Neuro-Oncology Advances
8(S2), vdaf043, 2026 | https://doi.org/10.1093/noajnl/vdaf043

# Targeted therapies in adolescent and young adult patients with central nervous system tumors

**Anna Mullins[‡], Julie Bennett[‡], Kee Kiat Yeo[‖], and Mary Jane Lim-Fat[‖]**

All author affiliations are listed at the end of the article.

**Corresponding Authors:** Kee Kiat Yeo, MD, 450 Brookline Ave, Boston MA 02215, USA (keek_yeo@dfci.harvard.edu); Mary Jane Lim-Fat, MD, 2075 Bayview Avenue, Toronto ON, Canada M4N 3M5 (maryjane.limfat@sunnybrook.ca).

[‡]These authors contributed equally to this study
[‖]These authors contributed equally to the supervision of this study.

**Abstract**

Adolescents and young adults (AYA: ages 15–39 years) are a unique population at risk of both pediatric-type and adult-type central nervous system (CNS) tumors. Targeted therapies are now available for a growing subset of CNS tumors represented within AYA. Gliomas represent 25% of all primary brain tumors in AYA, with up to 30% of these harboring a pediatric-type molecular alteration in the mitogen-activated protein kinase (MAPK) pathway. MAPK-pathway inhibitors are often utilized in AYA patients with a pediatric low-grade glioma (pLGG), however specific clinical trials spanning the entire AYA age range for this molecular alteration are absent. Isocitrate dehydrogenase (IDH) mutations are the most common molecular alteration found in AYA glioma. The IDH-mutant inhibitor vorasidenib has been demonstrated to prolong progression-free survival in grade 2 IDH-mutant glioma; however, there is a lack of evidence in patients younger than 18. Meningioma is the most common primary CNS tumor in adults and represents 15% of primary CNS tumors in the AYA population. Recent molecular characterization of meningioma has led to several targeted therapeutic clinical trials in the relapsed/refractory setting. Medulloblastoma is the most common embryonal CNS tumor in AYA patients and is primarily driven by a mutation in the sonic hedgehog (SHH) pathway. The SHH pathway is targetable with Smoothened (SMO) inhibitors which has been utilized in the relapsed/refractory setting for both pediatric and adult patients, with mixed responses. Clinical trials incorporating SMO inhibition upfront treatment have been hampered by low accrual numbers and lack of sponsor support. Craniopharyngioma is a rare CNS tumor in the AYA population, and BRAFV600E mutations in papillary craniopharyngioma represent a targetable alteration. Solutions to improving the care of AYA should include appropriate representation in clinical trials and specialized care by experienced clinicians.

## Key Points

- Adolescents and young adults (ages 15–39) are at risk for both pediatric and adult-type CNS tumors.
- The treatment paradigm for gliomas in AYA often relies on grading and the presence of targetable alterations such as RAS/MAPK mutations and IDH mutations.
- Medulloblastoma is the most common embryonal CNS tumor in AYAs, driven primarily by SHH pathway mutations.
- Craniopharyngiomas, though rare, often have targetable BRAFV600E mutations in the papillary subtype.

The past two decades have seen an unprecedented advancement in our understanding of the molecular underpinnings of multiple types of malignancies. This has led to the development of various novel therapeutics focused on precision oncology targeting specific alterations. In many cancer types, these advances have substantially improved outcomes, enabling better personalized approaches in the use of chemotherapy, radiotherapy, and surgery. Adolescents and young adult (AYA) patients (defined as individuals aged 15–39 years) face unique challenges as they present with both pediatric and adult-type central nervous system (CNS) tumors.[1,2] Additionally, the transition from adolescence through young adulthood is often a time of considerable change in psychosocial, economic, and emotional functioning, as well as the challenges that come from moving to an adult cancer center from a pediatric cancer center. AYA patients can experience disparate care whether they are treated at a pediatric or adult center and have historically been underrepresented in clinical trials due to a range of factors including restricted age of eligibility as well as institutional barriers.[3] Regrettably, this has resulted in AYA being an understudied population, resulting in a lack of understanding of their distinct tumor biology and epidemiology. The most common primary brain tumors seen in AYA and discussed in this review are summarized by location, subgroup, and molecular alteration in Figure 1. As the use of targeted therapies for various CNS tumors continues to grow, it is crucial for oncologists to stay abreast of the developments in onco-therapeutics, advocate for access, and encourage patient participation in clinical trials.[4] This review offers a summary of the current landscape of targeted therapies in AYA CNS oncology.

## Glioma in AYA

Gliomas account for 25% of CNS tumors and 83% of malignant brain tumors in the AYA population.[5] The fifth edition of the WHO Classification of Tumors of the CNS, published in 2021, recognizes distinct molecular differences and clinical outcomes between pediatric-type and adult-type gliomas.[6] In the AYA population, both types are present, with up to 30% of gliomas in AYA showing a mutational profile consistent with pediatric-type glioma.[7] Figure 2

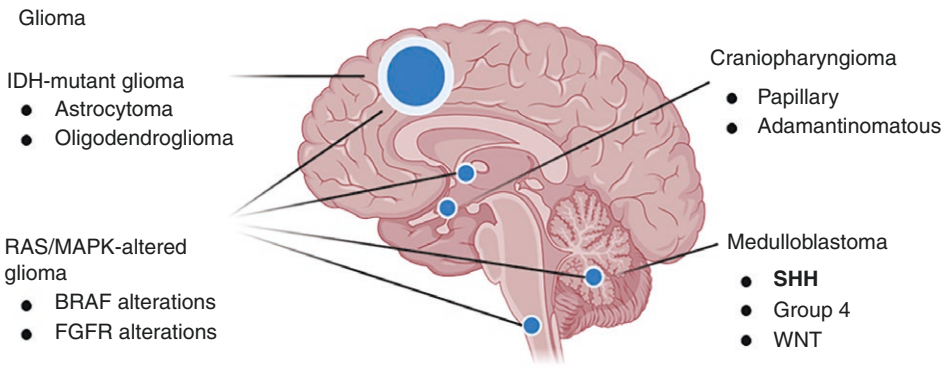


**Figure 1.** Location of relevant primary brain tumors seen in AYA patients by tumor type and molecular alteration or subgroup.

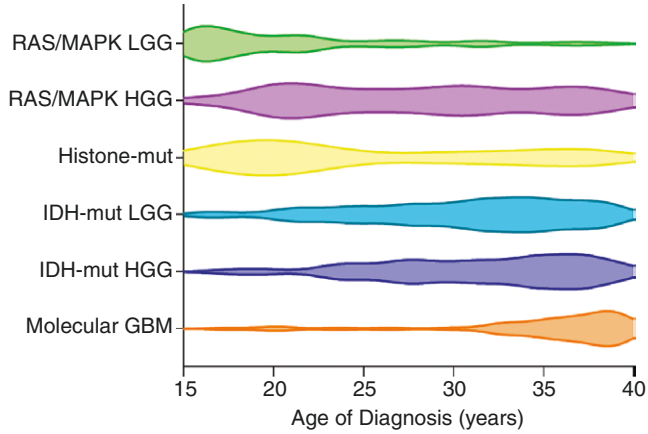


**Figure 2.** Relative incidence of newly diagnosed glioma in AYA population-based cohort based on molecular subgroup.

further illustrates the distribution of molecular signatures seen in AYA patients with glioma. This has significant clinical implications, as several molecularly targeted therapies are now available for both pediatric-type and adult-type gliomas. However, there is a paucity of evidence-based clinical practice data for the management of glioma in AYA. This has led to a variety of heterogeneous approaches for this cohort (depending on whether a patient is seen in an adult or pediatric practice setting) and highlights the importance of standard molecular sequencing and multidisciplinary tumor board discussions for all AYA patients to optimize treatment regimens and improve outcomes. Table 1 summarizes the trials currently enrolling patients with glioma and the respective age eligibility.

## RAS/MAPK-Activated Glioma

Pediatric low-grade gliomas (pLGGs; WHO grade 1 or 2) are generally considered a single pathway disease, characterized by alterations that lead to constitutive activation of the mitogen-activated protein kinase (MAPK)/RAS pathway.[8] In children, the most common alterations by frequency are KIAA1549-BRAF fusions, BRAF V600E mutations, and NF1 mutations.[8] In contrast, Bennett et al. examined the molecular landscape of 876 AYA gliomas and found 33% harbored pediatric-type mutations with the most common being BRAF V600E (11%) followed by FGFR alterations (7%).[9] Traditionally, treatment has consisted of a combination of maximal safe resection, and in patients requiring adjuvant therapy, systemic therapy, and much less frequently in the modern era, radiation therapy.[10] Tolerance to chemotherapy is generally worse among AYA and older adults relative to children. Similarly, with targeted therapy, there is emerging evidence that young adult patients have different toxicity profiles, specifically a higher incidence of arthralgias, cutaneous toxicity including keratoacanthomas and squamous cell carcinoma as well as cardiotoxicity with BRAF or MEK inhibition.[11] There are no studies dedicated to AYA patients with MAPK-altered pLGG and much of the approach to treatment for this cohort has been extrapolated from pediatric data and adult studies.[12,13]

In general, there are more MAPK-activated high-grade glioma (HGG) in AYA patients compared to pediatric patients, with BRAFV600E mutated HGG accounting for up to 6% of high-grade tumors in AYAs in the published literature.[14] While the exact reason for this remains to be determined, it is possible that some of these tumors originated as pLGG and transformed into higher-grade tumors.[15,16] It is also possible that some of these tumors represent the evolution of PXA grade 2/3 tumors, which are more common in AYA. Mackay et al identified 3 distinct clusters of tumors separate from the G34, K27, and IDH1 groups called WT-A, WT-B, and WT-C. WT-A cluster around the PXA- and LGG-like subgroup and are driven by BRAFV600E, NF1 mutations, or fusions in RTKs.[17] In the published cohort from Mackay et al, the WT-A subgroup had a favorable survival profile with a median OS of 63 months.[17]

While NF1 mutations are found less frequently in AYA glioma than in pediatrics, it is important to highlight that AYA patients with NF1-associated glioma are more likely to have a high-grade tumor than pediatric patients. A review of the molecular landscape of NF1-associated gliomas by D'Angelo and colleagues analyzed 23 high-grade and 32 low-grade gliomas and found that 78% of tumors in adults were high grade whereas the majority of tumors in children were low grade.[18] While the safety and efficacy of MEK inhibitors such as trametinib and selumetinib have been demonstrated in NF1-associated LGG, there have been no clinical trials conducted exploring their use in NF1-associated HGG.

## Targeting the RAS/MAPK-Pathway

A number of clinical trials examining MEK and RAF inhibitors for pLGG have been conducted in the last decade.[12,19–22] Unfortunately, these trials have typically enrolled pediatric patients under 21 years of age. Consequently, there is a lack of data that broadly applies to the AYA population. Of the FDA-approved MAPK-pathway inhibitors specifically for pLGG, only the FIREFLY-1 study with tovorafenib included patients up to 25 years, with 9 participants between 15 and 25 years of age enrolled in the study.[22] Encouragingly, there are clinical trials expanding their age cohorts to allow the inclusion of older young adults. A phase 2 trial exploring binimetinib for BRAF-driven LGG is open for enrollment for patients 12 years and older (NCT06159478) and a clinical trial utilizing Avutometinib, an RAF/MEK inhibitor, is enrolling patients up to 30 years, albeit limiting the number of patients >18 to <30 to no more than 5, and only after the dose escalation phase (NCT06104488). Most current clinical trials investigating targeted MEK inhibitors (including selumetinib, mirdametinib, and binimetinib) for pLGG have excluded patients over the age of 21 years (NCT03871257, NCT04576117, NCT04923126, NCT04166409). This highlights the ongoing challenge of access to appropriate clinical trials for this age group and the subsequent lack of robust evidence to guide treatment decisions. Often, patients in the AYA cohort are started on targeted agents outside of clinical trials and there is currently no concerted effort for data collection through registry studies to advance our understanding of their response and toxicity profile. Many questions remain including optimal duration of therapy, tolerability of treatment, safe strategies to discontinue therapy, impact on the natural history of the tumor, and long-term risks of prolonged use of these targeted agents.

There are a number of clinical trials that have been conducted in adult centers utilizing MAPK-pathway inhibitors which has allowed the inclusion of older AYA patients with glioma. The ROAR clinical trial is one such trial which examined the activity and safety of dabrafenib plus trametinib in adult patients with recurrent or progressive BRAFV600E mutant LGG and HGG.[13] This study was part of a multicenter, open-label, single-arm, phase 2, basket study in 9 cohorts of patients aged 18 or older with BRAFV600E mutation-positive rare cancers. In total, the trial enrolled 13 patients in the LGG cohort (median age 33 years, range 18–58 years). Subgrouping by age was not published for the LGG cohort, however, considering the median age of 33 years it is likely to be somewhat representative of the AYA population. Among these patients, one achieved a complete response, six achieved a partial response and 2 a

**Table 1.** Targeted Therapy Trials Currently Open to AYA Patients With LGG or High-Grade Glioma

| Clinical trial | Age inclusion (years) | Target | Drug | Patient population |
|---|---|---|---|---|
| 23-129 MSKCC (NCT06104488) - phase 1 | 3–30 | RAF and MEK | Avutometinib | Progressive or Recurrent pediatric tumor with activating MAPK-pathway alterations or; NF1 with symptomatic inoperable plexiform neurofibromas and progressive or recurrent pLGGs |
| ANCS1831 (NCT03871257) - phase 3 | 2-21 | MEK | Selumetinib | Newly diagnosed or not previously treated NF1-associated pLGG |
| ANCS1931 (NCT04576117) - phase 3 | 2-25 | MEK | Selumetinib | Progressive or recurrent pLGG |
| ACNS1833 (NCT04166409) - phase 3 | 2-21 | MEK | Selumetinib | Newly diagnosed or previously untreated pLGG |
| SJ901 (NCT04923126) - phase 1/2 | 2-24 | MEK | Mirdametinib | Cohort 1: Newly diagnosed and/or previously untreated pLGG<br>Cohort 2 and 3: Progressive or Recurrent Low-Grade Glioma with or without Previous MEK Inhibitor Exposure |
| PNOC021 (NCT04485559) - phase 1 | 1-25 | MEK + mTOR | Trametinib + everolimus | Progressive or recurrent pLGG or HGG |
| DETERMINE (NCT05768178) - phase 2/3 | >16 | BRAF and MEK | Vemurafenib + cobimetinib | BRAFV600E mutated solid tumors |
| DAY101/FIRELIGHT -1(NCT04985604) - phase 1b/2 | >12 | Pan RAF + MEK | Tovorafenib + pimasertib | Progressive or recurrent solid tumors with B/CRAF alteration |
| DAY101/ FIREFLY-2 LOGGIC (NCT05566795) | <25 | Pan RAF | Tovorafenib vs SOC chemotherapy | Newly diagnosed pLGG with known activating RAF alteration |
| PBTC055 (NCT04201457) - phase 1/2 | 1-30 | MEK and/or BRAF | Hydroxychloroquine + trametinib and/or Dabrafenib | Progressive or recurrent LGG or HGG with BRAF mutation/fusion or NF1 |
| F8394-201 (NCT05503797) - phase 2 | >10 | BRAF | Plixorafenib | BRAF-altered LGG or HGG |
| ARRY-440 (NCT05355701) - phase 1 | >16 | BRAF | PF-07799933 as monotherapy or in combination with binimetinib or cetuximab | Progressive or recurrent BRAF-altered advanced solid tumors including CNS tumors |
| ARRY 134 (NCT05538130) - phase 1 | >16 | MEK | PF-07799544 as monotherapy and in combination with PF-07799933 | Progressive or recurrent BRAF-altered solid tumors including CNS tumors |
| Nested Therapeutics NST-628-001 (NCT06326411) - phase 1 | >18 | MEK + Pan RAF | NST-628 | Solid tumor with genetic alteration of or evidence of tumor dependence upon the RAS/MAPK-pathway |
| Perfume (NCT06159478) – phase 2 | > 12 | BRAF | Binimetinib | Cohort A: BRAF-fusion positive LGG<br>Cohort B: pancreatic cancer |

minor response, providing solid evidence that dabrafenib and trametinib show promise in the recurrent setting. Notably, most patients had durable responses to treatment (median 27.5 months). Unfortunately, four (31%) patients in the LGG cohort died due to disease progression. This is in contrast with the generally favorable overall survival seen in pediatric patients with a BRAFV600E mutant LGG.[12,23] Comprehensive molecular profiling was not available, and it is therefore not possible to discern if there were additional mutations that may have heralded a poorer outcome. In previously published reports, concurrent CDKN2A homozygous mutations have been associated with a poorer prognosis and increased rates of malignant transformation in pediatric patients with BRAFV600E mutant glioma.[16,24]

Nevertheless, these results from the ROAR study suggest that there may be differences in biology, natural history, and clinical response between pediatric and AYA patients with LGG harboring a BRAFV600E mutation treated with MAPK inhibitors. Additionally, this highlights the importance of obtaining molecular sequencing for all AYA patients.

Lastly, there are a number of clinical trials currently underway exploring MAPK-pathway inhibitors in patients >18 years via a tumor-agnostic approach. DETERMINE is a tumor-agnostic trial being conducted in the United Kingdom recruiting patients with BRAFV600E mutations and assessing the combination of vemurafenib and cobimetinib (NCT05768178). Tovorafenib is also being explored in patients 12 years and older with recurrent, progressive, or refractory melanoma or other solid tumors with alterations in the key proteins of the RAS/RAF/MEK/ERK pathway (NCT04985604). Plixorafenib is a next-generation small molecule selective inhibitor of mutated BRAF that is being studied in both pediatric and adult patients with BRAF-altered solid tumors (NCT02428712, NCT05503797). Preliminary results for Plixorafenib have been presented in abstract form for 10 MAPK-naive adult patients (median age 45 years) with a BRAFV600 mutant LGG or HGG.[25] There were six patients with HGG and 4 patients with LGG that were evaluable for efficacy. The ORR was 60% (6/10) with 4/6 of these having a duration of response of over nine months, although it is not known from the abstract whether these four patients had HGG or LGG. These are small patient numbers the larger phase 2 study is currently underway to confirm these findings (NCT05503797) and ascertain whether the results apply to AYA patients specifically. There are several novel MAPK inhibitors in early-phase trials that are enrolling patients 16–18 years or older. PF-07799933 is a novel RAF inhibitor which spares non-BRAF mutated-containing RAF dimers and is being studied both alone and in combination with binimetinib for patients 16 years and older (NCT05355701) and with another novel MEK inhibitor PF- 07799544 (NCT05538130). NST-628 is a novel pan-RAF-MEK inhibitor which prevents phosphorylation of and subsequent activation of MEK by RAF. It is being studied in patients 18+ with a solid tumor harboring a RAS/MAPK alteration (NCT06326411).

While these basket clinical trials are not specific to glioma patients, the results will hopefully provide much-needed data in the AYA population in terms of efficacy and toxicity profile more broadly.

Following the success of targeting the MAPK-pathway in LGG, there have been a small number of clinical trials incorporating MAPK inhibitors in the treatment of relapsed/refractory HGG with a subset of AYA patients enrolled, in particular with dabrafenib and trametinib. The ROAR clinical trial HGG cohort enrolled 22 (48%) participants with relapsed/refractory disease between 18 and 39 years of age, who received dabrafenib and trametinib. In this study, 33% of enrolled patients had an objective response with three complete responses. The median OS from this study was 17.6 months, which is significantly longer than prior studies reporting OS in recurrent glioblastoma of three to nine months.[26] Similar to the LGG cohort, dabrafenib plus trametinib was well tolerated in the HGG cohort with no discontinuation due to side effects. The majority of reported adverse effects were grade 1–2 and were consistent with previous published data showing that pyrexia, fatigue, headache, nausea, and rash were common. One limitation of the ROAR clinical trial was the lack of a comparator group which the authors acknowledged, as well as the need for future randomized clinical trials to determine the true effect on survival in this rare cohort.

There have been several phase 2 clinical trials completed in the relapse/refractory setting for BRAFV600E mutant HGG patients.[27,28] These studies have demonstrated significant improvement in progression-free survival (PFS) and OS compared to molecularly unselected historical cohorts; however, these results should be interpreted with caution as historical data specifically for relapsed/refractory BRAFV600E HGG is lacking. Current clinical trials exploring BRAF inhibition in combination with other therapies in the relapsed/refractory setting are recruiting including PBTC-055 which incorporates hydroxychloroquine in combination with dabrafenib + trametinib for patients aged up to 30 years (NCT04201457). Following the promising results in the relapsed/refractory setting, the use of MAPK inhibitors upfront has been explored in a growing number of pediatric/AYA patients with promising and sustained responses.[29,30] To that end, a phase 2 single-arm Children's Oncology Group (COG) trial utilizing combination dabrafenib + trametinib following radiation therapy for patients with newly diagnosed BRAFV600E HGG aged 3–25 years is currently recruiting (NCT03919071). As BRAFV600E mutant HGG are more common in AYA than pediatric patients, it is hoped that this clinical trial will provide much-needed efficacy and safety data for this cohort in the upfront use of MAPK inhibitors in HGG.

## Toxicity of MAPK-Pathway Inhibitors in AYA

The side effect profile for AYA patients receiving MAPK inhibitors remains largely understudied. In adult patients, an increase in cardiovascular toxicity with asymptomatic left ventricular dysfunction, hypertension, venous thromboembolism, atrial arrhythmia, and QT interval prolongation has been well documented.[31] Cardiotoxicity in children has not been comprehensively nor longitudinally assessed, however a retrospective study in children and young adults <21 years receiving MEK inhibitors demonstrated borderline cardiac function (decreased ejection fraction and/or fractional shortening) in a number of patients.[32] These results have not been consistently replicated in the published phase 2/3 clinical trials utilizing a combination of MEK and RAF inhibitors, where there was minimal cardiac dysfunction reported.[12,33] In addition to cardiac toxicities, there have been reports of secondary malignancies in adult patients treated with BRAF inhibitors including development of SCC, secondary melanoma, gastrointestinal polyps, and recurrence of prior malignancies.[34] These secondary malignancies have not been reported in children and may be more common in adults due to other predisposing risk factors. It is likely that AYA patients will experience a combination of side effects that encompass the spectrum seen in both pediatric and adult patients; however, better evidence with registry studies and clinical trials are urgently needed to better inform our understanding.

## Adult-Type Diffuse Glioma

Adult-type diffuse gliomas are found in a subset of AYA patients and are subdivided into 1) astrocytoma, IDH-mutant 2) oligodendroglioma, IDH-mutant, and 1p/19q-codeleted and 3) glioblastoma, IDH-wild type.[35] IDH mutations were identified as potential drivers of oncogenesis through preclinical models demonstrating that reduction in d-2-hydroxyglutarate (D-2-HG), the oncogenic metabolite produced by mutant IDH, slowed tumor growth and promoted differentiation.[36] Most IDH-mutant gliomas in older patients express the canonical IDH1 mutation p.R132H detected through immunohistochemistry however other IDH1 and 2 mutations are of relatively higher frequency in younger patients and should be ruled out with comprehensive genetic sequencing.[37] Treatment approach for IDH-mutant gliomas in AYA can vary significantly, depending on whether the patient is treated in an adult or pediatric setting, with radiation-sparing approaches generally preferred for younger patients.[37] In general, the standard practice in recent years has included maximal safe resection followed by a period of either watchful waiting or upfront radiotherapy and/or systemic chemotherapy depending on prognostic factors. These factors historically included the extent of resection, age, genomics, and histological grade. This approach however is subject to review considering the development and efficacy of IDH inhibitors, specifically with the publication of landmark results from the INDIGO trial.[38] Subsequently, FDA approval for vorasidenib, an oral IDH inhibitor, was recently obtained in August 2024 for non-enhancing grade 2 IDH-mutant glioma.

## Targeting Mutant IDH

Ivosidenib is a potent oral mutant IDH1 inhibitor and was first investigated and given FDA approval in patients with IDH1 mutant relapsed/refractory AML followed by approval for cholangiocarcinoma and refractory/relapsed MDS.[39–41] Between 2014 and 2019 a single-arm, multicenter, open-label, phase I dose-escalation and dose-expansion study in patients with advanced IDH1-mutant solid tumors, including grade 2–4 gliomas was conducted.[42] The study was open to enrollment for those aged 18 or greater, and the youngest patient enrolled was 21 years of age. Based on the published data it is not known how many treated were between the ages of 15–39 years. In total, 66 patients were enrolled, 54 with lower-grade histology. One patient had a partial response, 44 showed stable disease and 21 showed progressive disease, demonstrating a mixed response. Importantly, no discontinued treatment due to side effects, and it was generally well tolerated with no maximal dose identified. Participants with non-enhancing lesions showed higher rates of stable disease (30/35, 85.7%) and prolonged responses (median PFS 13.6 months) when compared to enhancing lesions.

Vorasidenib is an oral brain-penetrant dual inhibitor of mutant IDH1 and IDH2 that was first evaluated for grade 2, 3, or 4 gliomas in a phase I study between 2020 and 2022.[43] 52 patients (48 with lower-grade gliomas and 4 with glioblastoma) were enrolled, the majority of whom had received either radiotherapy or chemotherapy prior to enrollment. The objective response rate (ORR) was 18% (one partial response and three minor responses), with a duration ranging from 7.4 to 27.7 months. 72.7% of patients with non-enhancing gliomas achieved stable disease with a number of these showing a reduction in tumor size which did not reach the minor response criteria of 25% reduction. The median PFS of individuals with non-enhancing gliomas was 36.8 months. Ultimately, vorasidenib was favored to progress to a phase 3 clinical trial following the results of a peri-operative phase 1 clinical trial demonstrated that vorasidenib had more consistent D-2-HG suppression, superior brain penetration, and clinical efficacy compared to ivosidenib.[44]

The INDIGO trial was a phase 3 double-blinded, randomized controlled trial in patients with residual or recurrent non-enhancing grade 2 IDH-mutant astrocytoma or IDH-mutant, 1p19q-codeleted oligodendroglioma.[38] The eligible participants were patients aged 12 years or older who were suitable for a watchful waiting approach. The primary endpoint was imaging-based PFS and the key secondary endpoint was the time-to-next intervention. There were 76 patients between the ages of 18–39 who received vorasidenib in this study. Despite the lower age limit of 12 years, only one patient under the age of 18 was enrolled and they were originally randomized to the placebo arm. Imaging-based PFS was significantly longer for the vorasidenib group compared to the placebo group with a median of 27.7 months (95% CI 17.0 to non-estimable) versus 11.1 months (95% CI: 11.0–13.7). Importantly, the vorasidenib group demonstrated a significantly longer time-to-next intervention. Based on these results, in August 2024 the FDA approved vorasidenib use for those 12 and up who have a non-enhancing grade 2 IDH-mutant astrocytoma or IDH-mutant, 1p19q-codeleted oligodendroglioma.

While IDH inhibitors in grade 2 IDH-mutant glioma have shown a promising PFS advantage, the results for aggressive, contrast-enhancing tumors have been less impressive.[38,44] In the phase I trial with vorasidenib in relapsed/refractory disease, the cohort of patients with enhancing tumors showed no objective responses, with 56.7% displaying stable disease and 43.3% displaying progressive disease with a median PFS of 3.6 months indicating a lack of efficacy in this group.[43] It is postulated that IDH inhibitors are less effective in higher-grade IDH-mutant glioma due to additional molecular alterations that bypass the need for mutant IDH enzyme to drive glioma progression. IDH-mutant astrocytoma with either homozygous deletion of CDKN2A/CDKN2B irrespective of histopathological features are classified as grade 4 tumors, highlighting the significance of additional mutations in accelerating glioma growth and malignant transformation, and portending worse prognosis in IDH-mutant glioma.

The potential benefits of IDH inhibitors specifically in grade 3 IDH-mutant gliomas have yet to be elucidated. However, there have been studies published with large datasets showing that there is no difference in outcome between grade 2 and grade 3 IDH-mutant glioma, highlighting the overlapping natural history of grade 2 and 3 tumors.[45] The exact oncogenic mechanisms that lead to malignant transformation in low-grade IDH-mutant glioma remain unclear, as does the optimal time to commence

vorasidenib and whether vorasidinib prevents malignant transformation. Furthermore, it is unclear whether monotherapy or combination therapy with radiation with or without chemotherapy would be more efficacious.

There are several early phase clinical trials exploring alternative targeted agents for IDH-mutant glioma including PARP inhibitors (NCT03914742 and NCT03991832), CDK4/6 inhibitors (NCT03220646), demethylating agents such as 5-azacitadine ((NCT03922555 and NCT03666559) as well as metabolic pathway inhibitors including the glutaminase inhibitor teleglenastat (NCT03528642). There are a number of unanswered questions with regard to the use of vorasidenib in adolescents and young adults. Despite the approved label for low-grade tumors, no patients under the age of 18 were treated with vorasidenib in the INDIGO trial. As such, the long-term effectiveness and toxicity profile in this age group remain unknown, as does the optimal timing to initiate treatment in the AYA population. Patients with IDH-mutant glioma are highly likely to experience disease progression and/or transformation during their lifetime and require several lines of therapy. Combined immune checkpoint inhibition and IDH inhibition are currently being investigated in clinical trials with nivolumab/ivosidenib and pembrolizumab/vorasidenib respectively (NCT04056910 and NCT05484622).

## High-Grade Glioma

HGG in AYA patients includes a diverse group of clinicopathological and molecularly divergent tumors that can span the spectrum of pediatric and adult genetic alterations. The recognition that distinct molecular differences exist between pediatric- and adult-type HGG has informed the most recent 2021 WHO classification of Tumors of the CNS. In general, pediatric HGG is divided into four subgroups: Diffuse midline glioma, H3K27M-altered, Diffuse hemispheric glioma, H3 G34-mutant, Diffuse pediatric-type HGG, H3 wildtype, IDH-wild type and infant-type hemispheric glioma.[6] In contrast, adult HGG often represents the malignant transformation from a lower-grade tumor to a higher grade and is categorized based on the presence or absence of an IDH1/2 mutation as well as tumor grade. The most commonly encountered HGGs include astrocytoma, IDH-mutant grade 3 and 4, oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, grade 3 and glioblastoma, IDH wild type.

A multicenter study by Roux et al. of HGG in AYA patients aged 15–25 years found that the most common molecular subgroup was the pediatric-type H3-histone mutant comprising up to 40% of tumors, with the H3 G34-mutant group comprising approximately one-third of these tumors.[14] Overall, H3 G34-mutant gliomas are more prevalent in the AYA population than either the pediatric or the adult population.[17] Finding effective targeted therapies for H3-histone mutant HGG has been challenging, and the prognosis has remained poor. As targeted therapy for this group of patients will be covered in a separate review, this review will not discuss specific therapies but acknowledges the severe unmet need for this highly aggressive subgroup of HGG in AYA patients. The second most common HGG subgroup is the adult-type IDH-mutant tumors, making up 27.5% of AYA HGG with a median age of 22.5 years.[14] The current standard treatment for these tumors is maximal safe resection combined with radiation therapy and either concurrent or adjuvant temozolomide.[46]

## Meningioma

Meningiomas are the most common CNS tumor in adults, and in the AYA population, they account for approximately 16% of all primary CNS tumors.[5] There has been incremental understanding of the methylomic and molecular profiling of meningiomas, enabling better risk stratification. Although tumors associated with genetic syndromes are not specifically covered in this review, a significant proportion of younger patients with meningiomas have a diagnosis of NF2-related schwannomatosis, which presents with multiple meningiomas with different patterns of growth, grades, and aggressiveness.[47,48] Current EANO adult guidelines advise asymptomatic meningiomas can be observed safely, with surgical resection the first line treatment for symptomatic or growing meningiomas followed by radiation therapy for those with residual and/or unresectable tumors or high-grade histology.[49] For recurrent meningioma, defining an appropriate/acceptable response to novel treatment has been challenging. To address this issue, a meta-analysis done in 2014 identified 6-month progression-free survival (PFS-6) of 26% for grade 2/3 tumors as a benchmark to assess future clinical trials.[50] Advancement in molecular techniques has uncovered several molecular drivers of meningioma associated with chromosomal copy number variations (CNVs), the most common being chromosome 22q which is home to the NF2 gene and is mutated in up to 80% of adult meningiomas.[51] Increasing risk of recurrence and aggressive clinical behavior is seen with the accumulation of CNVs including loss of chromosome 1p, 3p, 4, 6q, 10, 14q, 18, and 19.[52] These CNVs result in several known mutations including SMO, PIK3CA, AKT, SMARCB1, TRAF7, TERT, SMARCE1, and BAP1.[53] Emerging data from next-generation sequencing suggests that pediatric meningioma has a different molecular landscape to adult meningioma, highlighting the need for molecular analysis for AYA patients who may present with both pediatric and adult subtypes.[54] To our knowledge, no comprehensive clinical and molecular analysis of both pediatric and AYA patients has been published to guide whether AYA patients are more likely to have a molecular profile consistent with pediatric or adult meningioma.

Although not specific to AYAs, there have been several published clinical trials utilizing targeted therapy for recurrent meningioma in adult cohorts. Kaley et al. conducted a single-arm phase 2 trial using sunitinib in patients 18 years or older with recurrent or refractory grade 2–3 meningioma.[55] with a median PFS of 5.2 months, and median OS of 24.6 months. Despite some observed toxicity, the results suggest that sunitinib is active against meningioma and warrants further investigation. A phase 2 trial of bevacizumab for recurrent and refractory meningioma was conducted with 11 patients 39 years or under.[56] For grade 2/3 meningioma the median PFS-6 was 66% suggesting bevacizumab is a viable therapy once surgical options and radiotherapy have been exhausted. Alliance AO71401 is a

National Cancer Institute–supported Cooperative Group Trial exploring several targeted agents based on recurrent meningioma harboring specific mutations. The arms include an AKT inhibitor for AKT- or PIK3CA-mutated meningiomas, an SMO inhibitor for SMO-mutated meningiomas, a focal adhesion kinase (FAK) inhibitor for NF2-altered tumors, and a cyclin-dependent kinase (CDK) inhibitor for CDK pathway altered tumors. Preliminary results have been published in abstract form for the CDK inhibitor, abemaciclib, showing a PFS-6 of 55% in 35 evaluable patients (age range not provided).[57] The FAK inhibitor, GSK2256098, was evaluated in 37 patients with a median age of 64 years (22–76 years). 66.7% of patients achieved stable disease as the best response with acceptable toxicity observed. The PFS-6 for all patients was 50% and for the grade 2/3 cohort it was 33%.[58] Further research with larger patient populations will help delineate the response, toxicity profile, and longer-term side effects for AYAs with meningioma.

## Medulloblastoma

Medulloblastoma is the most common embryonal tumor in adolescents and young adults, with an annual incidence of 0.2 to 0.4 cases per 100 000 in those aged 15 to 39.[5] Most cases belong to the Sonic Hedgehog-activated (SHH) group, with a smaller percentage in the Wingless (WNT) and non-WNT, non-SHH groups.[59] The five-year overall survival rate for the SHH group (P53 wild type) is 50%–70%, and the treatment combines maximal safe resection, radiation therapy, and chemotherapy, adapted from pediatric protocols.[60] Compared to children, AYAs are subjected to significantly more severe short- and long-term toxicity from chemotherapy and radiation therapy. There is currently a lack of a standardized approach to systemic treatment for adult medulloblastoma and significant heterogeneity exists in treatment decisions between institutions.[61] A particular challenge in the AYA and adult population is the significantly higher rates and severity of vincristine-associated polyneuropathy and myelosuppression requiring dose reductions or early cessation of adjuvant chemotherapy.[62]This highlights the need for more novel therapies that are less toxic.[63] Common mutations in adult SHH-activated medulloblastoma include SMO and PTCH.[64] Targeted therapies like vismodegib, sonidegib, and glasdegib inhibit the mutated smoothened protein (disrupting the SHH pathway and are a promising therapeutic option to both improve PFS and OS as well as reduce long-term toxicity.[65] Vismodegib and sonidegib are FDA-approved for advanced basal cell carcinoma, while glasdegib is approved for AML in older adults or those unfit for intensive chemotherapy.[40,66,67]

Several phase 1/2 clinical trials using SMO inhibitors for relapsed/refractory medulloblastoma have shown mixed results. In a phase I study, Rodon et al enrolled 9 patients treated with sonidegib, achieving a 33% ORR, but responses were short-lived (4–8 months) suggesting rapid acquisition of resistance.[68] Similarly, The Pediatric Brain Tumor Consortium (PBTC) conducted two phase 2 studies of vismodegib, finding only 15% of SHH-activated medulloblastoma patients had sustained responses of at least eight weeks.[69] A 2017 study by Kieran et al reported an 18.8% ORR for adults treated with sonidegib, with responses exclusively in patients with an activated SHH pathway identified by a 5-gene signature assay.[70] In the phase 1/2 MEVITEM trial, adult patients with relapsed/refractory SHH-activated medulloblastoma were randomized 2:1 to either temozolomide or temozolomide + vismodegib. Only six patients out of 24 exposed to vismodegib had an OR and all of these were short-lived, with the median duration of response not exceeding four months for single agent vismodegib or in combination with temozolomide.[71] A 2019 meta-analysis of five studies found a pooled ORR of 37% for SHH-activated medulloblastoma treated with SMO inhibitors (vismodegib and sonidegib), while no responses were noted for non-SHH cases.[72] These findings suggest that the efficacy of treatment depends on mutation location; patients with mutations downstream of SMO or PTCH1 are significantly less likely to respond than those with upstream mutations. Thus, stratification by specific genomic aberrations could enhance the benefits of SMO inhibitors in medulloblastoma treatment, but responses remain transient, and mechanisms of resistance require further investigation to optimize their use in current treatment protocols.

The use of SMO inhibitors has been proposed in the upfront treatment of AYA and adults with medulloblastoma, leading to the development of several randomized clinical trials.[73,74] The SJMB12 clinical trial is the first upfront medulloblastoma trial to incorporate molecular risk stratification with clinical risk grouping and allowed enrollment of patients up to 39 years in the SHH subgroup.[75] For skeletally mature SHH-MB patients, 12 months of vismodegib as maintenance therapy has been included to investigate whether its use in the upfront setting can reduce rates of relapse. Preliminary results for the SHH-MB subgroup have been presented in abstract form, reporting excellent five-year event-free survival for low-risk SHH patients without a TP53 mutation upwards of 90%. The data for AYA patients specifically, including the tolerability and efficacy of vismodegib, has yet to be published. The European Organization for Research and Treatment of Cancer 1634-BTG/NOA-23 trial is designed to randomize newly diagnosed medulloblastoma patients aged 15 or older between standard-dose versus reduced-dosed craniospinal radiotherapy and SHH-subgroup patients between the SMO inhibitor sonidegib and standard chemotherapy with vincristine, lomustine, and cisplatin.[73] The Alliance AMBUSH trial proposed randomizing patients 18 years or older to 12 months of maintenance therapy of either an SMO inhibitor or placebo following radiation therapy and chemotherapy.[74] Unfortunately, the 1634-BTG/NOA-23 has been suspended due to low patient accrual, while the development of the Alliance AMBUSH trial has been discontinued due to lack of sponsor support. Trials such as these are greatly needed to help guide treatment based on prospective data that evaluates not only outcomes but toxicity as well as strategies to increase recruitment and ensure ongoing pharmaceutical engagement.

## Craniopharyngioma

Craniopharyngioma is a rare WHO grade 1 epithelial tumor of the CNS commonly arising along the pituitary stalk in

the suprasellar area with an annual incidence of 0.16 per 100 000 persons.[76] It has a bimodal age distribution with an increased incidence rate in those five to 14 years and 50 to 74 years of age.[77] Histologically, craniopharyngioma is divided into 2 subgroups: adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). ACP is found in both pediatric and adult patients while PCP is principally a disease of adults. Histologically, ACPs are characterized by well-differentiated palisading epithelium, stellate reticulum, and wet keratin nodules while PCPs have non-keratinizing mature squamous epithelium with the absence of stellate reticulum and wet keratin.[78] As well as histological differences, the molecular drivers of the 2 subgroups differ with ACP being driven by alterations in CTNNB1 and PCP almost exclusively harboring BRAFV600E mutations.[79] While these tumors have traditionally been considered benign, they can cause significant destruction of local structures which can lead to life-changing endocrinopathy and neurological sequelae.[80] While it is likely that the numbers of AYA patients with craniopharyngioma are small based on the bimodal distribution, it is important to be mindful of the features that may suggest a papillary craniopharyngioma as opposed to an adamantinomatous craniopharyngioma. With the increased understanding of the molecular underpinnings of both ACP and PCP there has been a change in treatment paradigms with the goal of reducing the potentially devastating long-term neuroendocrine complications.

Given the presence of BRAFV600E mutation in papillary craniopharyngioma, several case reports and clinical trials have explored the use of MAPK-pathway inhibitors in papillary craniopharyngioma (PCP) with promising clinical responses. Brastianos and colleagues published their results for a single-arm, phase 2 trial utilizing a combination of cobimetinib and vemurafenib in a small cohort of patients who had not received prior radiation or systemic therapy.[81] Sixteen patients were enrolled and evaluable with the median age being 49.5 years (33–83). The study prespecified that patients would receive definitive therapy with radiation or surgery after treatment with vemurafenib–cobimetinib for four cycles (one cycle = 28 days), however a number of patients continued well beyond four cycles up to 18 months post commencement on trial after it was deemed they either were continuing to benefit from the treatment and/or if definitive therapy was not recommended or declined by the patient. The median reduction in tumor volume was 91% with sustained responses at 12 months in 93% of patients. Additionally, 6/7 patients who received no therapy after cobimetinib and vemurafenib had no evidence of progression at a median follow-up time of 23 months suggesting this a promising therapy that can avoid the need for extensive surgery and radiation therapy. There were a number of grade 3 side effects, the most frequent being maculopapular rash in 35%, but generally, the treatment was well tolerated. Overall, the results of the study demonstrated that the use of BRAF and MEK inhibition can enable a less aggressive upfront surgical approach as well as delay the need for radiation therapy.

While adamantinomatous craniopharyngioma (ACP) tumorigenesis is primarily driven by alterations in CTNNB1, it has recently been found to express several growth factors in the MAPK pathway suggesting a potential role for MAPK inhibitors in its treatment.[82] There is also preclinical work demonstrating the role of immune and inflammatory pathways such as PD-1/PD-L1 in its pathogenesis.[83,84] Considering these findings, several clinical trials have been developed to explore the use of MAPK-pathway inhibitors with and without immune modulators in ACP. CONNECT2108 is a phase 2 clinical trial run through the CONNECT consortium exploring the use of the MEK inhibitor binimetinib in patients aged up to 25 years with a confirmed diagnosis of ACP having either progressive disease post radiation or having residual or progressive disease without radiation (NCT05286788). Additionally, the type II BRAF inhibitor tovorafenib is being studied both as a single agent and in combination with nivolumab in patients with craniopharyngioma up to the age of 39 years in PNOC029 (NCT05465174). It is hoped that by utilizing these agents in a neoadjuvant fashion prior to surgery, the potential for debilitating neuroendocrine dysfunction could be mitigated. Further research on the AYA subgroup in craniopharyngioma will be required to better understand the use of these therapies including their efficacy and toxicity profile.

## Conclusion

Molecularly driven targeted therapies have changed the conventional treatment paradigms of an increasing number of CNS tumors. AYA patients are a unique population that traverses the pediatric-adult divide and often have tumors driven by molecularly targetable alterations, underscoring the importance of comprehensive molecular analysis. The toxicity and efficacy of many targeted therapies have not been clearly defined in the AYA population and warrant attention through access to clinical trials and comprehensive care in centers with experienced physicians. Alongside targeted therapy, emerging novel therapies for CNS tumors including immune checkpoint inhibitors, CAR T cells, and vaccines are anticipated to further improve the treatment options available for AYA patients and ultimately provide effective and safe therapies in the future. Relevant endpoints for AYA-specific clinical trials will need to consider tumor biology and quality-of-life measures that may be unique to younger patients. Collaborative efforts such as prospective multi-institutional registries of real-world clinical experience with targeted therapies may supplement the current insights gleaned from clinical trials in the AYA population. These strategies will pave the way for lasting and effective therapies to improve outcomes for this vulnerable population.

## Keywords

AYA | adolescent and young adult | CNS tumor | targeted therapy

## Supplement sponsorship

This article appears as part of the supplement "Targeted Therapies in Pediatric Brain Tumors," sponsored by Day One Biopharmaceuticals.

## Conflict of interest statement

M.L. and J.B. have received honoraria from Servier unrelated to this work. M.L. has received honoraria from Chimerix unrelated to this work. A.M. and K.K.Y. declare no conflict of interest.

## Data availability

No new data was generated, and no third-party data was analyzed for this manuscript.

All authors contributed equally to drafting and editing of this manuscript.

## Affiliations

Department of Pediatric Oncology, Dana-Farber / Boston Children's Cancer and Blood Disorder Center, Boston, Massachusetts, USA (A.M.); Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada (J.B.); Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada (K.K.Y.); Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada (M.J.L.-F.)

## References

1. Yeo KK, Burgers DE, Brodigan K, et al. Adolescent and young adult neuro-oncology: A comprehensive review. *Neurooncol. Pract.*. 2021;8(3):236–246.
2. Lim-Fat MJ, Bennett J, Ostrom Q, et al. Central nervous system tumors in adolescents and young adults: A society for neuro-oncology consensus review on diagnosis, management, and future directions. *Neuro Oncol.* 2024;27(1):13–32.
3. Siembida EJ, Loomans-Kropp HA, Trivedi N, et al. Systematic review of barriers and facilitators to clinical trial enrollment among adolescent and young adults with cancer: Identifying opportunities for intervention. *Cancer.* 2019;126(949):949–957.
4. Weiser A, Sanchez Bergman A, Machaalani C, et al. Bridging the age gap: A review of molecularly informed treatments for glioma in adolescents and young adults. *Front Oncol.* 2023;13(1):1254645.
5. Price M, Neff C, Nagarajan N, et al. CBTRUS statistical report: American Brain Tumor Association & NCI neuro-oncology branch adolescent and young adult primary brain and other central nervous system tumors diagnosed in the United States in 2016–2020. *Neuro Oncol.* 2024;26(Suppl 3):iii1–iii53.
6. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: A summary. *Neuro Oncol.* 2021;23(8):1231–1251.
7. Bennett J, Levine A, Nobre L, et al. Lgg-34. The landscape of gliomas in children, adolescents and young adults reveals insights on gliomagenesis: A canadian adolescents and young adults neuro-oncology network (canon) study. *Neuro Oncol.* 2024;26(Suppl 4):0–0.
8. Ryall S, Zapotocky M, Fukuoka K, et al. Integrated molecular and clinical analysis of 1,000 pediatric low-grade gliomas. *Cancer Cell.* 2020;37(4):569–583.e5.
9. Bennett J, Nobre L, Sheth J, et al. The clinical and molecular landscape of gliomas in adolescents and young adults. *Neurooncol. Adv.*. 2023;5(Suppl 2):i2–i3.
10. De Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J. Management of pediatric low-grade glioma. *Curr Opin Pediatr.* 2019;31(21):21–27.
11. Rizzo D, Ruggiero A, Amato M, Maurizi P, Riccardi R. BRAF and MEK inhibitors in pediatric glioma: New therapeutic strategies, new toxicities. *Expert Opin Drug Metab Toxicol.* 2016;12(12):1397–1405.
12. Bouffet E, Hansford JR, Garrè ML, et al. Dabrafenib plus trametinib in pediatric glioma with BRAF V600 mutations. *N Engl J Med.* 2023;389(12):1108–1120.
13. Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutant low-grade and high-grade glioma (ROAR): A multicentre, open-label, single-arm, phase 2, basket trial. *Lancet Oncol.* 2022;23(1):53–64.
14. Roux A, Pallud J, Saffroy R, et al. High-grade gliomas in adolescents and young adults highlight histomolecular differences from their adult and pediatric counterparts. *Neuro Oncol.* 2020;22(1190):1190–1202.
15. Mistry M, Zhukova N, Merico D, et al. BRAF mutation and CDKN2A deletion define a clinically distinct subgroup of childhood secondary high-grade glioma. *J Clin Oncol.* 2015;33(9):1015–1022.
16. Lassaletta A, Zapotocky M, Mistry M, et al. Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas. *J Clin Oncol.* 2017;35(25):2934–2941.
17. Mackay A, Burford A, Carvalho D, et al. Integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma. *Cancer Cell.* 2017;32(4):520–537.e5.
18. D'Angelo F, Ceccarelli M, Tala, et al. The molecular landscape of glioma in patients with Neurofibromatosis 1. *Nat Med.* 2018;25(1):176–187.
19. Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: A multicentre, phase 2 trial. *Lancet Oncol.* 2019;20(7):1011–1022.
20. Robison N, Pauly J, Malvar J, et al. LTBK-04. Late breaking abstract: MEK162 (binimetinib) in children with progressive or recurrent low-grade glioma: A multi-institutional phase II and target validation study. *Neuro Oncol.* 2022;24(Suppl 1):i191–i192.
21. Kaley T, Touat M, Subbiah V, et al. BRAF inhibition in BRAFV600-mutant gliomas: Results from the VE-BASKET study. *J Clin Oncol.* 2018;36(35):3477–3484.
22. Kilburn LB, Khuong-Quang D-A, Hansford JR, et al. The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: The phase 2 FIREFLY-1 trial. *Nat Med.* 2023;30(1):207–217.
23. Tsai JW, Choi JJ, Ouaalam H, et al. Integrated response analysis of pediatric low-grade gliomas during and after targeted therapy treatment. *Neurooncol. Adv.*. 2023;5(1):vdac182.
24. Nobre L, Zapotocky M, Ramaswamy V, et al. Outcomes of BRAF V600E pediatric gliomas treated with targeted BRAF inhibition. *JCO Precis Oncol.* 2020;4:561–571.
25. de la Fuente M, Ahnert JR, Yaeger R, et al. Safety and efficacy of the novel BRAF inhibitor FORE8394 in patients with advanced solid and CNS tumors: Results from a phase 1/2a study. *J Clin Oncol* 2023;41(16_suppl):3006–3006.
26. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: A Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol.* 2020;22(8):1073–1113.

27. Hargrave DR, Terashima K, Hara J, et al. Phase II trial of dabrafenib plus trametinib in relapsed/refractory BRAF V600 mutant pediatric high-grade glioma. *J Clin Oncol.* 2023;41(33):5174–5183.
28. Hargrave DR, Moreno L, Broniscer A, et al. Dabrafenib in pediatric patients with BRAF V600-[positive high-grade glioma (HGG) V600–positive high-grade glioma (HGG). *J Clin Oncol.* 2018;36(10505_suppl):10505–10505.
29. Rosenberg T, Yeo KK, Mauguen A, et al. Upfront molecular targeted therapy for the treatment of BRAF-mutant pediatric high-grade glioma. *Neuro Oncol.* 2022;24(11):1964–1975.
30. Arbour G, Ellezam B, Weil AG, et al. Upfront BRAF/MEK inhibitors for treatment of high-grade glioma: A case report and review of the literature. *Neurooncol. Adv.*. 2022;4(1):vdac174.
31. Glen C, Tan YY, Waterston A, et al. Mechanistic and clinical overview cardiovascular toxicity of BRAF and MEK Inhibitors: JACC: Cardiooncology state-of-the-art review. *Cardio Oncol.* 2022;4(1):1–18.
32. Robison NJ, Su JA, Fang MJ, Malvar J, Menteer J. Cardiac function in children and young adults treated with MEK inhibitors: A retrospective cohort study. *Pediatr Cardiol.* 2022;43(6):1223–1228.
33. Bouffet E, Geoerger B, Moertel C, et al. Efficacy and safety of trametinib monotherapy or in combination with dabrafenib in pediatric BRAF V600-mutant low-grade glioma. *J Clin Oncol.* 2023;41(3):664–674.
34. Garutti M, Bergnach M, Polesel J, et al. BRAF and MEK inhibitors and their toxicities: A meta-analysis. *Cancers.* 2023;15(1):141.
35. Wu J, Heidelberg RE, Gajjar A. Adolescents and young adults with cancer: CNS tumors. *J Clin Oncol.* 2023;42(6):JCO2301747.
36. Rudà R, Horbinski C, van den Bent M, Preusser M, Soffietti R. IDH inhibition in gliomas: From preclinical models to clinical trials. *Nat Rev Neurol.* 2024;20(July 2024):395–407.
37. Lim-Fat MJ, Cotter J, Touat M, et al. A comparative analysis of IDH-mutant glioma in pediatric, young adult, and older adult patients analysis of IDH-mutant glioma in pediatric, young adult, and older adult patients. *Neuro Oncol.* 2024;26(12):2364–2376.
38. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al; INDIGO Trial Investigators. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N Engl J Med.* 2023;389(7):589–601.
39. Casak SJ, Pradhan S, Fashoyin-Aje LA, et al. FDA approval summary: Ivosidenib for the treatment of patients with advanced unresectable or metastatic, chemotherapy refractory cholangiocarcinoma with an IDH1 mutation. *Clin Cancer Res.* 2022;28(2733):2733–2737.
40. Heuser M, Robak T, Montesinos P, et al. Glasdegib (GLAS) plus low-dose cytarabine (LDAC) in AML or MDS: BRIGHT AML 1003 final report and four-year overall survival (OS) follow-up. *J Clin Oncol.* 2020;38(15_suppl):7509–7509.
41. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med.* 2018;378(25):2386–2398.
42. Mellinghoff IK, Ellingson BM, Touat M, et al. Ivosidenib in isocitrate dehydrogenase 1 - mutated advanced glioma. *J Clin Oncol.* 2020;38(29):3398–3406.
43. Mellinghoff IK, Penas-Prado M, Peters KB, et al. Vorasidenib, a dual inhibitor of mutant IDH1/2, in recurrent or progressive glioma; results of a first-in-human phase I trial. *Clin Cancer Res.* 2021;27(16):4491–4499.
44. Mellinghoff IK, Lu M, Wen PY, et al. Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: A randomized, perioperative phase 1 trial. *Nat Med.* 2023;29(3):615–622.
45. van den Bent MJ, French PJ, Brat D, et al. The biological significance of tumor grade, age, enhancement, and extent of resection in IDH-mutant gliomas: How should they inform treatment decisions in the era of IDH inhibitors? *Neuro Oncol.* 2024;26(10):1805–1822.
46. van den Bent MJ, Tesileanu CMS, Wick W, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): Second interim analysis of a randomised, open-label, phase 3 study. *Lancet Oncol.* 2021;22(6):813–823.
47. Wang JZ, Patil V, Landry AP, et al; International Consortium on Meningiomas (ICOM). Molecular classification to refine surgical and radiotherapeutic decision-making in meningioma. *Nat Med.* 2024;30(November 2024):3173–3183.
48. Wang JZ, Landry AP, Raleigh DR, et al; International Consortium on Meningiomas (ICOM). Meningioma: International Consortium on Meningiomas consensus review on scientific advances and treatment paradigms for clinicians, researchers, and patients. *Neuro Oncol.* 2024;26(10):1742–1780.
49. Goldbrunner R, Stavrinou P, Jenkinson MD, et al. EANO guideline on the diagnosis and management of meningiomas. *Neuro Oncol.* 2021;23(11):1821–1834.
50. Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: A RANO review. *Neuro Oncol.* 2014;16(6):829–840.
51. Nasrallah MLP, Aldape KD. Molecular classification and grading of meningioma. *J Neurooncol.* 2023;161(2):373–381.
52. Driver J, Hoffman SE, Tavakol S, et al. A molecularly integrated grade for meningioma. *Neuro Oncol.* 2022;24(5):796–808.
53. Ogasawara C, Philbrick BD, Adamson DC. Meningioma: A review of epidemiology, pathology, diagnosis, treatment, and future directions. *Biomedicines.* 2021;9(3):319.
54. Toland A, McNulty SN, Pekmezci M, et al. Pediatric meningioma: A clinicopathologic and molecular study with potential grading implications. *Brain Pathol.* 2020;30(3):1134–1143.
55. Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro Oncol.* 2015;17(1):116–121.
56. Kumthekar P, Grimm SA, Aleman RT, et al. A multi-institutional phase II trial of bevacizumab for recurrent and refractory meningioma. *Neurooncol. Adv.*. 2022;4(1):vdac123.
57. Brastianos PK, Dooley K, Geyer SM, et al. Alliance A071401: Phase II trial of abemaciclib in patients with grade 2/3 meningiomas harboring somatic NF2 or CDK pathway alterations. *J Clin Oncol.* 2024;42(Suppl_8):2001–2001.
58. Brastianos PK, Twohy EL, Gerstner ER, et al. Alliance A071401: Phase II trial of focal adhesion kinase inhibition in meningiomas with somatic NF2 mutations. *J Clin Oncol.* 2023;41(3):618–628.
59. Coltin H, Sundaresan L, Smith KS, et al. Subgroup and subtype-specific outcomes in adult medulloblastoma. *Acta Neuropathol.* 2021;142(November 2021):859–871.
60. Franceschi E, Giannini C, Furtner J, et al. Adult medulloblastoma: Updates on current management and future perspectives. *Cancers.* 2022;14(15):3708.
61. Majd NK, Mastall M, Lin H, et al. Clinical characterization of adult medulloblastoma and the effect of first-line therapies on outcome; The MD Anderson Cancer Center experience. *Neurooncol. Adv.* 2021;3(1):vdab079.
62. Beier D, Proescholdt M, Reinert C, et al. Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07). *Neuro Oncol.* 2018;20(3):400–410.
63. Stavinoha PL, Askins MA, Powell SK, Smiley NP, Robert RS. Neurocognitive and psychosocial outcomes in pediatric brain tumor survivors. *Bioengineering.* 2018;5(3):73.
64. Skowron P, Farooq H, Cavalli FMG, et al. The transcriptional landscape of Shh medulloblastoma. *Nat Commun.* 2021;12(1):1–17.
65. Kool M, Jones DTW, Jäger N, et al; ICGC PedBrain Tumor Project. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. *Cancer Cell.* 2014;25(3):393–405.

66. Sekulic A, Migden MR, Basset-Seguin N, et al; ERIVANCE BCC Investigators. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: Final update of the pivotal ERIVANCE BCC study. *BMC Cancer.* 2017;17(1):332.
67. Lear JT, Migden MR, Lewis KD, et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. *J Eur Acad Dermatol Venereol.* 2018;32(3):372–381.
68. Rodon J, Tawbi HA, Thomas AL, et al. A phase I, multicenter, open-label, first-in-human, dose-escalation study of the oral smoothened inhibitor Sonidegib (LDE225) in patients with advanced solid tumors. *Clin Cancer Res.* 2014;20(7):1900–1909.
69. Robinson GW, Orr BA, Wu G, et al. Vismodegib exerts targeted efficacy against recurrent sonic Hedgehog–Subgroup medulloblastoma: Results from phase II pediatric brain tumor consortium studies PBTC-025B and PBTC-032. *J Clin Oncol.* 2015;33(2646):2646–2654.
70. Kieran MW, Chisholm J, Casanova M, et al. Phase I study of oral sonidegib (LDE225) in pediatric brain and solid tumors and a phase II study in children and adults with relapsed medulloblastoma. *Neuro Oncol.* 2017;19(11):1542–1552.
71. Frappaz D, Barritault M, Montané L, et al. MEVITEM-a phase I/II trial of vismodegib + temozolomide vs temozolomide in patients with recurrent/refractory medulloblastoma with Sonic Hedgehog pathway activation. *Neuro Oncol.* 2021;23(11):1949–1960.
72. Li Y, Song Q, Day BW. Phase I and phase II sonidegib and vismodegib clinical trials for the treatment of paediatric and adult MB patients: A systemic review and meta-analysis. *Acta Neuropathol Commun.* 2019;7(1):123.
73. Hau P, Pajtler K, Sahm F, et al. P20.16.B first-line treatment of medulloblastoma in adolescents and adults - update on the Eortc 1634-btg/noa-23 phase II trial. *Neuro-Oncol.* 2023;25(Suppl_2):ii130–ii131.
74. Mahajan A, Shih H, Penas-Prado M, et al. The alliance AMBUSH trial: Rationale and design. *Cancers.* 2022;14(2):414.
75. Gajjar AJ, Orr B, Ellison D, et al. MDB-49. outcomes of SONIC HEDGEHOG (SHH) MEDULLOBLASTOMA (MB) in children and adults treated with risk-adapted therapy on a prospective international protocol (SJMB12). *Neuro Oncol.* 2024;26(Suppl_4):0–0.
76. Momin AA, Recinos MA, Cioffi G, et al. Descriptive epidemiology of craniopharyngiomas in the United States. *Pituitary* 2021;24(4):517–522.
77. Nielsen EH, Feldt-Rasmussen U, Poulsgaard L, et al. Incidence of craniopharyngioma in Denmark (n = 189) and estimated world incidence of craniopharyngioma in children and adults. *J Neurooncol.* 2011;104(3):755–763.
78. Adamson TE, Wiestler OD, Kleihues P, Gazi Yasargil M. Correlation of clinical and pathological features in surgically treated craniopharyngiomas. *J Neurosurg.* 1990;73(1):12–17.
79. Piloni M, Gagliardi F, Bailo M, et al. Craniopharyngioma in pediatrics and adults. *Adv Exp Med Biol.* 2023;1405(1):299–329.
80. Wijnen M, van den Heuvel-Eibrink MM, Janssen JAMJL, et al. Very long-term sequelae of craniopharyngioma. *Eur J Endocrinol.* 2017;176(6):755–767.
81. Brastianos PK, Twohy E, Geyer S, et al. BRAF–MEK inhibition in newly diagnosed papillary craniopharyngiomas. *N Engl J Med.* 2023;389(2):118–126.
82. Apps JR, Carreno G, Gonzalez-Meljem JM, et al. Tumour compartment transcriptomics demonstrates the activation of inflammatory and odontogenic programmes in human adamantinomatous craniopharyngioma and identifies the MAPK/ERK pathway as a novel therapeutic target. *Acta Neuropathol.* 2018;135(5):757–777.
83. Whelan R, Prince E, Gilani A, Hankinson T. The inflammatory milieu of adamantinomatous craniopharyngioma and its implications for treatment. *J Clin Med.* 2020;9(2):519.
84. Coy S, Rashid R, Lin J-R, et al. Multiplexed immunofluorescence reveals potential PD-1/PD-L1 pathway vulnerabilities in craniopharyngioma. *Neuro Oncol.* 2018;20(8):1101–1112.