median overall survival (OS) of 10-18 months (8), despite continuous advances in surgical and adjuvant chemoradiation therapies (10, 11). There is still no effective treatment for DIPG which carries only 10% 2-year survival, decreasing to 2% at 5 years (12-14). Hence, there is an evident need to develop more effective treatments than the current standard of aggressive surgery with chemoradiation, particularly owing to the considerable toxicities and subsequent long-term sequelae in developing children and adolescents.

Objective. Significant research efforts are aimed at understanding the underlying tumour biology, genetics, and molecular profile of HGG to help uncover possible therapeutic targets for novel targeted agents (15). This review discusses the diagnostics, molecular genetics, driver oncogenic mutations of childhood malignant glioma along with recently discovered genetic and epigenetic aberrations, the clinical implications of these, and possible treatment approaches including molecular targeted therapies.

Diagnostics

Molecular diagnostic classification. Genetics offer significant insight into the prognosis, clinical course, and treatment optimisation of glioma. Hence, although histology-based diagnosis and grading remains the most reliable, quick and cost-effective diagnostic method for brain tumour classification, in 2016, the WHO updated its brain tumour classification system to include molecular characteristics with histology for tumour grading (8, 16). An example classification algorithm is shown in Figure 1. Tumours are classified into astrocytomas, oligoastrocytomas, oligodendrogliomas or glioblastomas with further subclassification. Information from tumour histological appearance, genetic testing, and tumour grading are integrated in reaching a final diagnostic classification of the tumour entity. Of note, molecular features may override information from histological assessment in reaching a final tumour classification.

Diagnostic discrepancies by age. Paediatric cancers differ from those in adults in terms of clinico-biological behaviour, genetics, and molecular characteristics. Tumour location classically differentiates paediatric brain tumours from those in adults, with the former occurring in infratentorial brain regions (brainstem and cerebellum) and the latter occurring in the supratentorial compartment (cerebral hemispheres and midline structures above the tentorium) (17, 18). Paediatric HGGs (pHGG) display a different mutation profile to adult HGGs (aHGG) (19-21) as children display more stable genomes with fewer mutations, however, pHGG and aHGG are similar histologically and cannot be differentiated by histology alone (22). Due to their distinct genetic alterations, pHGGs and aHGGs should be considered as separate tumour entities (23, 24). Routine diagnostic assessment of diffusely infiltrating HGG for all ages should at least include formalin-fixed and paraffin-embedded tumour samples with haematoxylin and eosin (H&E) staining and reticulin silver staining in addition to immunohistochemistry against glial fibrillary acidic protein (GFAP), p53, and Ki-67 (proliferation marker) (22). However, recommendations for additional staining differ between pHGG and aHGG. In the paediatric population, staining for microtubule-associated protein 2 (MAP2), oligodendroglial lineage marker (Olig-2) and alpha-thalassemia/mental retardation X-linked (ATRX) can be useful, while isocitrate dehydrogenase 1 (IDH1) is of less use in young children who rarely display this mutation (22).

Molecular Genetics of pHGG

Advances in genome-wide array-based sequencing technologies, allowing for whole genome and exome sequencing, have contributed ground-breaking insights into the genetic alterations underpinning pHGG, uncovering unique molecular drivers (25-29) (Table II). The subsequent paragraphs in this section discuss the role of core signalling pathways, histone modifications, and other genetic mutations in pHGG.

Core mutated signalling pathways.

Three core signalling pathways commonly implicated in aHGG have also been implicated in pHGG but with different frequency of mutated effectors (25). These pathways include the receptor tyrosine kinase (RTK)/rat sarcoma (RAS)/phosphatidylinositide 3-kinase (PI3K) pathway, p53, and retinoblastoma (RB) pathway (Figure 2) (30). Within each signalling pathway multiple different effectors can be mutated at different frequencies. The mutation profile helps delineate HGG subtypes but also indicates potential therapeutic targets (15) (Figure 2).

Table I. *World Health Organization (WHO) tumour classification for gliomas including tumour biology, histology, and prognosis.*

WHO grade	Description
I (circumscript)	Non-malignant tumours of low proliferative potential associated with cure and long-term survival following surgical resection.
II (low grade)	Not evidently malignant tumours of low proliferative potential, however, may infiltrate and tend to transform into high grade or recur. Survival typically >5 years.
III (diffuse, high-grade)	Malignant appearance characterised by nuclear atypia and mitotic activity; tend to grow fast and infiltrate or recur. Patients often require additional radiation or chemotherapy. Survival typically does not exceed 3 years.
IV (high-grade)	Malignant appearance characterised by cellular atypia, mitotic activity and necrosis; tend to grow rapidly and infiltrate or recur; aggressive phenotype. Heterogenous survival times depending on treatment and patient data, often not exceeding 1 year[a].

[a]Caution is advised for WHO grade IV as some subtypes, such as medulloblastomas, feature much higher survival rates of 80% at 5 years. Information collated and summarised from (16).

EGFR and PDGFRA. Components of the RTK/RAS/PI3K pathway and downstream effectors are commonly activated in pHGGs through gain of function and loss of function mutations, gene fusions, and gene amplifications (25). EGFR (ERBB1) and PDGFRA are both receptor components of the RTK/RAS/PI3K signalling cascade which is affected in 90% of aHGG (25). Yet, in pHGG *EGFR* mutations are less frequent (31, 32), with gene amplification and EGFRvIII overexpression detected in only few (4%) pHGGs (33-35). In contrast, amplification and/or activating mutation of *PDGFRA*, which encodes platelet-derived growth factor receptor-α (PDGFRα), has been shown to drive glioma formation in mural models resembling human diffuse HGGs (36, 37). This is the most common event in DIPG and paediatric non-brainstem high-grade glioma (pNBS-HGG), occurring in 20-30% of pHGG (20, 21, 24, 26, 27, 29, 36, 38, 39) whilst rarely occurring in aHGG (40).

Other RTKs and NTRK. *RTK* gene fusions have also been identified in *ALK*, *ROS1*, *FGFR*, *MET*, and *NRTK* genes particularly in a subset of hemispheric HGG, specifically GBM and in younger infants, corresponding to heterogeneous survival rates (41-43). Concurrence of point mutations or amplifications affecting at least two of the *MET*, *ERBB2* (*HER-2*), *EGFR* and *PDGFRA* genes suggest that genomic activation may be a mechanism for co-activated RTKs (44, 45). Neurotrophic receptor kinase (*NTRK*) gene fusions involving the kinase domain of the three *NTRK* genes and the five N-terminal fusion partners have been observed in 10% of NBS-HGGs and 4% of DIPGs (24). These drive glioma formation *in vivo* by activation of the PI3K/MAPK signalling (24). *NTRK* gene fusions have been identified in 40% of infantile (<3 years old) NBS-HGGs yet this percentage is much lower in the paediatric population overall (24, 24, 43, 46). They have also been observed in aGBM and pLGG though with far less recurrence (47-49). The prognosis for pNBS-HGG in children <3 years of age is significantly better than for older children (50). NTRK can be a valuable therapeutic target for this group (25).

BRAF. The serine threonine protein kinase BRAF is a component of the RAS/RAF/MEK/ERK signalling cascade downstream of the MAPK pathway which regulates cellular survival, metabolism, and proliferation. *BRAF* point mutations which substitute valine to glutamic acid at position 600 ($BRAF^{V600E}$) resulting in activation of the MAPK pathway are observed in 10-15% of pHGG (51, 52) and 17% of pLGG (53) and co-occur with *PDGFRA* amplification (40) and homozygous *CDKN2A* deletions (54, 55). *BRAF* mutations occur in cortical brain tumours and have not been identified in DIPG. *BRAF* mutations and *CDKN2A* deletions dysregulate cellular proliferation (54) which is thought to drive malignant transformation of pLGG to a subset of secondary pHGGs (41, 56) which are associated with slightly improved OS compared to primary HGGs (42, 57).

PI3K–AKT–mTOR. Constitutive PI3K–AKT–mTOR pathway activation is a hallmark of GBM (30, 44). Mutations, amplifications and deletions affecting the PI3K complex, and its downstream effectors occur in different frequencies in aHGG and pHGG. Mutually exclusive mutations in *PIK3CA* (encoding for the p110α catalytic PI3K subunit) and *PIK3R1 (encoding for the* regulatory subunit) *are observed in 7-21% and 6-11%* of aHGGs *respectively* (58). *PIK3R1 mutations* are observed in similar frequency in pHGG, including DIPG. *PIK3CA* mutations are more frequently observed in DIPG (15-25%) and less common in supratentorial HGG (5%) which corresponds to adult presentations (39, 59-64). The tumour suppressor gene *PTEN* on chromosome 10q is mutated in 5-

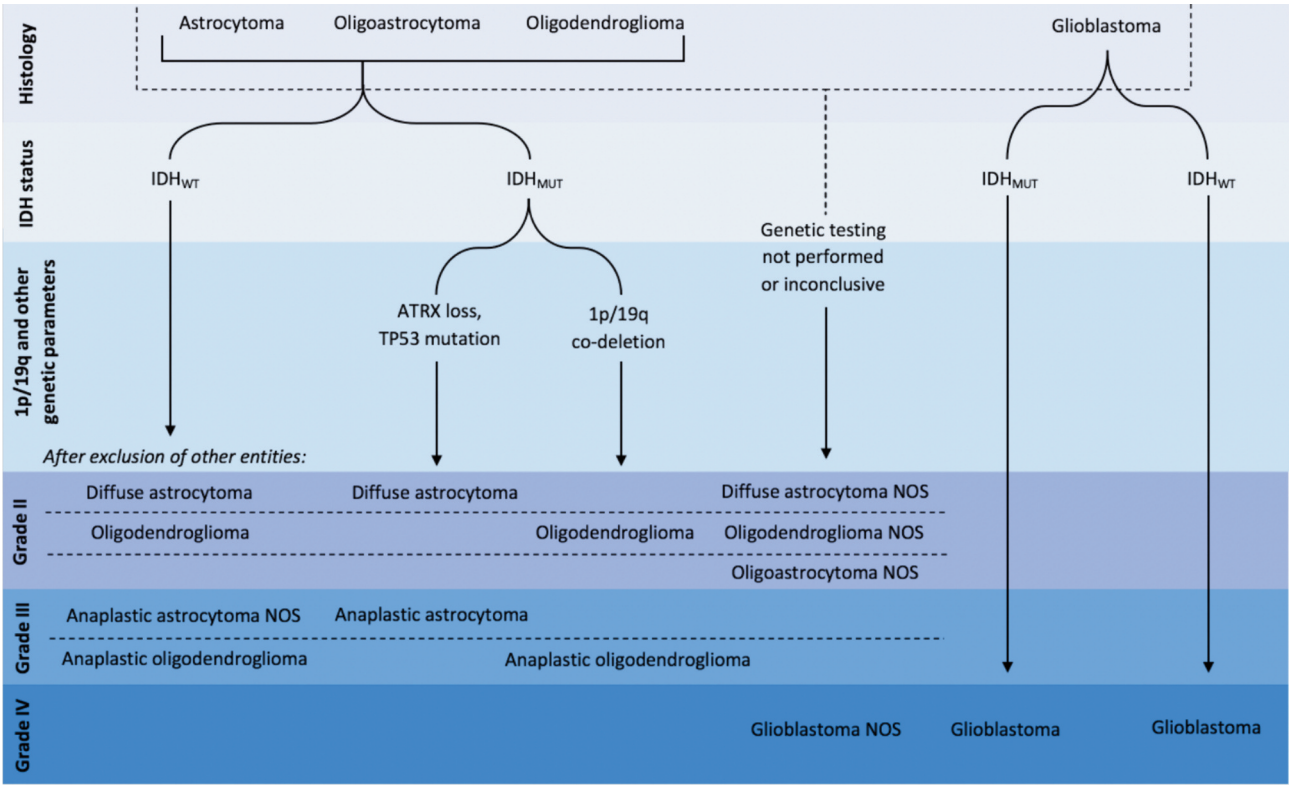

Figure 1. *Simplified classification algorithm for diffuse gliomas incorporating molecular genetics in addition to histology. Tumours are classified into astrocytomas, oligoastrocytomas, oligodendrogliomas or glioblastomas with further subclassification. Information from tumour histological appearance, genetic testing, and tumour grading are integrated in reaching a final diagnostic classification of the tumour entity. Note, molecular features may override information from histological assessment in reaching a final tumour classification. Information adapted from WHO classification. IDH, Isocitrate dehydrogenase; WT, wild-type; MUT, mutant; ATRX, alpha-thalassemia/mental retardation X-linked gene; TP53, tumour protein P53; NOS, not otherwise specified.*

15% of pHGGs while loss of 10q heterozygosity is observed in 30% (23, 28, 29, 31, 59). These figures are lower than aHGGs which feature 25-40% *PTEN* mutation and 80% loss of 10q heterozygosity (65-67). Occasionally, *AKT* amplification (2%) and *FOXO* mutation (1%) may contribute to downstream signalling activation (30, 44).

RB pathway. RB pathway dysregulation is common in both pNBS-HGGs and DIPG. *CDKN2A* codes for the tumour suppressor genes p16/INK4a and ARF which keep cell cycle progression in check along with p21 (68). Homozygous deletion of *CDKN2A* and *CDKN2B* is exclusive to pNBS-HGG tumours and almost entirely absent in DIPG (20, 21, 26). Notably, 30% of DIPGs feature amplifications in *CDK4/6* or *CCND1/2/3* (26, 29, 38, 69), which code for cyclin D-dependent kinases and cyclin D family members, respectively. These amplifications facilitate pRB phosphorylation which catalyses the release of E2F1 transcription factor to promote transcription of genes required for G1 to S phase transition (68).

p53 pathway. *TP53* mutations are more common in pHGG (35-37%) than aHGG (20-29%) (70), with higher frequencies reported in DIPGs (42-50%) than in pNBS-HGGs (18-35%) (24, 32, 39). *TP53* mutations are also less frequent (9%) in children <3 years and these cases also observe a better prognosis (71). p53 pathway mutation frequencies in DIPGs (42-50%) and pNBS-HGGs rise up to 83% when including alterations to other pathway elements such as *CDKN2A* (ARF) and *MDM2* (25).

Histone modifications.

H3.1/H3.3 K27M and G34R/V: In 2012, two independent studies on paediatric GBM (23) and DIPG (72) produced landmark discoveries implicating recurrent somatic histone H3 gene mutations in pHGG tumorigenesis (Figure 3) (25) which are extremely rare in aHGG (23). These recurrent mutations occur on histone tails, at or near important modification sites, specifically affecting genes that encode for the histone variants H3.3 (encoded by *H3F3A*) and less frequently H3.1 (encoded

Table II. *Select genetic and epigenetic molecular drivers in paediatric high-grade glioma with respective genomic analysis techniques used for profiling.*

Oncogenic driver	pHGG type	Genomic analysis techniques	References
EGFR	pHGG, pGBM	NGS, F-PHF, ICH, FISH, CISH, DHPLC, RT-PCR, qPCR, PNA-LNA PCR clamp, dPCR	(65, 180, 181)
PDGFRA gene amplification	DIPG, pNBS-HGG	DNA/RNA microarrays, bioinformatic analyses, FISH and mutation screening (genetic analyser)	(38)
NTRK	DIPG, pHGG	WGS, WES, RNA-seq., microarray copy number and expression analysis using Affymetrix expression array, TERT promoter mutation analysis	(182)
ALK, ROS1, FGFR, MET, HER-2	pHGG	Targeted SNV, fusion profiling, copy number arrays, transcriptome-wide discovery strategies, WGS, WES, RNA-seq.	(43, 46)
ACVR1 (ALK2)	DIPG, pHGG	Illumina WGS, allelic expression of ACVR1 sequencing, RNA-seq.	(24, 64, 73, 183)
BRAF	DIPG, pNBS-HGG	aCGH, SNP array, dPCR	(184)
CDKN2A/B	pNBS-HGG	WGS, dPCR	(65)
Ras/Akt activation and YB1 (inducing EGFR overexpression)	pGBM	Microarray analysis, RT-PCR	(19, 185)
PIK3CA	pHGG, DIPG	qPCR, mutation analysis	(60, 186)
PIK3R1	pHGG, DIPG	qPCR, mutation analysis	(186)
PTEN (10q)	pHGG	FISH, HiMAP, PCR	(67, 187-190)
AKT amplification	pHGG, pGBM	Microarray analysis, RT-PCR	(19, 185)
FOXO	pHGG, GBM	Post-translational analysis, IP analysis	(191)
CCDN1/2/3	DIPG	PCR, WGS	(65, 192)
CDK4/6	DIPG	dPCR, WGS	(24, 65)
TP53	DIPG, pNBS-HGG	dPCR	(65)
MDM2	DIPG, pNBS-HGG	dPCR	(65)
H3K27M mutation in histone 3.1/3.3 (H3F3A/HIST1H3B, HIST1H3C)	DIPG, pNBS-HGG	Illumina WGS, SNP array, telomere specific FISH	(72, 76)
G34R/V	pGBM, pHGG	ChIP-seq analysis, NGS	(193)
MYCN	pHGG, pGBM	MeDIP, GSEA, WGS, ChIP-Seq.	(77)
ATRAX, DAXX	pHGG, pGBM	WGS	(23, 91)
MLL, KDM5C, KDM3A and JMJD1C chromatin-remodelling genes	pHGG	PCR amplification, WGS	(4)
MGMT hypermethylation and subsequent silencing	pHGG, pGBM	MSP, MLPA	(6, 122)
IDH1/2	pGBM	PCR, WGS	(96)
ADAM3 (8p12)	pHGG, DIPG	RT-PCR	(28, 194)

NSG, Next-generation sequencing; F-PHFA, fluorescence resonance energy transfer (FRET)-based preferential homoduplex formation assay; ICH, immunohistochemistry; FISH, fluorescence in situ hybridization; CISH, chromogenic *in situ* hybridization; DHPLC, denaturing high pressure liquid chromatography; RT-PCR, reverse transcription polymerase chain reaction; qPCR, quantitative polymerase chain reaction; PNA-LNA PCR clamp, peptide nucleic acid-locked nucleic acid polymerase chain reaction; dPCR, duplex polymerase chain reaction; WGS, whole-genome sequencing; WES, whole-exome sequencing; RNA-seq., transcriptome sequencing analysis; SNV, single nucleotide variants; aCGH, array comparative genomic hybridisation; HiMAP, human interactome map (bioinformatics site); IP, immunoprecipitation; ChIP-seq., chromatin immunoprecipitation with parallel DNA sequencing; MeDIP, methylated DNA immunoprecipitation; GSEA, gene set enrichment analysis; MSP, methylation-specific polymerase chain reaction; MLPA, (methylation-specific) multiplex ligation-dependent probe amplification.

by *HIST1H3B*, *HIST1H3C)* (72, 73). All H3 mutations in pHGG are heterozygous and only 1 of 16 genes encoding H3 is mutated in any tumour, which clearly indicates a dominant mutation that causes gain of function (25). Mutations result in amino acid substitutions at two key residues in the N-terminal of histone tails: lysine-to-methionine at position 27 (K27M) and glycine-to-arginine (or less frequently glycine-to-valine) at position 34 (G34R/V) (74). K27M and G34R/V are mutually exclusive, present in 38% of paediatric and young adult (<30 years) HGGs (70) and are not observed in LGGs (23, 72, 75). They are also mutually exclusive with recurrent point mutations in IDH1 (23).

Notably, H3 mutations are associated with specific anatomical regions in the brain. G34R/V mutations are observed in non-midline cortical tumours (hemispheric and supratentorial) while K27M mutations are found in midline

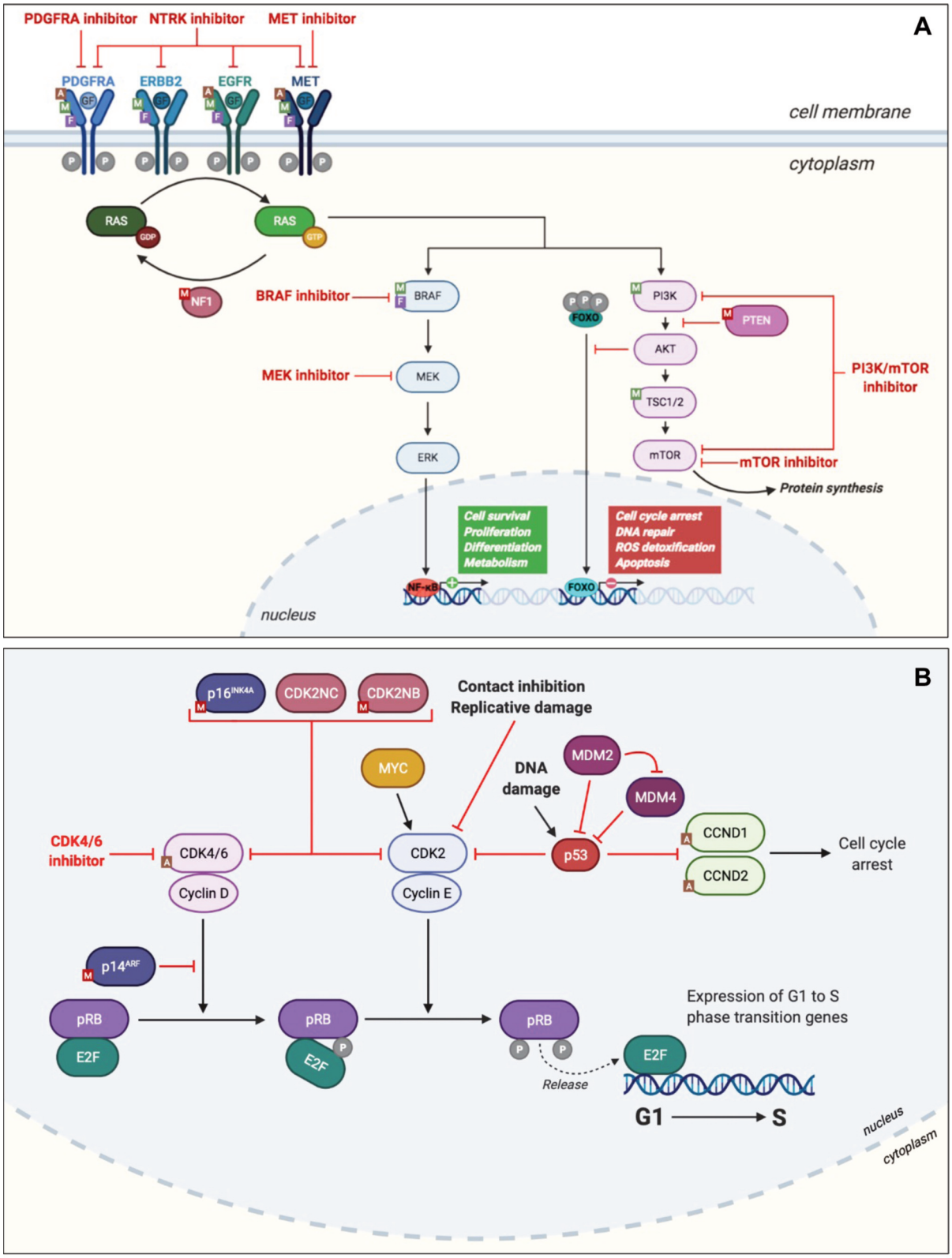

Figure 2. *Core signalling pathways implicated in paediatric high-grade glioma depicting the types of mutations affecting different signalling components and associated targeted therapy inhibitors. (A) Constitutively activated receptor tyrosine kinase (RTK), RAS-activated MAPK/ERK and PI3K/AKT/mTOR signalling pathways; (B) p53-regulated retinoblastoma (RB) signalling pathway. Figure 2A adapted with permission from Mueller et al., 2020 (42).*

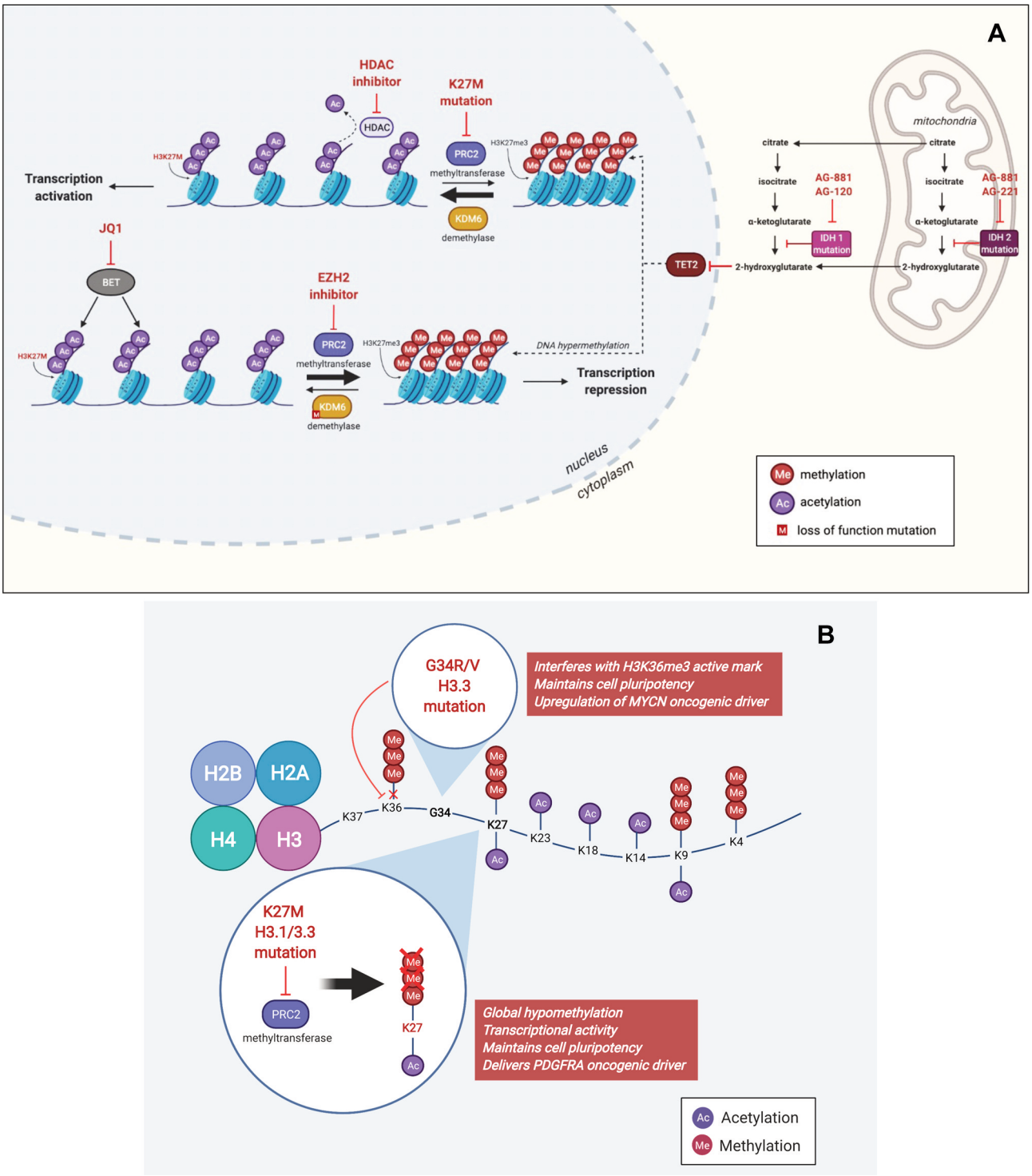

Figure 3. *Epigenetic modifications in paediatric high-grade glioma with associated targeted therapy inhibitors: (A) H3K27M mutations depress the function of the histone methyltransferase (HMT) complex polycomb repressive complex 2 (PRC2) resulting in preferential KDM6-mediated histone demethylation and transcriptional activation which can be countered with HDAC inhibitors. Loss of function mutations on KDM6 result in preferential PRC2-mediated histone methylation and transcriptional repression which can be countered with EZH2 inhibitors or BET inhibitors. IDH1/2 mutations result in DNA hypermethylation via TET2 inhibition from the oncometabolite 2-hydroxyglutarate which can be countered by IDH1 and IDH2 inhibitors; (B) G34R/V H3.3 and K27M H3.1/3.3 mutations maintain transcriptional activity and upregulate oncogenic drivers by interfering with the H3K36me3 active mark and reducing H3K27 global trimethylation, respectively. Figure 3A adapted with permission from Mueller et al., 2020 (42) and Long et al., 2017 (195).*

paediatric non-brainstem HGGs (pNBS-HGGs), midline GBM, and DIPG (thalamus, cerebellar vermis, brainstem, and spine) (23, 72, 76). Moreover, the specific mutation frequency and amino acid substitutions at histone H3 differ between DIPG and pNBS-HGG (25). In DIPGs, H3 mutations are observed in 78% of cases, where 60% of mutations are in *H3F3A* and 11-31% are in *HIST1H3B*. Conversely, in pNBS-HGG only 35% exhibit H3 mutations, where *H3F3A* and *HIST1H3B* K27M substitutions account for 19% and 3% of cases respectively, while 14% are somatic mutations in *H3F3A* leading to G34R substitution which is not observed in DIPG (72).

During malignant transformation, dysregulation of the histone modification machinery affects the recruitment of transcription factors and therefore patterns of gene expression. Histone H3 mutations were shown to be of particular significance as they rewire the epigenome to maintain cell pluripotency and deliver oncogenic drivers such as PDGFRA and MYCN in K27M and G34R/V respectively (77, 78). The H3K27M mutation results in a reduction of the global H3K27 trimethylation (H3K27me3) by depressing the function of the histone methyltransferase (HMT) complex polycomb repressive complex 2 (PRC2) (42) (Figure 3). H3K27me3 is associated with transcriptional silencing and chromatin condensation, inhibiting the expression of genes that oppose normal development and differentiation (79). Hence, H3K27 hypomethylation leads to transcriptional activity at these loci (80). A recent systematic review and meta-analysis totalling 474 pHGG patients across 6 studies concluded that the presence of H3K27M mutation was independently and significantly associated with a worse prognosis (HR 3.630, $p<0.001$) and shorter overall survival (2.3 years; $p=0.008$) compared to their counterparts without the mutation (81). Targeting H3K27 through lysine-specific demethylase 1 (LSD1) inhibition *via* catalytic inhibitors has been shown to exhibit selective cytotoxicity and promote an immune gene signature that increases NK cell killing *in vitro* and *in vivo*, representing a therapeutic opportunity for pHGG (82). Conversely, G34R/V does not lead to global hypomethylation of H3K27M but instead interferes with the regulation of H3K36me3 which is an activating mark for gene expression (77, 83). Alternatively, downregulation of the H3K36me3 active mark may occur through mutation of the H3K36 trimethyl-transferase SET domain containing 2 (*SETD2*) which occurs in a mutually exclusive pattern with *H3F3A* G34R/V mutations (84). *SETD2* loss-of-function mutations are present in 15% of pHGG and 8% of aHGG and is exclusively found in cerebral tumours (84). H3K36me3 depletion following *SETD2* downregulation leads to an increased spontaneous mutation frequency and chromosomal depletion (85).

Novel data science and network reconstruction techniques have enabled the identification and delineation of transcriptional networks that reprogram high-grade glioma behaviour patterns. These transcriptional regulatory networks act as enhances and regulators of oncogenes and oncohistone variants observed in paediatric glioma (*i.e.*, K27M and G34 V/R) (86). Moreover, three-dimensional genomic structural variations have the potential to hijack transcriptional enhancers and gene co-amplification contributing to the epigenetic landscape and contributing to tumorigenesis in pHGG (87). The cellular context also interacts with genetics, as oligodendrocyte precursor cells have been shown to exhibit greater tumorigenic potential to more differentiated malignant cell counterparts, partly due to sustained by PDGFRA signalling. This signifies potential candidate therapeutic targets (88).

ATRX/DAXX. Mutations affecting the chromatin remodelling histone chaperone complex ATRX/DAXX, responsible for H3.3 incorporation into telomeres, pericentric heterochromatin and actively transcribed regions (89, 90), have also been associated with paediatric gliomagenesis (91). *ATRX/DAXX* mutations were identified in 31% of pGBM samples, and in 100% of tumours harbouring *G34R/V H3.3* mutations suggesting a synergy between the two mutations (23), which are thought to be key in a subgroup of very young patients with HGG (22). There is also an association of *H3.3* and or *ATRX* mutation with *TP53* mutations (23). ATRX and DAXX loss is strongly associated with alternative lengthening of telomeres (ALT), particularly in concurrent *ATRX*, *H3F3A* and *TP53* mutations (92). ALT is a telomerase-independent telomere maintenance mechanism which enhances telomere lengthening leading to uncontrolled cellular proliferation. ALT is a common phenotype in pGBM and it typically presents with hypomethylation (23, 75).

Other epigenetic regulators. Recurrent mutations in other histone writers and erasers and in chromatin-remodelling genes including MLL, KDM5C, KDM3A and JMJD1C have also been reported (24). These often co-occur with H3 mutations as observed in 91% of DIPG and 48% of hemispheric HGG (24).

Other genetic signatures.

Recurrent methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter has been observed in pHGG with studies indicating a 30% recurrence in pHGG overall (53) and 40-50% recurrence in paediatric GBM (54, 55). MGMT promoter methylation is more frequent in adult GBM (45%) compared to pHGG (16-50%) (93). Mutations in IDH, which encodes for isocitrate dehydrogenase, are common in aHGG and almost entirely absent in pHGG (5%) (75, 94). Most IDH mutations occur in adolescents >14 years with one study showing 35% recurrence (52). Despite their overall rarity in pHGG, IDH mutations are present in a subset of paediatric patients suggesting a biological similarity of this

Table III. *Late term adverse effects of treatment regimens for paediatric high-grade glioma. Information collated from Roddy and Mueller, 2016 (190).*

	Late term effects
Neurocognitive	- Mild to severe deficits in academic functioning and language ability 90. - Associated 15-25 IQ point decline; may be more severe in younger children (196). - Radiotherapy induces neuronal cell apoptosis leading to microvascular injury preventing brain development (197).
Sensory	- Peripheral neuropathy. - Ototoxicity, especially with alkylating agents. More severe in <5 years old (198).
Endocrine	- Growth hormone defect reported in up to 97% of survivors (199). - Radiotherapy causes thyroid hormone dysfunction in up to 60% of survivors (200). - Future fertility problems and delayed puberty (201) due to follicular destruction associated with many chemotherapy and radiotherapy regimens (202).
Vascular	- Moyamoya vasculopathy[a] more prevalent in survivors (203). - Cavernous malformations and cerebral microhaemorrhages also more common (204). - 30-fold increased risk of stroke (205).
Psychosocial deficits	- Psychological distress and high rates of depression of up to 16% more than compared to controlled siblings (206). - Lower future life satisfaction and quality of life (207, 208). - Reduced employment due to intellectual and physical impairment (209). - Reduced income compared to control siblings free of disease (210). - Poorer social skills compared to control siblings (207, 208). - Reduced rate of marriage (210) and fewer friends reported in survivors (211).
Secondary cancers	- Prone to primary thyroid carcinomas (papillary carcinoma) (212). - Prone to breast cancers (213). - Prone to secondary brain cancers (213).

[a]Disorder in which the carotid artery is progressively narrowed restricting blood flow to the brain.

subgroup with aHGG (42, 94, 95). In adult tumours, IDH mutations are associated with better prognosis (96). Normally, IDH1/2 enzymes convert isocitrate to α-ketoglutarate in the citric acid cycle. IDH mutations result in neomorphic enzymes that convert α-ketoglutarate to the oncometabolite 2-hydroxyglutarate which competitively inhibits the function of TET enzymes responsible for DNA demethylation and transcriptional activation (97). TET inhibition is associated with carcinogenesis across malignancies (97, 98). ACVR1 (ALK2) which encodes a receptor serine threonine kinase that mediates signal transduction for bone morphogenic protein (BMP), is mutated in 20-32% of DIPGs and frequently co-occurs with H3.1 K27M substitutions (44-46). Similarly to H3K27M, ACVR1 mutations are only observed in brainstem pHGGs and in DIPG patients of younger age, thus delineating DIPG subgroups (25). Lastly, homozygous loss at 8p12 leading to loss of ADAM3A confirmed by quantitative real-time PCR (qPCR) was observed in 16% of pHGGs including one DIPG patient making it the most commonly deleted gene in one study (28).

Conventional Treatment Strategies and Long-Term Side Effects

Surgery. Initial treatment for pHGG is surgery aiming at maximal safe surgical resection as the amount of resection correlates to prognosis (99). Gross-total resection (GTR) is of paramount importance as it offers the only chance for significant survival benefit in patients. Subtotal resection increases mortality by 50-100%, while the difference in survival can reach up to 35 months (100). Yet, even when complete radiographic GTR is achieved, some cancerous cells may still remain due to the infiltrative nature of the disease as it is practically impossible to achieve clear margin GTR without significant morbidity or morality (10, 15). Therefore, adjuvant therapy is offered to reduce chances of local recurrence.

Radiotherapy. Focal radiation therapy within tumour margins has become the mainstay adjuvant therapy for children >3 years old (50, 59), while younger children are treated with a radiation-sparring approach using sole chemotherapy to prevent radiotherapy-induced sequelae (101). Neurocognitive problems, endocrinopathy, vasculopathy with stroke, psychosocial issues and secondary malignancies are common long term adverse effects of radiation (Table III) (102-106). The standard dose of radiation for pHGG is 50-60Gy focal radiation which is delivered in 180-200cGy daily dose fractions over 6 weeks (107). Hyper-and hypo-fractionation has not shown consistent benefit for pHGG (107). Still, hypo-fractionation is being investigated for recurrent DIPG (108).

Re-irradiation in the setting of recurrent disease has typically been avoided due to dose-dependent radiotoxicities (41, 109)

though this is changing as recent studies demonstrate superior median survival times from re-irradiation which was well-tolerated in pHGG (110); re-irradiation is currently being trialled for progressive or recurrent DIPG (111). Studies are investigating combination of immunotherapies such as PD-1 immune checkpoint inhibitors with re-irradiation (112). Combination immunotherapy with radiation is set to replace standard chemoradiotherapy protocols in other solid tumours (113). Radiotherapy can modulate the immune system and mount an immune response causing immunogenic cell death by enhancing tumour antigen retrieval (114). Radiotherapy can initiate innate and adaptive immunity by conferring pro-immunogenic effects in the tumour microenvironment (115, 116).

Chemotherapy. Temozolomide (TMZ) is the standard chemotherapeutic treatment offered for aHGGs as it increases 2-year survival rates from 10.4% to 26.5% when combined with radiation (117). Even though multimodality therapy with radiation and TMZ offers minimal survival benefit in children (93, 118), TMZ is still typically used in current clinical practice for newly diagnosed pHGG not enrolled in clinical trial due to tolerability and ease of administration (15). TMZ works as a DNA alkylating agent, eventually leading to single-stranded and double-stranded DNA breaks to induce cell cycle arrest at G2/M and apoptosis. It achieves this by methylating DNA at the N-7 or O-6 positions of guanine residues (119). TMZ is well-tolerated with minor toxicities including grade I thrombocytopenia, neutropenia, or nausea even with long-term therapy extending to 85 cycles (120). Although alkylating agents are known to increase secondary cancer risk, particularly acute myeloid leukaemia, there is no evidence to support such risks with TMZ (121). However, long-term effects of TMZ have not been studied in children yet.

Precision Medicine and Novel Treatments

There is a clear need to optimise the therapeutic management of pHGG to improve survival, reduce recurrence rates, but also minimize long-term adverse effects associated with conventional aggressive treatments. Several clinical trials are underway to investigate new molecular targeted therapies (Table IV), but also chemoradiation sensitization strategies, and immunotherapies.

MGMT promoter methylation as a biomarker for TMZ treatment response. TMZ resistance is mediated *via* the DNA repair gene *MGMT*. MGMT removes methyl adducts from the O6-guanine position of damaged DNA, thus, reversing the DNA damage induced by the action of TMZ. Hence, high levels of MGMT indicate resistance to TMZ. In contrast, in a subset of patients with *MGMT* promoter methylation, resulting in transcriptional silencing of the gene, the efficiency of DNA repair was reduced and response to TMZ treatment was significantly higher (13.7 months with methylated *MGMT* promoter *vs*. 2.7 months without) (122). Therefore, *MGMT* promoter methylation is a predictive biomarker for good TMZ response and can aid in treatment stratification (123).

NTRK, EGFR, FGRF and MET inhibitors. NTRK inhibitors currently being trialled for pHGG include larotrectinib) (124-127) and entrectinib (NCT02650401) which also targets ALK, ROS1. RTK inhibitors targeting VEGF, ALK, WEE1, BCR-ABL and RET are also being investigated as monotherapy and as combination therapies in phase I/II trials for pHGG (Table IV).

EGFR overexpression in glioma is associated with greater tumour invasion and tumour cells resistance to treatment (128-130). In aHGG, studies of EGFR inhibition using novel third generation drugs such as osimertinib (AZD9291) have demonstrated effectiveness in overcoming resistance and mediating tumour regression (131). For pHGG, ongoing phase II trials are investigating the use of drugs such as nimotuzumab (NCT03620032, NCT04532229, NCT00561873, NCT00600054), erlotinib (NCT00418327) and cetuximab (NCT01884740) individually and in combination with mTOR inhibitors (NCT02233049). The limitation observed with EGFR inhibition is high recurrence rates due to acquired tumour resistance tumour (132). However, combination therapy, especially with PI3K inhibitors, has been shown to improve treatment response in pHGG patients (133, 134). The efficacy of FGFR inhibitors is being investigated in phase II trials for advanced solid tumours and recurrent/progressive pHGG using erdafitinib (NCT03210714) and cabozantinib (NCT02885324), respectively.

MET signalling and high levels of c-MET are associated with poor prognosis in GBM patients (135), thereby rendering it a potential therapeutic target. A phase I trial is investigating volitinib monotherapy in patients with recurrent/refractory primary CNS tumours including pHGG (NCT03598244). Volitinib has previously demonstrated preclinical efficacy in rodents with *MET*-amplified GBM (136).

BRAF and MEK inhibitors (MAPK pathway). BRAF and MAPK inhibitors are promising potential treatments for pHGG tumours displaying $BRAF^{V600E}$ mutations having shown remarkable efficacy in melanoma patients with the same mutation. One case report demonstrated complete response in a 12-years old child treated with vemurafenib for $BRAF^{V600E}$ positive GBM (137). Other reports show benefit in $BRAF^{V600E}$ positive pHGG from the MEK inhibitor trametinib and $BRAF^{V600E}$-specific inhibitors dabrafenib and vemurafenib (52, 138). Studies are investigating $BRAF^{V600E}$ and MEK inhibition with dabrafenib and trametinib in a subset of HGG (NCT03975829, NCT04201457) and in combination with

radiotherapy (NCT03919071). In pLGGs, BRAF inhibition is promising with 40% objective response rate and prolonged stable disease with a relatively well-tolerated side effect profile (139-142). Yet, similarly to adults, resistance rates to BRAF inhibitors are higher in the pHGGs compared to pLGGs given that concurrent mutations such as in *CDKN2A/B* and *ATRX* are more often (53). Paradoxical tumour hyper-progression observed in LGG treated with the unselective BRAF inhibitor sorafenib highlights the importance of careful consideration of the molecular targets of such agents in clinical trial setting (143, 144). Combination of MEK and BRAF inhibitors reduces squamous cell carcinoma risk observed with BRAF monotherapy in adult melanoma patients and improves survival and response rates (144, 145).

PI3K/mTOR inhibitors. In August 2020, the brain-penetrant PI3K/mTOR inhibitor paxalisib (GDC-0084) was granted rare paediatric disease FDA-designation approval for DIPG based on significantly improved survival benefit observed in a phase II trial of patients with newly-diagnosed GBM with unmethylated O6-MGMT promoter status who had completed initial radiation with concomitant TMZ (146). A first-in-paediatric phase I study is underway to investigate the safety and preliminary antitumor action of paxalisib in DIPG and DMG (NCT03696355). Additionally, the dual PI3K and mTOR inhibitor LY3023414 is undergoing phase II trial in advanced solid tumours including pHGG (NCT03213678). Combination of PI3K/mTOR inhibitors with dasatinib, an oral inhibitor against *BCR-ABL* and *Src*-family tyrosine kinases, is undergoing phase II investigation in *PDGFRA*-mutated tumours (NCT03352427). Recent *in vitro* studies suggest that dual EGFR and PI3K inhibition with or without HDAC inhibition is a viable therapeutic option for adult and paediatric HGG warranting further investigation *in vivo* (133, 147). PI3K/mTOR inhibitors also represent an attractive therapeutic target for *IDH*-mutant gliomas as they repress the oncometabolite 2-hydroxyglutarate, the levels of which may serve as a response-prediction biomarker (148).

CDK4/6 inhibitors. Clinically, CDK4/6 inhibitors function by inhibiting the CDK4/6-dependent phosphorylation of the RB1 protein (NCT02255461) (54, 149). The dependent interaction of CDK4/6 inhibitors with RB1, means the patient's *RB1* status must be screened prior to therapy (144). Murine DIPG models have demonstrated a significant survival benefit from cyclin/CDK complex inhibition using a highly selective non-ATP competitive inhibitor of CDK4/6, namely PD-0332991 (54). Yet, clinical data from CDK4/6 inhibitor monotherapy has not been promising (146, 150). Combination of CDK4/6 inhibitors with mTOR and MEK inhibitors (56), radiotherapy, or chemotherapeutics are potentially viable options (146, 151, 152) and are being investigated in clinical trials (NCT03709680, NCT03355794, NCT03434262) following superior pre-clinical results compared to CDK4/6 inhibitor monotherapy (151, 152). Ensuring sufficient blood-brain-barrier penetrance is paramount when investigating CDK4/6 agents with the different agents demonstrating different brain-penetrance (152, 153). In the case of ribociclib, co-administration of the ABCB1 inhibitor elacridar dramatically improves brain penetrance (154).

HDAC inhibitors. Histone deacetylase inhibitors (HDACi) have shown promising therapeutic potential in many malignancies and have been investigated in HGG due to the high frequency of *K27M* and *G34R/V* mutations. HDACis prevent the condensation of chromatin and genetic silencing caused by histone tail deacetylation (Figure 3A). Phase I and II trials have investigated the efficacy of HDAC inhibitors vorinostat, panobinostat, romidepsin and valproic acid for paediatric and adult HGG (155). However, results from HDACi monotherapy appear disappointing. Combination therapy may improve prognosis, though further research is necessary. Ongoing trials are investigating the combination of PI3K and HDACi in a single drug agent (fimepinostat, CUDC-907) in pHGG (NCT02909777, NCT03893487). Encouraging preliminary results were reported in a phase I study of MTX110, a water-soluble form of panobinostat, which allows for convection-enhanced delivery (CED) at potentially chemotherapeutic doses directly to the tumour site *via* catheter system (CED or fourth ventricle infusion) thereby bypassing the blood-brain barrier (NCT03566199).

DRD2/ClpP (ONC201). ONC201, a small molecule inhibitor, crosses the blood-brain barrier and directly antagonises the dopamine receptors D2 (DRD2) and D3 (156). ONC201 also activates the mitochondrial caseinolytic protease P (ClpP) protein which is dysregulated in cancer (157, 158). Both DRD2 antagonism and ClpP activation from ONC201 result in ATF4 and CHOP transcription factor-mediated upregulation of the pro-apoptotic TRAIL receptor DR5 which induces cancer cell death (42, 156). Anecdotal clinical evidence suggests that ONC201 mediates significant tumour regression in young adults and children with *H3K27M*-mutated HGGs (159, 160) which is supported by pre-clinical data (161). A phase II trial is underway to investigate ONC201 in paediatric *H3K27M*-positive gliomas (NCT03416530).

Interestingly, mitochondrial DNA copy number depletion has been associated with cancers including pHGG and is postulated to underlie the molecular basis for the Warburg effect (162). Shifting glucose metabolism to mitochondrial oxidation with kinase modulators significantly inhibits pHGG viability, and pairing this therapeutic strategy with metformin to simultaneously target mitochondrial function was shown to disrupt energy homeostasis of tumour cells, increasing DNA damage and apoptosis (162).

Table IV. *Active clinical trials investigating novel targeted molecular therapies for paediatric high-grade gliomas.*

Molecular target	Drug	Disease	Upfront/recurrent	Trial	Phase
NTRK	Larotrectinib	Solid tumours (incl. CNS)	Recurrent	NCT03213704	2
	Larotrectinib	Solid tumours (incl. CNS)	Recurrent	NCT02637687	1/2
	Larotrectinib	Solid tumours (incl. CNS)	Recurrent	NCT02576431	2
	Entrectinib	Solid tumours (incl. CNS)	Recurrent	NCT02650401	1/2
	Larotrectinib	HGG	Recurrent	NCT04655404	1
EGFR	Nimotuzumab	DIPG	Upfront	NCT03620032	2
	Nimotuzumab	DIPG	Upfront	NCT04532229	2
	Nimotuzumab	HGG	Recurrent	NCT00561873	2
	Erlotinib, everolimus dasatinib	DIPG	Upfront	NCT02233049	2
	Cetuximab + bevacizumab	GBM, DIPG (CNS)	Recurrent	NCT01884740	1/2
	Erlotinib	CNS tumours (incl. HGG)	Recurrent	NCT00418327	1
	Nimotuzumab	DIPG	Recurrent	NCT00600054	2
FGFR	Erdafitinib	Solid tumours (incl. CNS)	Upfront/recurrent	NCT03210714	2
	Cabozantinib	GBM, HGG	Upfront	NCT02885324	2
c-MET	Volitinib	CNS tumours (incl. DIPG, HGG)	Recurrent	NCT03598244	1
VEGF	Bevacizumab	DIPG	Upfront	NCT04250064	2
	Bevacizumab	HGG, DIPG	Upfront	NCT00890786	1
	Valproic acid + bevacizumab	CNS tumours (incl. HGG, GBM)	Upfront	NCT00879437	2
	Apatinib	HGG	Recurrent	NCT02848794	1/2
ALK	Ensartinib	Solid tumours (incl. HGG)	Recurrent	NCT03213652	2
Tyrosine kinase WEE1 (SETD2 deficient tumours)	Adavosertib + radiotherapy	DIPG	Upfront	NCT01922076	1
BRAF	Vemurafinib	Glioma (BRAF-mut)	Recurrent	NCT01748149	1
	Vemurafinib	Advanced solid tumours (HGG)	Recurrent	NCT03220035	2
	Dabrafenib + trametinib + hydroxychloroquine	LGG (BRAF-mut), HGG (BRAF-mut)	Upfront	NCT04201457	1/2
	PLX8394	Solid tumour (BRAF-mut)	Recurrent	NCT02428712	1/2
BRAF/MEK	Dabrafenib + trametinib	LGG (BRAF-mut)/ HGG	Upfront/recurrent	NCT02684058	2
	Dabrafenib + trametinib	CNS tumours (incl. GBM)	Upfront/recurrent	NCT03975829	4
	Dabrafenib + trametinib + radiotherapy	CNS tumours (incl. HGG)	Upfront	NCT03919071	2
PI3K/mTOR	LY3023414	Solid tumours (incl. CNS)	Recurrent	NCT03213678	2
	Temsirolimus	DIPG	Upfront	NCT02420613	1
	Paxalisib (GDC-0084)	CNS tumours (incl. DIPG, DMG, GBM)	Upfront	NCT03696355	1
BCR-ABL + mTOR	Dasatinib + everolimus	HGG/LGG/DIPG (PDGFR)	Upfront/recurrent	NCT03352427	2
RET + BCR-ABL	Vandetanib, dasatinib	DIPG	Upfront	NCT00996723	1
CDK4/6	Palbociclib-isethionate	CNS tumours	Recurrent	NCT02255461	1
	Abemaciclib	HGG	Recurrent	NCT02644460	1
	Ribociclib	CNS tumours	Recurrent	NCT03434262	1
	Palbociclib, irinotecan, temozolomide	Solid tumours, DIPG	Upfront	NCT03709680	1
	Palbociclib	Solid tumours, HGG	Upfront/recurrent	NCT03526250	2
	Abemaciclib	CNS tumours	Recurrent	NCT04238819	1
	Ribociclib	DIPG, HGG, CNS tumours	Upfront	NCT03355794	1
HDAC	Panobinostat	DIPG	Recurrent	NCT02717455	1
	MTX110	DIPG, DMG, thalamic gliomas	Upfront	NCT04264143	1
	MTX110	Medulloblastoma	Recurrent	NCT04315064	1
	MTX110	DIPG	Upfront	NCT03566199	1/2
HDAC + PI3K	Fimepinostat (CUDC-907)	Solid tumours (incl. CNS)	Recurrent	NCT02909777	1
	Fimepinostat (CUDC-907)	DIPG, HGG, medulloblastoma	Recurrent/upfront	NCT03893487	1
DRD2/ClpP	ONC201	HGG (H3K27M)	Recurrent/upfront	NCT03416530	1
	ONC201	GBM, HGG	Recurrent	NCT02525692	2
	ONC201	HGG, DIPG	Upfront	NCT03134131	NA
IDH	Ivosidenib	Solid tumours (incl. CNS)	Recurrent	NCT04195555	2

Table IV. *Continued*

Table IV. *Continued*

Molecular target	Drug	Disease	Upfront/recurrent	Trial	Phase
PARP	BGB-290	LGG/HGG (IDH-mut)	Recurrent/upfront	NCT03749187	1
	Olaparib	Solid tumours (incl. HGG)	Upfront/recurrent	NCT03233204	2
	Veliparib + temozolomide	HGG, GBM	Recurrent	NCT03581292	2
UPS + HDAC	Marizomib (MRZ) + panobinostat	DIPG	Recurrent	NCT04341311	1
ADAM10	INCB7839	GBM, DIPG	Recurrent	NCT04295759	1
IDO	Indoximod	DIPG, GBM, ependymoma	Upfront	NCT04049669	2
SINE	Selinexor	Solid tumours (incl. HGG, GBM)	Recurrent	NCT02323880	1
EZH2	Tazemetostat	CNS tumours	Recurrent	NCT03155620	2
	Tazemetostat	Solid tumours (HGG)	Recurrent	NCT03213665	2
BET proteins	BMS-986158	Solid tumours (incl. CNS)	Recurrent	NCT03936465	1
PKC	2-hydroxyoleic acid				
	Solid tumours, HGG	Recurrent	NCT04299191	1/2	
PD-1	Cemiplimab	CNS tumours (incl. HGG)	Upfront/recurrent	NCT03690869	1
	Nivolumab	DIPG, DMG (H3K27M)	Recurrent	NCT02960230	2
BMI 1 + EZH2	PTC596	DIPG, HGG	Upfront	NCT03605550	1
Antineoplaston	Atengenal, astugenal	DIPG	Upfront	NCT02742883	2
αvβ3 integrin	Cilengitide	DIPG	Recurrent	NCT01165333	1
FTI	Tipifarnib	CNS tumours (incl. HGG)	Recurrent	NCT00070525	2

NTRK, Neurotrophic tyrosine receptor kinase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; c-MET, mesenchymal epithelial transition factor; VEGF, vascular endothelial growth factor; ALK, anaplastic lymphoma kinase; WEE1, nuclear serine/threonine-protein kinase associated with western equine encephalitis; SETD2, SET domain containing 2; BRAF, serine/threonine-protein kinase B-Raf; MEK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; mTOR, mechanistic target of rapamycin; BCR-ABL, breakpoint cluster region protein-abelson murine leukemia viral oncogene homolog 1; RET, rearranged during transfection proto-oncogene; CDK, cyclin-dependant kinases; HDAC, histone deacetylase; DRD2, dopamine receptor D2; ClpP, caseinolytic protease proteolytic subunit;IDH, isocitrate dehydrogenase; PARP, poly-ADP ribose polymerase; UPS, ubiquitin/proteasome system; ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; IDO, indoleamine 2,3-dioxygenase; SINE, short interspersed nuclear element; EZH2, enhancer of zeste homolog 2; BET, bromodomain and extraterminal domain; PKC, protein kinase C; PD-1, programmed cell death protein 1; BMI 1, B cell-specific moloney murine leukaemia virus integration site 1; FTI, farnesyltransferase inhibitor; CNS, central nervous system; HGG, high-grade glioma; GBM, glioblastoma multiforme; DIPG, diffuse intrinsic pontine glioma; DMG, diffuse midline glioma; LGG, low-grade glioma.

IDH inhibitors and PARP inhibitors. IDH inhibitors induce a dose-dependent reduction of the oncometabolite 2-hydroxyglutarate and partially reverse histone modification and DNA hypermethylation inhibiting tumour growth *in vivo* and *in vitro* (163). Ivosidenib (AG-120) and enasidenib (AG-221), two reversible selective inhibitors of *IDH1*- and *IDH2*-mutant enzymes, respectively, have received FDA-approval for acute myeloid leukaemia (AML). Early phase trials demonstrate an acceptable safety profile from IDH1/2 inhibitors in advanced solid tumours including glioma, however, further research is necessary to evaluate efficacy (164, 165).

IDH mutations inhibit DNA double-strand break repair by homologous recombination. Hence, inhibiting the alternative method of repair [base-excision repair (BER)] *via* poly ADP-ribose polymerase (PARP) inhibitors is an effective strategy to mediate synthetic lethality of *IDH*-mutant cancer cells (166). BER also reverses DNA-alkylation damage from TMZ, thus the addition of PARP inhibitors to TMZ may increase efficacy compared to TMZ alone (41). BGB-290, a PARP inhibitor which can penetrate the blood-brain barrier, is being investigated in combination with TMZ for *IDH*-mutant glioma (NCT03749187). In a phase I study, the PARP inhibitor olaparib reliably penetrated recurrent GBM at radiosensitizing concentrations (167). A phase II study of olaparib in advanced solid tumours including pHGG is underway (NCT03233204). Veliparib is also being investigating in combination with TMZ (NCT03581292).

UPS proteasome inhibitors. The ubiquitin-proteasome system (UPS) maintains cellular homeostasis by regulating intracellular protein degradation through polyubiquitination and subsequent degradation of the ubiquitin-tagged target (168). Proteosome inhibitors act on this pathway, preferentially inducing programmed cell death in transformed malignant cells (168). Marizomib is being tested for the first time in children in a phase I trial for paediatric DIPG, individually, and in combination with the HDACi panobinostat (NCT04341311). In adults, following successful assessment in phase I trials for newly diagnosed and recurrent GBM, marizomib is being investigated in phase III trial in combination with standard TMZ-based radiochemotherapy (NCT03345095).

ADAM10/17 inhibitors. Currently, 22 different ADAMs (a disintegrin and metalloproteases) have been identified with functions of adhesion, sperm-egg fusion, angiogenesis, migration, cell survival, degradation, and proliferation (169, 170). ADAM10/17 overexpression is observed in cancer cell lines while deficiency decreases growth (170). INCB7839, a novel, orally available, potent and selective inhibitor of ADAM10 and 17 proteases designed to block EGFR pathway activation, has been evaluated in phase I and II trials for previously treated solid tumours, with promising results especially in breast cancer (171). However, the dose-limiting toxicity of INCB7839 monotherapy was deep venous thrombosis. A phase I study is investigating INCB7839 in children with recurrent/progressive HGGs (NCT04295759).

IDO inhibitors. Indoleamine 2,3-dioxygenase (IDO) acts as an immune checkpoint preventing autoimmunity. In cancer, increased IDO levels enable tumour immune escape. IDO-inhibition reinstates cancer immune surveillance (172). In a preclinical GBM model, the addition of IDO-blocking drugs to TMZ and radiotherapy enhanced survival due to a tumour-directed inflammatory response (173). In a phase I trial, the combination of the IDO inhibitor Indoximod with radiation and chemotherapy in upfront paediatric DIPG was tolerable and offered prolonged survival to historical controls (174). Hence, a phase II trial is underway (NCT04049669). IDO inhibition in combination with radiotherapy, immunotherapy, and immunogenic chemotherapies was serve as an important adjunct in turning immunogenically 'cold' tumours into 'hot' (175). The importance of tumour immune profiling in pHGG to characterise treatment responsiveness and further enhance therapeutic decision-making has been highlighted in phase II trials (176).

Selective inhibitors of nuclear export (SINE) and XPO1. XPO1 (exportin 1) mediates nuclear export of cellular proteins during interphase (177). Overexpression is associated with poor prognosis across cancers including gliomas (178). Selective inhibitors of nuclear export (SINE), such as Selinexor, inhibit XPO1 and have demonstrated safety and broad antitumour efficacy in a phase I study in adults with advanced solid tumours including GBM (179). Selinexor is being investigated in phase I trial in children and young adults with recurrent or refractory solid tumours or HGGs (NCT02323880).

Conclusion

Paediatric HGG is a highly heterogeneous disease characterised by distinct molecular signatures which may be used for diagnostics, clinical characterisation, and treatment optimisation. Despite advances in targeted molecular therapies, pHGG features poor outcomes. Future clinical trials of pHGG will stratify patients into subgroups according to their molecular characteristics through biomarker identification. Numerous clinical trials are underway to investigate novel targeted therapeutic agents. Combination therapies may offer clinical benefit and require further systematic investigation.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

Conceptualization: K.S.R.; Reviewing the literature: K.S.R.; Drafting the article: K.S.R, A.M.G.; Figure and table illustrations: K.S.R, A.M.G., A.M.W., C.M.B., B.C.; Revising the article: K.S.R., A.M.G., A.M.W., C.M.B., B.C., J.G.H., M.S.; Supervising the work: J.G.H., M.S.; Final approval of the version to be published: K.S.R., A.M.G., A.M.W., C.M.B., B.C., J.G.H., M.S.

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