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Pediatric neuro-oncology: Highlights of the last quarter-century

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ABSTRACT

The last quarter century has heralded dramatic changes in the field of pediatric neuro-oncology, with the era defined by profound developments in the understanding of the biological underpinnings of childhood central nervous system (CNS) tumors and translational therapeutics. Although there have been momentous strides forward in biologic, diagnostic, therapeutic, and experimental domains, considerable challenges remain and CNS tumors remain the leading cause of pediatric cancer-related mortality. Here, we review the significant advances in the field of pediatric neuro-oncology over the last 25 years and highlight ongoing hurdles facing future progress.

Introduction

The last 25 years in pediatric neuro-oncology have been transformative, marked by significant advancements in the understanding of brain tumor biology, the development of novel therapies, and collaborative research efforts. Herein, we attempt to summarize the key discoveries and developments that have defined this era and highlight the ongoing challenges for the field (Fig. 1).

Epidemiology of pediatric CNS tumors

Central nervous system (CNS) tumors are the most common pediatric solid tumor and second most common pediatric malignancy overall [1]. With an incidence rate of 6.23 per 100,000, over 5000 cases of pediatric CNS tumors are diagnosed in the United States each year [1]. The incidence of pediatric CNS tumors is increasing overall, likely related in part to improvements in diagnostic imaging techniques and detection of otherwise asymptomatic lesions [1]. Whilst childhood cancer mortality has significantly decreased over the last 50 years, this is in large part driven by dramatic improvements in leukemia outcomes [1]. Conversely, mortality rates from pediatric CNS tumors have remained static since 2007 and consequently, CNS tumors are now the leading cause of childhood cancer-related death [1]. Globally, the majority of children presenting with CNS tumors each year live in low- and middle-income countries (LMICs) and the data on true incidence and mortality in these settings is limited [2].

Abbreviations: **BBB**, Blood brain barrier; **CAR**, Chimeric antigen receptor; **CED**, Convection enhanced delivery; **CNS**, Central nervous system; **DIPG**, Diffuse intrinsic pontine glioma; **DTI**, Diffusion tensor imaging; **DMG**, Diffuse midline glioma; **FUS**, Focused ultra-sound; **HGG**, High grade glioma; **HIC**, High income country; **LMIC**, Low-middle income country; **MAPK**, Mitogen-activated protein kinase; **MRI**, Magnetic resonance imaging; **ORR**, Overall response rate; **PET**, Positron emission tomography; **PFS**, Progression-free survival; **pLGG**, Pediatric low-grade glioma; **PRC2**, Polycomb repressive complex 2; **PRT**, Proton radiation therapy; **RAPNO**, Response Assessment in Pediatric Neuro-Oncology; **RRD**, Replication-repair deficiency; **RRD-HGG**, Replication-repair deficient high-grade glioma; **RT**, Radiation therapy; **SEGA**, Subependymal giant cell astrocytoma; **TMB**, Tumor mutational burden; **WHO**, World health organization.

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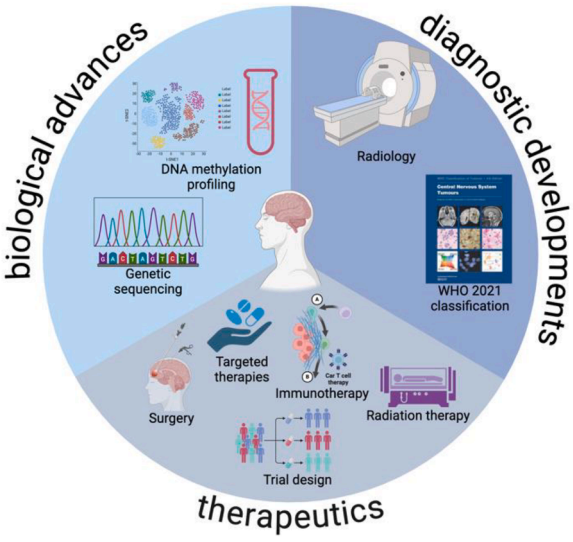

Fig. 1. Key advancements in pediatric neuro-oncology over the last quarter-century. A representative schematic highlighting the major areas of development, including biological, diagnostic and therapeutic advances.

Diagnostic and biologic advances in pediatric brain tumors

WHO 2021 classification

The World Health Organization (WHO) published the first edition of the CNS tumor classification in 1979, and since then has released sequential categorization schemes incorporating evolving clinical, histopathological and immunohistochemical developments to further refine tumor diagnoses.

With the discovery of the molecular drivers of many diseases and the advent of sophisticated diagnostic techniques, the most recent 2021 WHO classification system marks a fundamental shift towards hybrid histopathological-molecular diagnoses, which aim to better delineate and describe disease entities, improving the accuracy of diagnosis and hopefully translating to better prognostication and more informed clinical practice [3,4]. Following this format, twenty-two tumor types were newly defined across the adult and pediatric disease spectra in the WHO 2021 edition (Table 1) [4,5]. Emblematic of the shift toward molecularly-defined entities are the new delineations within the pediatric-type diffuse high-grade glioma category. High-grade midline tumors, previously radiographically defined as Diffuse Intrinsic Pontine Glioma (DIPG), were discovered to be epigenetically driven by histone mutations in landmark genomic discoveries in 2012 [6–8]. This was reflected in the 2016 guideline with the new diagnostic category of H3K27M-*mutant* Diffuse Midline Glioma (DMG), which in the 2021 classification has now expanded as H3K27-*altered* Diffuse Midline Glioma, recognizing tumors lacking the canonical H3 mutations but still exhibiting loss of H3K27-trimethylation (driven instead by alterations in EGFR or EZHIP) and thus a similar mechanism of cell proliferation [3,4]. As well as H3K27-altered DMGs, three further pediatric-type diffuse high-grade glioma subtypes were defined in the 2021 edition; H3G34R-mutant diffuse hemispheric gliomas, H3-wildtype and IDH-wildtype diffuse high-grade gliomas, and infant-type hemispheric gliomas. The latter is now known to harbor distinct driver fusions and exhibit a significantly improved outcome to other pediatric high-grade glioma diagnoses, thus demonstrating the profound clinical and therapeutic implications of hybrid molecular tumor classification [3].

Molecular advances

Genetic sequencing

Advances in genetic sequencing have unveiled the molecular underpinnings of many pediatric brain tumor types over the last two decades. One of the most clinically impactful examples is in the case of pediatric low-grade glioma (pLGG). The most common type of brain tumor in children, pLGG is an umbrella diagnosis for a range of low-grade histologic entities that make up around 30-40 % of all pediatric brain tumors [1]. pLGGs were discovered in several landmark genetic profiling efforts to be almost universally driven by single alterations within the MAPK pathway, such that pediatric low-grade gliomas are now considered a 'single pathway disease' [9–13]. The sentinel discovery of the tandem duplication in the BRAF gene in pilocytic astrocytomas in 2008, identified the fusion of the uncharacterized KIAA1549 protein with the 3′ terminal of the BRAF kinase, causing loss of its inhibitory domain and subsequent constitutive activation [12,13]. Following this, sequential mapping projects went on to describe other recurrent alterations converging on the MAPK pathway; most commonly somatic BRAF or germline NF1 alterations, as well as alterations involving FGFR1/2/3, NTRK2, RAF1, ALK and ROS1, and also non-MAPK alterations (such as MYB and MYBL1) [9–11]. Understanding pLGGs as a single driver disease, and the identification of the pathway involved, has allowed for the development and implementation of effective targeted therapeutics which are now established treatment modalities, (as discussed in further detail below).

In pediatric high-grade gliomas, the defining biologic breakthrough of the last two decades was the discovery of the role of driver histone mutations and epigenetic modification in tumorigenesis. Pioneering sequencing studies demonstrated that DIPGs were driven by recurrent mutations in genes encoding histone 3 variants (namely, H3F3A encoding H3.3, or less frequently HIST1H3B and HIST1H3C encoding H3.1) [6–8]. These mutations lead to a lysine to methionine substitution at critical locations within the histone tail (p.K27M), which are involved in key regulatory post-translational modifications [14,15]. Subsequent work went on to demonstrate the pathogenic effects of these mutations; namely that H3K27M results in suppression of polycomb repressive complex 2 (PRC2) function, leading to global reduction of repressive H3K27 trimethylation (H3K27me3) [14,15]. Several other recurrent mutations (in EGFR and EZHIP) are now known to cause similar PRC2 inhibition and loss of H3K27me3 in a small subset of these tumors (around 4 %), now encompassed within the molecularly defined H3K27-altered Diffuse Midline Glioma diagnosis [16]. Unfortunately, the identification of these epigenetic drivers of pediatric high grade gliomas has not yet meaningfully impacted survival outcomes in these very aggressive tumors, with the median survival in DIPG remaining <12 months [17].

Medulloblastoma is another pediatric brain tumor that has been newly understood in the era of genetic sequencing. Advancements in transcriptional analysis combined with DNA sequencing led to groundbreaking studies describing four distinct molecular subgroups: WNT-driven, SHH-driven, Group 3 and Group 4 medulloblastoma [18,19]. Large-scale molecular analyses subsequently confirmed the biologic and clinical heterogeneity of these subgroups, and have further delineated 12 subtypes; the clinical implications of these subtypes are an area of active investigation [20,21]. Importantly, the four major subgroups can be distinguished by immunohistochemistry, meaning that subgroup-based diagnosis and clinical recommendations could have widespread implementation [22]. With the increasing understanding of the heterogeneity within medulloblastoma, subgroup-specific characteristics are now being incorporated into modern medulloblastoma trial design, risk stratification algorithms, and treatment protocols.

Finally, genetic sequencing efforts have revealed the significant biologic heterogeneity of ependymomas. These tumors have traditionally been defined by their histologic appearance and grade, but the latter has long being the subject of controversy given the high degree of

Table 1
WHO 2021 classification for pediatric CNS tumors.

Gliomas, glioneuronal tumors, and neuronal tumors	
Pediatric-type diffuse low-grade gliomas	
	Diffuse astrocytoma, MYB- or MYBL1-altered*
	Angiocentric gliomas
	Polymorphous low-grade neuroepithelial tumor of the young*
	Diffuse low-grade gliomas, MAPK pathway-altered*
Pediatric-type diffuse high-grade gliomas	
	Diffuse midline gliomas, H3K27-altered
	Diffuse hemispheric glioma, H3 G34-mutant*
	Diffuse pediatric-type high-grade gliomas, H3-wildtype and IDH-wildtype*
	Infant-type hemispheric glioma*
Circumscribed astrocytic gliomas	
	Pilocytic astrocytoma
	High-grade astrocytoma with piloid features
	Pleomorphic xanthoastrocytoma
	Subependymal giant cell astrocytoma
	Choroid glioma
	Astroblastoma, MN1-altered
Glioneuronal and neuronal tumors	
	Ganglioglioma
	Desmoplastic infantile ganglioglioma/ desmoplastic infantile astrocytoma
	Dysembryoplastic neuroepithelial tumor
	Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters*
	Rosette-forming glioneuronal tumor
	Papillary glioneuronal tumor
	Diffuse leptomeningeal glioneuronal tumor (DLGNT)
	Myxoid glioneuronal tumor*
	Gangliocytoma
	Multinodular and vacuolating neuronal tumor*
	Dysplastic cerebellar gangliocytoma
	Extraventricular neurocytoma
	Cerebellar liponeurocytoma
Ependymal tumors	
	Supratentorial ependymoma
	Supratentorial ependymoma, ZFTA fusion-positive
	Supratentorial ependymoma, YAP1 fusion-positive*
	Posterior fossa ependymoma
	Posterior fossa ependymoma, group PFA*
	Posterior fossa ependymoma, group PFB*
	Spinal ependymoma
	Spinal ependymoma, MYCN-amplified*
	Myxopapillary ependymoma
	Subependymoma
Choroid plexus tumors	
	Choroid plexus papilloma
	Atypical choroid plexus papilloma
	Choroid plexus carcinoma
Embryonal tumors	
Medulloblastoma	
	Medulloblastomas, molecularly defined
	Medulloblastoma, WNT-activated
	Medulloblastoma, SHH-activated and TP53-wildtype
	Medulloblastoma, SHH-activated and TP53-mutant
	Medulloblastoma, non-WNT/non-SHH
	Medulloblastomas, histologically defined
Other CNS embryonal tumors	
	Atypical teratoid/rhabdoid tumor
	Cribriform neuroepithelial tumor*
	Embryonal tumor with multilayered rosettes
	CNS neuroblastoma, FOXR2-activated*
	CNS tumor with BCOR internal tandem duplication*
	CNS embryonal tumor, NOS
Germ cell tumors	
	Germinoma
	Mature teratoma
	Immature teratoma
	Teratoma with somatic-type malignancy
	Embryonal carcinoma
	Yolk sac tumor
	Choriocarcinoma
	Mixed germ cell tumor

* Denotes newly recognized tumor type in 2021 WHO Classification.

variability in interpretation among pathologists [23]. Genetic sequencing has unveiled the distinct molecular features of ependymoma, which are now used as a more definitive tool for classification. As such, there are now 10 different ependymal tumor subtypes, including supratentorial ependymoma, ZFTA fusion-positive, supratentorial ependymoma, YAP1 fusion-positive, posterior fossa group A ependymoma, posterior fossa group B ependymoma, spinal ependymoma MYCN-amplified, myxopapillary ependymoma and subependymoma [3,4,24]. These molecular subgroups are now known to correlate with clinical behavior and prognosis [24,25]. Additionally, several cytogenetic patterns within subgroups have become prognostically significant; for example, posterior fossa ependymomas with 1q gain have a poorer prognosis than those with a balanced profile [26]. Recognition of the molecular and clinical heterogeneity within ependymal tumors has allowed for more accurate diagnosis and prognostication while continuing to inform better risk-stratified treatment approaches.

Whilst the insights afforded by genomic sequencing listed above have had profound diagnostic, prognostic, and therapeutic implications for many pediatric brain tumor types, it is important to recognize that the technology, equipment, and expertise for genomic analysis is not universally available, especially for patients in LMICs. Innovative and collaborative strategies are needed to reduce the widening gap between care in high-income countries (HICs) and LMICs [27].

DNA methylation profiling

In addition to molecular sequencing, DNA methylation profiling, a method which classifies tumors based on their epigenetic signature, has emerged as a key tool in solid tumor diagnosis and classification at large over the last two decades. Broadly, methylation of CpG islands (regions of DNA with a high frequency of cytosine and guanine nucleotides) in promoter regions of genes causes suppression of transcription [28]. The particular epigenetic DNA methylation signature of cancer cells has been seen to reflect both the tumor cell of origin and genetic changes acquired during tumor formation, thus differentiating individual cancer types and subtypes [29,30]. These characteristic methylation patterns have since been utilized for tumor classification and diagnosis, initially in medulloblastoma and subsequently in a number of other brain tumor types. Methylation profiles have been shown to be a reproducible and accurate diagnostic tool across a range of sample types, including archival samples and tissues with scarce or low purity tumor tissue [25,31,32]. These efforts were followed by the creation of a DNA methylation-based CNS tumor reference cohort and subsequent algorithmic machine-learning classifier by the DKFZ group in 2018, which allowed the prospective evaluation of new samples [33]. In addition to increasing diagnostic accuracy, DNA methylation has allowed for rare and novel tumor types to be recognized as biologically distinct entities. For example, the term 'Primitive Neuroectodermal Tumor' has been abolished as methylation has unveiled multiple distinct tumor types within this previous umbrella diagnosis [34].

Importantly, DNA methylation testing is not currently routinely accessible worldwide and treatment decisions are still based on histopathologic diagnosis in many countries. However, recent developments in long-read sequencing and methylation have created tools for ultra-fast molecular tumor characterization, which may lead to more easily accessible point of care methylation testing and even real-time intra-operative tumor DNA methylation classification [35].

Radiology advances

Parallel to the progress in molecular diagnostics, neuro-oncologic imaging techniques have experienced significant advancements over the last 25 years. Magnetic resonance imaging (MRI) has evolved to become the gold-standard imaging technique for diagnosis and monitoring of brain tumors. However, there are key radiographic differences between adult and pediatric tumors; in response to this, the Response Assessment in Pediatric Neuro-Oncology (RAPNO) international working group has published imaging criteria designed to allow a more standardized approach to pediatric brain tumor diagnosis, surveillance, and particularly objective trial response assessment that can be universally applied [36].

Advanced MR techniques have also become important and widely used tools in modern pediatric neuro-oncology. MR perfusion weighted imaging can be helpful in distinguishing true tumor progression from radiation effect or pseudo progression, a commonly encountered clinical challenge with increasing relevance in this era of immunotherapy [37]. Functional MRI can 'map' areas of the brain used in specific tasks, allowing optimization of surgical planning [38]. Diffusion tensor imaging (DTI) tractography can similarly be applied preoperatively to identify important white matter tracts to guide surgery and predict motor outcomes [39]. MR spectroscopy, which measures metabolite signals in tissue, has been used to help inform tumor grading and there is increasing promise in expanding its use to differentiate between molecular disease subtypes and predict treatment responses [40]. Finally, positron emission tomography (PET) also has an evolving role in pediatric neuro-oncology for identification of CNS neoplastic lesions and also prognostication [41]. Overall, there has been rapid expansion in both the knowledge and implementation of advanced imaging techniques over the last several decades, which is set to continue, particularly with the incorporation of artificial intelligence tools and machine learning algorithms. However, accessibility to these newer modalities and the expertise for interpretation limits the application in many clinical settings, particularly in LMICs.

Therapeutic advances in pediatric brain tumors

Targeted therapies

The dramatic increase in understanding of molecular disease drivers over the last two decades has led to the development of many novel therapeutics to target aberrantly functioning cellular pathways. Nowhere has the clinical effect of these targeted therapies been more profound than in the pediatric low-grade glioma setting.

The majority of patients with pLGGs survive well into adulthood, and as such, pLGG is effectively a chronic disease [1,42]. The emphasis of treatment has thus shifted to focus on functional outcomes and maintaining quality of life whilst minimizing toxicity for these patients. The mainstay of therapy remains surgical resection, which can be curative in over 90 % of these tumors [43]. Low-dose metronomic chemotherapy approaches remain the widely accepted standard of care for patients requiring further treatment for surgically inaccessible tumors, or those with residual or recurrent disease. These regimens generally achieve 5-year progression-free survival rates in the order of 45-55 %, meaning that around 50 % of patients will experience progression and require further therapy [44–46]. However, these chemotherapy regimens are associated with significant short- and long-term toxicities, including immunosuppression, neuropathy, ototoxicity, allergic reactions, renal and hepatic dysfunction.

Leveraging the new biologic understanding of pLGG tumorigenesis, numerous inhibitors targeting the culprit MAPK/ERK and mTOR pathways have since been developed and tested in phase 1 and 2 trials, with multiple phase 3 randomized controlled trials now underway (Table 2). The MEK inhibitors selumetinib, trametinib, and binimetinib have all demonstrated early-phase responses in the recurrent/progressive pLGG setting, ranging from 15-56 % [47–50]. Type I RAF inhibitors vemurafenib and dabrafenib, as well as combination trametinib and dabrafenib have also shown early phase safety and efficacy as single agents in recurrent $BRAF^{V600E}$ mutant pLGG [47,51,52]. The type II RAF inhibitor tovorafenib was seen in the recent PNOC026/FIREFLY-1 phase II trial to induce profound responses in BRAF-altered recurrent or progressive pLGG with an overall response rate (ORR) of 64 %, leading to its FDA approval for this indication in 2024 [53].

These impressive response rates have prompted investigation of

Table 2
Past and current clinical trials using targeted therapies for pLGG.

Sponsor (Trial name)	Phase/ NCT#	Drug	Population	Primary study objectives	Status	Results
PBTC (PBTC-029/ PBTC-029B) [48,49,56]	I/II; NCT01089101	Selumetinib	Recurrent/ progressive pLGG	Phase I: determine MTD and RP2D Phase II: assess sustained response rate (CR + PR for 8 weeks)	Active, not recruiting	Phase II: **Stratum 1** (pilocytic astrocytoma with KIAA1549: BRAF fusion or BRAFV600E mutation): 9/25 patients had sustained PR **Stratum 2** (pilocytic astrocytoma without above aberrations): await **Stratum 3 (**NF1-assocaited pLGG): 10/25 patients had sustained PR **Stratum 4** (non-NF1 optic pathway glioma): 6/25 patients had PR **Stratum 5 (**non-pilocytic LGG with KIAA1549:BRAF fusion or BRAFV600E mutation): await **Stratum 6** (non-NF1 pLGG with no available tissue for testing): await
COG (ACNS1831)	III; NCT03871257	Selumetinib vs. carboplatin + vincristine	Untreated NF1-associated pLGG	RCT; characterize EFS, determine number participants with visual acuity improvement	**Recruiting**	
COG (ACNS1833)	III; NCT04166409	Selumetinib vs. carboplatin + vincristine	Untreated non-BRAFV600E-mutant, non-NF1 pLGG	RCT; characterize EFS	**Recruiting**	
COG (ACNS1931)	III; NCT04576117	Selumetinib vs. selumetinib + weekly vinblastine	Recurrent/ progressive non-BRAFV600E, non NF1 pLGG	RCT; determine MTD/ RP2D and EFS	**Recruiting**	
NFCTC (NFCTC MEK162) [50]	I/II; NCT02285439	Binimetinib (MEK162)	Recurrent/ progressive pLGG	Phase I: determine MTD Phase II: assess preliminary efficacy	Active, not recruiting	Phase II: 22/44 evaluable patients showed minor (n=7) or partial (n=15) response
Novartis [47]	I/II; NCT02124772	Trametinib monotherapy, trametinib + dabrafenib combination therapy	Recurrent BRAFV600E-mutant pLGG	Phase I: establish safe dose trametinib monotherapy and in combination with dabrafenib Phase II: determine preliminary activity of trametinib monotherapy and in combination with dabrafenib	Completed	Trametinib monotherapy (n=13): ORR 15 % Dabrafenib + trametinib combination therapy (n=36): ORR 25 % NB treatment-related AEs more common with monotherapy (54 % vs. 22 %)
CHU Sainte-Justine, Montreal (TRAM-01)	II; NCT03363217	Trametinib	Progressive/ refractory tumors with MAPK/ERK pathway activation	Determine response rate of trametinib as a single agent	Active, not recruiting	
University Hospital, Strasbourg, France (PLGG – MEKTRIC)	III; NCT05180825	Trametinib vs. weekly vinblastine	Untreated non-BRAFV600E-mutant, non-NF1 pLGG	RCT; determine in the experimental arm a 20 % superiority of 3-year PFS rate in comparison with standard treatment over 18 courses	**Recruiting**	
PNOC (PNOC002) [52]	I/II; NCT01748149	Vemurafenib	Recurrent/ progressive BRAFV600E-mutant brain tumors	Phase I: determine RP2D, DLTs Phase II: characterize ORRs	Active, not recruiting	Phase I: 1 CR, 5 PR, 13 SD Phase II: ongoing
Novartis [51]	I/IIa; NCT01677741	Dabrafenib	Recurrent BRAFV600E-mutant glioma	Phase I: determine MTD and RP2D Phase II: evaluate safety/ tolerability profile, assess possible efficacy	Completed	ORR in pLGG patients 44 %, 1-year PFS 85 %
Novartis [54]	II/ NCT02684058	Dabrafenib + trametinib vs. carboplatin + vincristine (2:1)	Untreated BRAFV600E-mutant pLGG	RCT; Assess efficacy by overall response (CR + PR), clinical benefit and PFS	Completed	ORR D+T: 47 % ORR C+V: 11 % Clinical benefit D+T: 86 % Clinical benefit C+V: 46 % PFS D+T: 20.1months PFS C+V: 7.4months
PBTC (PBTC-055)	I/II; NCT04201457	Hydroxychloroquine + trametinib (BRAF-fusion or NF1-	Recurrent/ progressive glioma	Phase I: determine RP2D, MTD	**Recruiting**	

(*continued on next page*)

Table 2 (*continued*)

Sponsor (Trial name)	Phase/ NCT#	Drug	Population	Primary study objectives	Status	Results
		glioma) OR + combination dabrafenib/ trametinib (BRAFV600E-mutant glioma)	after prior therapy with RAF and/or MEK inhibitor	Phase II: sustained ORR (as defined by 'better response' criteria; comparison of response on protocol therapy vs. best previous response to inhibitor)		
PNOC (PNOC014 and PNOC026/ FIREFLY-1) [53]	I/II; NCT03429803 NCT04775485	Tovorafenib	Recurrent/ progressive BRAF-altered pLGG	Phase I: determine MTD and RP2D Phase II: evaluate safety and efficacy of tovorafenib monotherapy	Active, not recruiting; **recruiting**	Phase II: ORR per RANO-HGG (primary endpoint) in patients with evaluable disease was 67 %; 17 % with CR and 49 % with PR; 26 % patients had best response of SD, giving clinical benefit rate of 93 %
Day One (LOGGIC/ FIREFLY-2)	III; NCT05566795	Tovorafenib vs. SoC chemotherapy (investigator's choice)	Untreated pLGG with known activating RAF alterations	RCT; compare ORR of tovorafenib monotherapy vs. SoC chemotherapy	**Recruiting**	
Hospital for Sick Children (VICTORY)	I; NCT06381570	Tovorafenib + vinblastine	Recurrent/ progressive RAF-altered pLGG	Feasibility phase: establish MTD/RP2D Expansion/ efficacy phase: ORR by RANO-LGG criteria	**Recruiting**	
NFCTC (NFC-RAD001) [57]	II; NCT01158651	Everolimus	Recurrent/ progressive NF1-pLGG	Assess best response to everolimus	Completed	15/22 (68 %) patients had response (1CR, 2 PR, 12 SD), and 10/15 had no progression after median follow up of 33 months
PNOC (PNOC001) [58]	II; NCT01734512	Everolimus	Recurrent/ progressive pLGG	Estimate 6-month PFS associated with everolimus	Active, not recruiting	PFS for cohort of 65 subjects 63 % at a median number of 8 treatment cycles; 1 PR, 1 CR, 33 SD and 17 PD.
POETIC [59]	II; NCT00782626	Everolimus	Recurrent/ progressive non-NF1 pLGG	Determine response rate to everolimus (aim ≥25 %)	Completed	Response rate 52.2 % (12/23 participants); 2 PRs, 10 SD after 12 cycles
PNOC (PNOC021)	I; NCT04485559	Trametinib + everolimus	Recurrent/ progressive pLGG	Estimate RP2D of combination trametinib + everolimus and describe DLTs	**Recruiting**	

PBTC, Pediatric Brain Tumor Consortium; pLGG, pediatric low-grade glioma; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; CR, complete response; PR, partial response, SD, stable disease; RCT, randomized controlled trial; EFS, event-free survival; NFCTC, Neurofibromatosis Clinical Trials Consortium; ORR, overall response rate; AE, adverse event; DLT, dose-limiting toxicity; PNOC, Pediatric Neuro-Oncology Consortium; SoC, standard of care; POETIC, Pediatric Oncology Experimental Therapeutics Investigators' Consortium; PFS, progression-free survival; NB, note well.

these agents in the upfront treatment setting, where they pose a potential true shift in treatment paradigm. The recent prospective phase II trial in children with untreated $BRAF^{V600E}$ mutant pLGG comparing combination dabrafenib-trametinib therapy to carboplatin-vincristine demonstrated an ORR and median progression-free survival (PFS) of 47 % and 20.1 months in the dabrafenib-trametinib group compared to 11 % and 7.4 months in the carboplatin-vincristine group, with notably less toxicity [54]. This finding led to the 2023 FDA approval for dabrafenib-trametinib combination therapy in the upfront setting for $BRAF^{V600E}$ mutant pLGGs, changing the standard of care treatment for this select group of patients.

It is important to note that aside from the above dabrafenib-trametinib combination for $BRAF^{V600E}$ mutant pLGGs, selumetinib for NF1-associated plexiform neurofibromas, and everolimus for tuberous-sclerosis complex-associated subependymal giant cell astrocytomas (SEGAs), the role of targeted inhibitors in the upfront setting in pLGG remains uncertain and is the subject of ongoing investigation in multiple prospective trials (Table 2). Presently, conventional chemotherapy remains the most widely accepted standard treatment whilst these investigations are ongoing, and upfront targeted inhibitor use is reserved for the clinical trial setting. This is important as there remain many unanswered questions of targeted inhibitor use in pLGG. Whilst the acute toxicity profiles have generally been favorable, little is known about the long-term side effects of these medications. The optimal duration of treatment is also unclear; whilst most trials were used a treatment duration of 24 months, this was not based on any scientific rationale. Furthermore, it has been observed that a proportion pLGGs will exhibit rapid 'rebound' growth after cessation of targeted therapy, but the clinical and biologic factors underpinning this mechanism are incompletely understood [55].

In summary, targeted therapies are changing the treatment paradigm for some diseases, particularly pLGGs which benefit from being primarily single-driver entities. The role of targeted therapies in other diseases is still evolving but there is hope that similar therapeutic leaps will soon be realized in other pediatric CNS tumor types.

Immunotherapy

Over the last quarter century, great progress in the understanding of the immune mechanisms involved in cancer have led to significant advancements in immune based therapies, and they are being increasingly explored as therapeutic strategies for CNS tumors.

T-cells express several proteins on their cell surface (such as PD-1 and CTLA-4), known as 'checkpoint regulators', which act to downregulate T-cell activity when they bind to specific ligands (such as PDL-1 and CD80/86 respectively) on antigen-presenting and other cells in the body [60]. By blocking the checkpoint receptor-ligand interaction, the balance is tipped in favor of T-cell stimulation and supports T cell activation and engagement [60]. The strategy was first clinically employed in adult melanoma, where remarkable responses were achieved in previously treatment-resistant advanced disease [61]. Importantly, ICI sensitivity has been seen to relate to tumor mutational burden (TMB) or

microsatellite instability, a surrogate marker of TMB [62]. A higher number of tumor mutations drives an increased burden of neoantigens, and a greater likelihood of recognition by the patient's T-cells, thus enhancing the efficacy of immune checkpoint inhibition. This concept has underscored work in patients with biallelic replication repair deficiency (RRD), whose tumors harbor a high mutation burden. Historically, RRD-associated high-grade glioma (RRD-HGG) is seen to rapidly progress with a median post-relapse survival of 2.6 months, but a recent prospective pediatric trial using nivolumab for refractory non-hematologic cancers harboring a high TMB and/or MMRD demonstrated a best overall response of 50 %, with several sustained complete remissions including patients with refractory malignant gliomas [63]. This work has shifted the treatment paradigm for this small group of patients and has led to the FDA approval of pembrolizumab in 2020, for pediatric patients with relapsed solid tumors with a high TMB.

Adoptive cellular therapies, which use modified lymphocytes (usually T-cells or NK cells) to target tumor cells, have been the subject of much excitement and investigation over the last decade, particularly since the profound clinical impact of CD19-directed chimeric antigen receptor (CAR) T-cell therapy in high-risk hematologic malignancies. CAR T-cell therapy uses cytolytic T cells that have been engineered to express a receptor that recognizes a particular surface antigen on target tumor cells [64]. These CARs are comprised of an antigen-binding domain and a cell signaling domain and they bestow MHC-unrestricted antigen specificity to involved T-cells [64]. Several phase I studies have tested multiple CAR constructs against several antigens which demonstrate differential expression between tumor and normal tissue. Pediatric phase I clinical trial data has been published for GD2, HER2 and B7H3-CAR T-cell therapy in diffuse midline glioma and other relapsed/refractory pediatric brain tumors including ependymoma and medulloblastoma [65–67]. It should be noted that these phase I trials have unveiled several significant toxicities associated with CAR T-cell therapy for CNS tumors; primarily on-tumor on-target toxicity that can cause significant tumoral/peritumoral swelling, leading to CSF obstruction and/or neural dysfunction [68]. Additionally, these studies have revealed significant challenges facing CAR efficacy in brain tumors, including limitations in CAR T cell expansion and persistence, uncertainty in the optimal delivery route and the role of lymphodepletion, and antigen-loss recurrence. However, several radiographic and clinical responses have also been reported among these trials in traditionally treatment-resistant pediatric CNS tumors, highlighting the promise of this approach [65,67]. Multiple phase I trials are

Table 3
Currently active CAR T-cell trials for pediatric CNS tumors (*Active trials as of clinicaltrials.gov on October 12th, 2024).

Trial name	Phase; NCT#	Sponsor	Target	Tumor types	Delivery	Trial status
HER2-specific CAR T Cell Locoregional Immunotherapy for HER2-positive Recurrent/Refractory Pediatric CNS Tumors (BrainChild-01)	I; NCT03500991	Seattle Children's Hospital	HER2	Recurrent/ refractory HER2-positive CNS tumors, excluding DIPG	IT, ICV	Active, not recruiting
EGFR806-specific CAR T Cell Locoregional Immunotherapy for EGFR-positive Recurrent or Refractory Pediatric CNS Tumors (BrainChild-02)	I; NCT03638167	Seattle Children's Hospital	EGFR806	Recurrent/ refractory EGFR-positive CNS tumors, excluding DIPG	IT, ICV	Active, not recruiting
Study of B7-H3-Specific CAR T Cell Locoregional Immunotherapy for Diffuse Intrinsic Pontine Glioma/Diffuse Midline Glioma and Recurrent or Refractory Pediatric Central Nervous System Tumors (BrainChild-03)	I; NCT04185038	Seattle Children's Hospital	B7H3	DIPG, DMG and other recurrent/ refractory CNS tumors	IT, ICV	**Recruiting**
Study of B7-H3, EGFR806, And IL13-Zetakine (Quad) CAR T Cell Locoregional Immunotherapy For Pediatric Diffuse Intrinsic Pontine Glioma, Diffuse Midline Glioma, And Recurrent Or Refractory Central Nervous System Tumors (BrainChild-04)	I; NCT05768880	Seattle Children's Hospital	B7H3, EGFR806, HER2, IL13-zetakine	DIPG, DMG and other recurrent/ refractory CNS tumors	ICV	**Recruiting**
Loc3CAR: Locoregional Delivery of B7-H3-CAR T Cells for Pediatric Patients with Primary CNS Tumors	I; NCT05835687	St. Jude Children's Research Hospital	B7H3	Recurrent/ refractory B7-H3-positive CNS tumors, OR DIPG	IT, ICV	**Recruiting**
T Cells Expressing HER2-specific Chimeric Antigen Receptors(CAR) for Patients With HER2-Positive CNS Tumors (iCAR)	I; NCT02442297	Baylor College of Medicine	HER2	Recurrent/ refractory HER2-positive primary CNS tumor, excluding DIPG	IT, ICV	Active, not recruiting
C7R-GD2. CAR T Cells for Patients With GD2-expressing Brain Tumors (GAIL-B)	I; NCT04099797	Baylor College of Medicine	GD2	Newly diagnosed DIPG/ DMG OR recurrent/ refractory GD2-positive embryonal tumor/ HGG or ependymal tumor	IV, ICV	**Recruiting**
GD2 CAR T Cells in Diffuse Intrinsic Pontine Gliomas (DIPG) & Spinal Diffuse Midline Glioma (DMG)	I; NCT04196413	Stanford University	GD2	H3K27M-mutant DIPG (brainstem only), or H3K27M-mutant DMG of spinal cord	IV, ICV	**Recruiting**
GD2-CAR T Cells for Pediatric Brain Tumors	I; NCT05298995	Bambino Gesu Hospital and Research Institute	GD2	Relapsed/ refractory CNS tumors	IV	**Recruiting**
CAR T Cells After Lymphodepletion for the Treatment of IL13Rα2 Positive Recurrent or Refractory Brain Tumors in Children	I; NCT04510051	City of Hope Medical Center	IL13Rα2	Recurrent/ progressive IL13Rα2-positive malignant brain tumor	ICV	**Recruiting**
Safety and Efficacy of Loco-regional B7H3 IL-7Ra CAR T Cell in DIPG (CMD03DIPG)	I; NCT06221553	Chulalongkorn University Thailand	B7H3	DIPG	ICV	**Recruiting**
Leveraging Chimeric Antigen Receptor-Expressing T Cells for Children with Diffuse Midline Glioma	I; ACTRN12622000675729	Sydney Children's Hospitals Network	GD2	DIPG, H3K27-altered DMG	IV, ICV	**Recruiting**

IT, intra-tumor cavity; ICV, intra-cerebroventricular; IV, intravenous.

ongoing (Table 3). Several other important immunotherapeutic approaches developed over the last several decades include therapeutic cancer vaccines, oncolytic viral therapy, and other cellular therapies such as cytotoxic T-lymphocytes and engineered T-cell receptors, all of which are being investigated in clinical trials for various pediatric CNS tumor types.

Radiation therapy

Radiation therapy (RT) has long been a mainstay in pediatric CNS tumor treatment, however, is known to be associated with a range of significant short- and long-term side effects. Over the last 25 years, the field of pediatric radiation oncology has witnessed significant advancements that have largely been aimed at improving outcomes whilst minimizing the significant long-term side effects associated with radiation.

A key development over this time has been the implementation and greater access to proton beam radiation therapy (PRT). In contrast to traditional photon radiation therapy, which irradiates a target using multiple x-ray beams (and deposits radiation in tissues beyond the target area), PRT directs protons towards the tumor target, depositing them with minimal residual radiation beyond the target tissue [69]. This is an attractive feature particularly in the pediatric population, where RT-related damage to the surrounding structures during childhood development have can significant long-term consequences. In pediatric CNS tumors, the use of protons for medulloblastoma has been a major focus over the last few decades, as most children with medulloblastoma require irradiation of the entire craniospinal axis under standard of care treatment. Comparative dosimetric modelling showed that protons are able to not only eliminate exit radiation dosing to the chest, abdomen and pelvis of children, but also reduce the dose to the normal brain and critical CNS structures including the hearing apparatus, pituitary, optic pathway and hypothalamus.[70,71]. Additionally, there is now clinical follow up data demonstrating the favorable long term toxicity profile of PRT in pediatric medulloblastoma patients, specifically demonstrating advantages in intellectual and endocrine sparing [72,73]. Importantly, the disease control and patterns of failure in PRT-treated patients have been comparable to historical controls in these studies [72,73]. Of note, given these studies were not randomized and instead utilized historical photon-treated controls, differences in median age, RT technique, dose, volume and follow-up time prevent any definitive comparative conclusions. Also, whilst the role of PRT in other entities continues to be explored, photon beam RT remains the preferred modality in several pediatric CNS tumors, including high-grade glioma. Finally, despite the rapid increase in the number of proton radiation centers around the world, proton therapy remains inaccessible for many children, particularly in LMICs.

In addition to the expanding use of PRT, many other areas of pediatric radiation oncology continue to advance, including the integration of advanced imaging techniques, machine-based learning approaches, and the incorporation of molecular and biomarker-driven RT plans, all largely focused on minimizing long-term sequelae to improve treatment outcomes and quality of life for young CNS tumor patients.

Surgery

Pediatric neurosurgery has been shaped over the last quarter century by developments that have improved procedural precision, safety and outcomes. Whilst craniotomies remain a pivotal workhorse for many types of tumor resection, endoscopic and other minimally invasive techniques have been used to increase precision and reduce surgical morbidity. Stereotaxis, the process of using a 3-dimensional coordinate system in combination with CT or MRI to locate CNS targets, has allowed the use of minimally invasive techniques in a greater number of tumor types and locations. A pertinent example of this is in the setting of brainstem biopsy in diffuse intrinsic pontine glioma. Previously a solely radiographic diagnosis, DIPGs were considered too risky for tissue sampling given their intricate location within the brainstem. Stereotactic techniques have allowed the safe biopsy of these lesions, first pioneered in 2007 and subsequently shown in several large series to be feasible and safe, with low incidence of transient morbidity (<5 %), and the majority of procedures yielding sufficient tissue for molecular sequencing [74,75]. Brainstem biopsy for DIPG has now become widely accepted and adopted practice, and has facilitated a monumental shift in the understanding of the molecular underpinnings of this disease and consideration for clinical trials that utilize targeted therapies. Whilst these advancements are unfortunately yet to translate to any meaningful improvement in the dismal prognosis of DIPG, it is hoped that greater understanding of tumor biology, facilitated by tissue sampling, will eventually lead to effective treatments.

Other novel surgical therapeutic techniques have focused on improving delivery of drugs into tumor tissue, either through direct delivery or disruption of the blood brain barrier (BBB). Convection enhanced delivery (CED) involves surgical placement of a cannula directly into the brain or tumor to facilitate infusion of a drug or treatment via a pressure gradient, thereby circumventing the BBB [76]. Another technique being explored is focused ultrasound (FUS), which entails trans-cranial delivery of low-frequency waves, temporarily disrupting the BBB, and can be visualized in real time on MRI by contrast extravasation in the area of interest [77]. This technique is enhanced by the intravenous injection of lipid-encased perfluorocarbon microbubbles, which are hypothesized to aid in mechanical disruption of the BBB through US-induced oscillation; they have been shown to lower the US frequency threshold for BBB disruption [77]. Following preclinical demonstration of safety and potential efficacy, this technique is now under active investigation in several trials for pediatric DIPG, using FUS with doxorubicin administration (NCT05615623), etoposide administration (NCT05762419), or aminolaevulinic acid (NCT05123534). Both CED and FUS have been shown safe in phase I trials and have high potential to improve drug delivery to the most challenging to treat pediatric brain tumors, though trials require significant resources and specialized equipment, so will likely be limited to select tertiary or quaternary cancer centers [78,79].

Evolution of trial design

A fundamental key to the successful translation of the innovation detailed above has been the evolution of pediatric clinical trial medicine over the last 25 years. Firstly, adaptive trial designs have now been widely adopted in pediatric phase I trials. These models, such as the 'Rolling 6′ design first published in 2008, allow more efficient trial enrolment whilst upholding safety [80]. This is of particular benefit in pediatric oncology where trial medicine is significantly impacted by the rarity and heterogeneity of pediatric cancers, ethical considerations of using experimental therapies in minors, regulatory hurdles and funding constraints. Many pediatric oncology trials are now molecularly stratified, which allows for better understanding, interpretation, and applicability of trial results, as well as potentially increased efficacy of trial agents when applied to specific molecularly selected targets. Finally, underpinning the ability to apply translational therapeutics, implement clinical trials, and ultimately effect tangible change in the field over the last 25 years has been the development of pediatric neuro-oncology consortia. Given the rarity of pediatric brain tumors, collaboration is vital to pool knowledge and resources and particularly to action experimental trials. Various consortia have collectively transformed the landscape of pediatric neuro-oncology over the last 25 years, fostering collaboration, advancing research, and improving outcomes for children with brain tumors.

Ongoing challenges

Whilst the field of pediatric neuro-oncology has witnessed

remarkable strides forward over the last 25 years, significant challenges remain to further improve the outcomes of children with brain tumors. In the preclinical setting, generation of accurate preclinical models is important for faithful testing of new drugs and therapies against a replica tumor and microenvironment, however, this remains challenging and costly. In the realm of diagnostics, despite a wealth of new knowledge about the molecular drivers of various tumors, molecular testing modalities are not standardized nor are universally available, which can limit accurate diagnosis, access to molecularly targeted treatments and trial enrolment, and unified approaches are needed. In addition, targeted therapies have been impactful only in carefully selected patient populations, (mostly in the minority of tumors that have a single genetic driver), and the differential responses seen in seemingly identical histologic and molecular tumors is not yet well understood. Clinical trials in pediatric neuro-oncology face many ongoing challenges given the rare and heterogeneous nature of childhood brain tumors as well as resource and personnel constraints. For novel therapies that are changing the treatment paradigms in several disease entities, the potential late effects of these therapies remain unknown. Finally, it should be addressed that a major global pediatric neuro-oncology challenge is ensuring equity of access; many of the advancements described in this review are not yet able to benefit patients and families in LMICs, where diagnostic and therapeutic opportunities can be limited. Overall, however, the remarkable progress made over the last 25 years in pediatric neuro-oncology heralds a promising future with even greater potential for breakthroughs in the next quarter-century.

CRediT authorship contribution statement

Phoebe Power: Writing – original draft, Investigation, Conceptualization. **Joelle P Straehla:** Writing – review & editing. **Jason Fangusaro:** Writing – review & editing. **Pratiti Bandopadhayay:** Writing – review & editing. **Neevika Manoharan:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jason Fangusaro serves on the Educational Speaker's Bureau for Day One Biopharmaceuticals. Pratiti Bandopadhayay has served on paid advisory boards for QED Therapeutics and Day One Biopharmaceuticals, and she currently serves on the Board of the Justice Resource Institute as a Trustee. Her laboratory has also received grant funding from the Novartis Institute of Biomedical Research.

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