Childhood brain tumors: current management, biological insights, and future directions

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Brain tumors are the most common solid tumors in children, and, unfortunately, many subtypes continue to have a suboptimal long-term outcome. During the last several years, however, remarkable advances in our understanding of the molecular underpinnings of these tumors have occurred as a result of high-resolution genomic, epigenetic, and transcriptomic profiling, which have provided insights for improved tumor categorization and molecularly directed therapies. While tumors such as medulloblastomas have been historically grouped into standard- and high-risk categories, it is now recognized that these tumors encompass four or more molecular subsets with distinct clinical and molecular characteristics. Likewise, high-grade glioma, which for decades was considered a single high-risk entity, is now known to comprise multiple subsets of tumors that differ in terms of patient age, tumor location, and prognosis. The situation is even more complex for ependymoma, for which at least nine subsets of tumors have been described. Conversely, the majority of pilocytic astrocytomas appear to result from genetic changes that alter a single, therapeutically targetable molecular pathway. Accordingly, the present era is one in which treatment is evolving from the historical standard of radiation and conventional chemotherapy to a more nuanced approach in which these modalities are applied in a risk-adapted framework and molecularly targeted therapies are implemented to augment or, in some cases, replace conventional therapy. Herein, the authors review advances in the categorization and treatment of several of the more common pediatric brain tumors and discuss current and future directions in tumor management that hold significant promise for patients with these challenging tumors.

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BRAIN tumors are the leading cause of childhood cancer-related deaths.50 Although advances in surgical and adjuvant therapy have improved the survival rates of children with medulloblastoma and low-grade glioma (LGG), for which 5-year survival now exceeds 75%,45,73 the prognosis for other tumors such as diffuse intrinsic pontine glioma (DIPG) and other midline high-grade gliomas (HGGs) remains poor.18 In addition, as survival rates for children with prognostically favorable tumors have improved, there has been growing concern that “cure” often exacts a high price in terms of late sequelae, particularly when craniospinal radiation therapy (RT) is used in young children. Accordingly, during the last 15 years, increasing emphasis has been placed on reducing the morbidity of therapy for favorable-risk tumors by applying risk-adapted treatment protocols, while attempting to improve cure rates in poor-risk tumors through the use of novel treatment regimens.

The feasibility of these goals has been dramatically augmented by the revolution in molecular biology during the last 5–10 years, which has yielded progressively more detailed insights into the genetic basis for virtually every type of childhood brain tumor. This information has not only helped to identify different subsets of tumors, now recognized by the World Health Organization (WHO) and warranting distinct approaches to treatment, but also

ABBREVIATIONS COG = Children’s Oncology Group; DIPG = diffuse intrinsic pontine glioma; GTR = gross-total resection; HGG = high-grade glioma; LGG = low-grade glioma; MAPK = mitogen-activated protein kinase; NF1 = neurofibromatosis type 1; NTR = near-total resection; PBTC = Pediatric Brain Tumor Consortium; PFS = progression-free survival; RT = radiation therapy; SHH = Sonic Hedgehog; SIOP = International Society of Paediatric Oncology; WHO = World Health Organization; WNT = Wingless/Integrated.


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indicated molecular targets that can be exploited in therapy for certain tumors, such as pilocytic astrocytomas, dramatically changing the therapeutic landscape during the last 2–3 years. Conversely, for other tumors such as DIPGs, these insights have yielded valuable information, but translation of this knowledge to prognosis-altering therapeutics remains a work in progress, albeit one with great promise. The goal of the present review is to depict the current state of the art in molecular classification and therapeutic stratification for the most common childhood brain tumor types and to present these data in the context of recent studies and future trials.

Low-Grade Glioma
Background and Historical Therapy

Low-grade gliomas comprise several subgroups, including pilocytic, pilomyxoid, subependymal giant cell, and diffuse astrocytomas. Two cancer-predisposition syndromes, neurofibromatosis type 1 (NF1) and tuberous sclerosis complex, are associated with an increased frequency of pilocytic astrocytomas and subependymal giant cell astrocytomas, respectively. However, the majority of LGGs arise sporadically. Extensive resection is the treatment goal for superficial lesions within the cerebral and cerebellar hemispheres. After complete resection, 10-year progression-free survival (PFS) exceeds 85%, versus less than 50% if there is radiologically visible residual tumor. After complete resection, RT or chemotherapy is rarely warranted.

Unfortunately, complete resection is not usually feasible for deep-seated, infiltrative tumors, such as those involving the hypothalamus and optic pathways, which have a worse prognosis than superficial lesions. The management of such tumors is made even more challenging by their often large size and frequent occurrence in young children, increasing the risks of adverse late effects from RT. Accordingly, conventional chemotherapy has been used during the last 2 decades to delay or avoid RT in young children. Conventional chemotherapy regimens, such as vinblastine, have shown activity against these tumors, but long-term disease control has remained elusive. Conventional treatment options, including pilocytic, pilomyxoid, subependymal giant cell astrocytomas, respectively. However, the majority of LGGs arise sporadically. Extensive resection is the treatment goal for superficial lesions within the cerebral and cerebellar hemispheres. After complete resection, 10-year progression-free survival (PFS) exceeds 85%, versus less than 50% if there is radiologically visible residual tumor. After complete resection, RT or chemotherapy is rarely warranted.

Molecular Insights, Current Status, and Future Directions

While the above studies were in progress, a series of molecular analyses demonstrated that many pilocytic astrocytomas exhibit translocations or, less commonly, activating mutations of the BRAF gene, which may promote tumor development. Activating mutations of the BRAF gene, which may promote tumor development, including NF1 mutations and RAF fusions. This convergence of mutations on a single downstream pathway prompted interest in the targeted inhibition of MAPK signaling as a therapy for these tumors. Recent studies using agents that inhibit MAPK activation by blocking MEK1/2 (MAPK/ERK kinase), such as selumetinib, have had promising initial results. In a Pediatric Brain Tumor Consortium (PBTC) phase I study of this agent, 5 of 25 LGGs had durable partial (> 50%) responses, and the majority had at least some tumor shrinkage. Based on these results, a phase II study of this agent was launched, which stratified patients by MAPK pathway mutation status (e.g., BRAF translocations or mutations), histological diagnosis, and presence of NF1. Given the strong activity observed in several of these strata, new clinical trials are already incorporating MEK inhibitors alone or in combination for newly diagnosed patients.

Studies have also been conducted with vemurafenib (NCT01748149) and dabrafenib (NCT01677741), which specifically target tumors with BRAFV600E mutations. Given promising preliminary results, one ongoing phase II randomized clinical trial is already testing the activity of dabrafenib and trametinib (MEK inhibitor) against the combination of carboplatin and vincristine in children with newly diagnosed BRAFV600E-mutated LGGs (NCT02684058). In addition, building on evidence that tumors in children with tuberous sclerosis have activated mTOR signaling, studies of mTOR inhibitors, such as everolimus, have been launched and demonstrated activity. Similarly, antiangiogenic agents, such as bevacizumab, have shown promising rates of disease control in preliminary studies. Table 1 shows a list of additional ongoing studies for patients with LGGs.

Medulloblastomas
Background and Historical Therapy

Medulloblastomas are the most common malignant brain tumors in children. Overall, the outcome of children older than 3 years with medulloblastoma has improved significantly in the past 40 years with the use of craniospinal RT and multi-agent chemotherapy following an extensive resection. Unfortunately, surviving children experience a myriad of long-term debilitating sequelae associated with therapy. Although a subset of patients younger than 3 years at diagnosis, specifically those with nodular/desmoplastic tumors, have a good prognosis when treated with multi-agent chemotherapy combined
FIG. 1. A: Schematic of the frequency of MAPK pathway alterations detected by biopsy of pilocytic astrocytomas. This underestimates the frequency of NF1 mutations among children with LGGs because the tumors in patients affected by NF1 often do not undergo biopsy. Although BRAF fusions (BRAF Fus) constitute the majority of alterations in pilocytic astrocytoma, BRAF mutations are more commonly observed in pleomorphic xanthoastrocytomas and gangliogliomas. B: Frequency of the different BRAF abnormalities as a function of tumor location and histological diagnosis.
with intrathecal methotrexate but no RT, the remaining patients, including those with the classic or large cell/anaplastic variants and/or metastatic disease, continue to experience poor outcomes despite the use of intensive therapies.

Although medulloblastomas were historically subdivided into standard- and high-risk groups based on the amount of postoperative residual disease, metastatic stage, and patient age, tremendous advances in our understanding of the molecular underpinnings of these cancers have taken place during the last several years. These cancers are now subdivided in the WHO 2016 classification into four genetically defined, clinically and prognostically significant subgroups: Wingless/Integrated (WNT)–activated, Sonic Hedgehog (SHH)–activated, group 3, and group 4 (Fig. 2).12,55 Medulloblastoma subgroups can now be identified by multiple methods, including immunohistochemistry.
Molecular Insights, Current Status, and Future Directions

WNT-activated medulloblastomas, which almost exclusively occur in older children and young adults, have unique clinical, radiological, and biological characteristics, including an origin close to the brainstem and a predisposition to hemorrhage. The majority of WNT-activated medulloblastomas can be readily identified by nuclear expression of beta-catenin by immunohistochemistry combined with the detection of monosomy 6 and/or CTNNB1 mutations. Patients with WNT-activated medulloblastoma have an excellent prognosis when treated with standard doses of craniospinal RT and chemotherapy following surgery. Therefore, at least four multi-institutional clinical trials are currently evaluating the PFS of patients with newly diagnosed non-metastatic WNT-activated medulloblastoma treated using no RT (NCT02212574) or reduced doses of craniospinal RT at 18 Gy (COG ACNS1422, NCT02724579; and SIOP PNET5, NCT02066220) or 15 Gy (SJM12, NCT01878617) and less intensive chemotherapy (COG ACNS1422 and SIOP PNET5). Eligibility criteria for all studies are strict in order to avoid the inclusion of patients with high-risk characteristics (e.g., large cell/anaplastic histology, MYC or MYCN amplification, etc.) and to include only those patients with at least two of the three positive markers described above. SHH-activated medulloblastomas, which predominate in children younger than 3 years and in young adults, represent one of the most heterogeneous and best clinically and molecularly characterized subgroups. Agents targeting smoothened, a key proximal component in the SHH signaling pathway, have been approved for adults with basal cell carcinoma. Two smoothened inhibitors (vismodegib and sonidegib) have shown modest and temporary activity against recurrent SHH-activated medulloblastomas, particularly in tumors harboring molecular abnormalities upstream to smoothened. Given these early results, one multi-institutional clinical trial added vismodegib as a 12-month maintenance treatment for patients with SHH-activated medulloblastoma (SJM12, NCT01878617). Unfortunately, this study had to be amended to allow accrual of only skeletally mature patients since younger children developed significant chondropathy and growth impairment with prolonged SHH inhibition.

The incorporation of novel agents and/or major changes in treatment strategies for patients with newly diagnosed group 3 and 4 medulloblastoma lags behind that for patients with WNT- and SHH-activated tumors. One multi-institutional clinical trial (SJM12, NCT01878617) is evaluating the addition of pemtrexed and gemcitabine to standard chemotherapy for patients with high-risk group 3 and 4 medulloblastoma (e.g., metastatic disease, MYC or MYCN gain or amplification, large cell/anaplastic histology) based on the promising preclinical activity of these two agents.

Two recent clinical trials in North America (SJYC07, NCT00602667; and COG ACNS1221, NCT02017964) have shown inferior PFS of younger children with non-metastatic nodular/desmoplastic medulloblastoma treated using combination chemotherapy without RT. In one of these trials (COG ACNS1221), the 1-year PFS was 66% compared to a 5-year PFS of 90% in two consecutive German studies in which treatment consisted of similar intensive combination intravenous chemotherapy, but with the addition of intrathecal methotrexate.

Two clinical trials, one recently completed (COG ACNS0334, NCT00363024) and one still ongoing (HeadStart-4, NCT02875314), have used intensive induction chemotherapy with or without intravenous methotrexate followed by high-dose chemotherapy with stem-cell rescue to treat children younger than 3 years or younger than 10 years, respectively, with all types of medulloblastoma. The preliminary results of these studies are still not available.

Overall, although 5-year survival for older children (≥ 5 years of age at diagnosis) with medulloblastoma is above 75% in the United States, innovative therapies are badly needed for several molecularly defined subsets of patients, including those with metastatic MYC-amplified group 3 or SHH-driven TP53-mutated MYCN-amplified tumors or those younger than 3 years with group 3 medulloblastoma, which continue to have poor prognoses.

The prognosis is even worse for children with recurrent medulloblastoma. Only a small minority of children with recurrent medulloblastoma can be cured even with the use of multimodal therapies such as high-dose chemotherapy and stem-cell rescue. Patients who have not undergone upfront RT, particularly younger children, can still be cured using this treatment modality with or without chemotherapy.

Experimental (e.g., phase I and II) studies represent a common treatment alternative for such patients. Multiple innovative agents and treatment approaches are currently available for children with recurrent medulloblastoma targeting the genomic features of these tumors either pharmacologically or immunologically (Table 2).

### Table 2. Current experimental protocols for recurrent medulloblastoma

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<tr>
<th>Therapeutic Approach</th>
<th>Study Design</th>
<th>Clinical Trial Identification</th>
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<tr>
<td>Immunotherapy w/ total tumor RNA-load ed dendritic cells &amp; ex vivo expanded autologous lymphocyte transfer</td>
<td>Phase I/II</td>
<td>NCT01326104</td>
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<tr>
<td>Local (local recurrence) or intrathecal (metastatic recurrence) administration of modified measles virus</td>
<td>Phase I</td>
<td>NCT02962167</td>
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<tr>
<td>Treatment w/ intravenous gemcitabine &amp; oral ribociclib (CDK4/6 inhibitor)</td>
<td>Phase I</td>
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<td>Treatment w/ oral ribociclib &amp; trametinib (MEK inhibitor)</td>
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<td>Treatment w/ oral ribociclib &amp; sonidegib (smoothened inhibitor)</td>
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<tr>
<td>Treatment w/ oral LY3023414 (PI3K/mTOR inhibitor)</td>
<td>Phase I</td>
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### Ependymomas

#### Background and Historical Therapy

Ependymomas account for approximately 6% of all childhood brain cancers. Approximately 190 children...
with an age ≤ 14 years are diagnosed with ependymoma in the United States each year, less than two-thirds of whom will survive 10 years after diagnosis.44 Despite outcome improvements in affected children as compared to reports from the 1970s and 1980s, the survival of children with ependymoma has reached a plateau in the past 20 years.44

Maximal safe surgery with the intent of achieving near-total resection (NTR; maximum longest diameter of residual tumor < 5 mm) or gross-total resection (GTR) followed by local fractionated RT is considered standard therapy for children with newly diagnosed non-metastatic ependymoma, except for extremely young infants.40 In a single-institution phase II study, which consisted of aggressive and frequently multiple attempts to achieve radical resection and local RT at conformally delivered age-dependent doses between 54 and 59.4 Gy, the 7-year local control, PFS, and survival were 87.3%, 69.1%, and 81%, respectively.40 While 80% of the tumor progressions were equally split between local or metastatic failures, 20% of cases involved both areas.40 Extensive data have also been published about the long-term endocrinological, audiologival, and neuropsychological outcomes of children treated with this approach.3,9,41

With the goal of validating this strategy in a multi-institutional setting, the COG conducted a phase II clinical trial using a similar treatment in 281 children between the ages of 1 and 20 years with non-metastatic ependymoma who underwent GTR or NTR between 2003 and 2007 (COG ACNS0121, NCT00027846). Preliminary results of this study demonstrated a 5-year PFS of 68.5%.38

Several clinical trials (e.g., Baby POG 1, CCG-9942) have demonstrated the activity of a combination of alkylating agents with or without cisplatin against newly diagnosed ependymomas.10,17 In the CCG-9942 study, children with non-metastatic ependymoma and residual disease following maximal safe surgery received 4 cycles of cisplatin, cyclophosphamide, and vincristine before local RT. Patients who had undergone GTR received RT only. Five-year PFS for the patients with NTR who received neoadjuvant chemotherapy was comparable to that in the patients who underwent GTR (67% ± 9% vs 58% ± 9%, respectively).17

Molecular Insights, Current Status, and Future Directions

Since the benefits of combining chemotherapy with local RT in patients with newly diagnosed non-metastatic ependymoma remain unproven, a few ongoing randomized clinical trials are testing this combination. A phase III randomized COG trial (ACNS0831, NCT01096367) is primarily evaluating PFS in children between 1 and 20 years of age with non-metastatic newly diagnosed ependymoma treated with local RT alone versus local RT followed by 4 cycles of adjuvant combination chemotherapy with cisplatin, cyclophosphamide, etoposide, and vincristine. All patients who have undergone NTR or GTR, except those with WHO grade II supratentorial ependymomas who have undergone microscopically complete GTR, are eligible for this randomization. Patients who have undergone subtotal resection and whose tumors have a complete response to adjuvant chemotherapy or those who have undergone “second look” NTR or GTR are also candidates for the randomization. Completely resected, differentiated supratentorial ependymomas are eligible for observation without RT.

In a SIOP clinical trial (EP-II, NCT02265770), patients between 1 and 21 years of age who undergo a GTR (stratum 1) are randomized either to receive a 16-week combination chemotherapy regimen with cisplatin, cyclophosphamide, etoposide, and vincristine or to undergo observation only after local RT. Patients with residual tumor following initial surgery (stratum 2) are randomized to receive neoadjuvant chemotherapy consisting of cyclophosphamide, etoposide, and vincristine with or without methotrexate. All patients with residual macroscopic tumors are eligible to receive the same post-RT 16-week chemotherapy regimen as stratum 1 patients.

Two phase II clinical trials, which have completed accrual and are in follow-up, are evaluating the outcome of patients treated with chemotherapy and local RT following maximal safe resection. In a multi-institutional study in the United States (SJYCY07, NCT00602667), patients with non-metastatic ependymoma received 4 cycles of cisplatin, cyclophosphamide, intravenous methotrexate, and vincristine, followed by local RT and 6 cycles of oral cyclophosphamide and topotecan alternated with erlotinib. A European multi-institutional clinical trial (E-HIT-2000, NCT00303810) also evaluated the combination of 5 cycles of carboplatin, cyclophosphamide, etoposide, and vincristine (regimen AB4) after local hyperfractionated RT for children older than 4 years at diagnosis with WHO grade III ependymomas. Patients younger than 4 years received 5 cycles of carboplatin, cyclophosphamide, etoposide, intravenous methotrexate, and vincristine (regimen BIS4), followed by conventional fractionated local RT.

During the time that the above studies have been conducted, it has been shown that the clinical and molecular characteristics of ependymomas and the prognosis of affected patients are strongly influenced by lesion location within the central nervous system (i.e., supratentorial, posterior fossa, and spine) and patient age, reflecting the impact of distinct molecular etiologies (Fig. 3).46 Supratentorial ependymomas in children comprise two main subgroups: RELA fusion-positive (ST-RELA) ependymoma and YAP1 fusion-positive (ST-YAP1) ependymoma.46 Posterior fossa ependymomas are generally referred to as group A (PF-EPN-A) and group B (PF-EPN-B).46 Three groups of spinal ependymomas have also been identified. Although therapeutic strategies targeting these subgroups have yet to be tested in clinical trials, preclinical studies are in progress in multiple laboratories to evaluate potential therapeutic vulnerabilities as well as pharmacological and immunological targets.

These novel targets may be most applicable initially in children with recurrent ependymomas. At present, reirradiation in the setting of minimal residual disease after reoperation is the only curative option for a minority of children with recurrent ependymoma.48 The outcome of patients with recurrent ependymoma who undergo a second round of RT is dependent on the pattern of recurrence and tumor molecular subtype.48 Multiple experimental clinical trials are available for patients with recurrences who are unable to receive further RT (Table 3).
High-Grade Glioma and Diffuse Intrinsic Pontine Glioma

Background and Historical Therapy

Malignant (high-grade) gliomas, such as anaplastic astrocytomas (WHO grade III) and glioblastomas (WHO grade IV), have a poor prognosis in children, as they do in adults. Traditionally, non-brainstem HGGs have been considered separately from DIPGs based on the fact that DIPGs, by virtue of their location within the brainstem and infiltrative growth pattern, are not amenable to extensive resection, whereas tumor debulking is often an initial goal for HGGs. For DIPGs, one of the historical limitations to overcome was that these tumors were rarely biopsied, resulting in a lack of tumor material to define molecular abnormalities and identify novel therapeutic targets. Recent efforts have focused on the acquisition of fresh or fresh-frozen tumor material from autopsy or biopsy specimens for use in whole-genome analyses. Several groups have begun applying stereotactic biopsy to confirm the diagnosis and obtain tumor material, which has allowed DIPGs to be molecularly characterized in parallel with HGG, as noted in analyses discussed below.

Unfortunately, progress in the management of these tu-
mors has been frustratingly slow. Although the addition of nitrosourea-based chemotherapy to postoperative RT was shown to more than 20 years ago to increase survival rates for patients with HGG compared to rates following treatment with RT alone, subsequent studies with different regimens have failed to further improve outcome. Two clinical factors most consistently associated with prognosis are extent of resection and tumor histology, with grade IV lesions having worse outcomes than grade III tumors and with lesions not amenable to extensive resection having a dismal prognosis. Levels of expression of methylguanine-DNA-methyltransferase, which confers resistance to alkylating chemotherapy, have also been adversely associated with outcome in some studies.

Recent trials have examined the activity of chemotherapy administered during and after RT. One COG study (ACNS0126) incorporated daily temozolomide during pre- and post-RT chemotherapy have been equally disappointing. More recent studies have attempted to enhance the activity of RT by concurrently administering chemotherapy, radiosensitizing agents, or growth factor inhibitors, but results have been uniformly discouraging.

Molecular Insights, Current Status, and Future Directions

In recent years, it has become increasingly clear that HGGs and DIPGs in children differ on a molecular basis from HGGs in adults, and many of the molecularly targeted strategies that have been employed based on adult data have little applicability in the pediatric context. Moreover, distinct subgroups of pediatric HGG and DIPG have been distinguished based on patterns of recurring mutations and epigenetic features, which associate with biological and clinical characteristics. One landmark observation was the detection of novel mutations in histones H3F3A (positions K27 and G34) and HIST1H3B (position K27). It was also recognized that a subset of tumors, particularly from older children, have mutations in the IDH1 or IDH2 genes, whereas another subset has frequent BRAFV600E mutations, similar to pleomorphic xanthoastrocytomas. Genome-wide methylation profiling suggested the existence of six epigenetically distinct subgroups of glioblastoma that include pediatric patients. The K27 subgroup is characterized by a midline location, typified by DIPGs and thalamic HGGs, and a predilection for affecting young children, whereas the G34, IDH, and BRAF subgroups most commonly arise in the cerebral hemispheres of older children, along with a subset of tumors (RTK-I) that exhibit amplification of the PDGFRA gene and a subset of so-called mesenchymal tumors.

Retrospective cohort analysis has reported that the K27 subgroup has a particularly poor long-term survival rate, whereas IDH and BRAF tumors have a comparatively favorable outcome; G34, mesenchymal, and RTK tumors have an intermediate, but still poor, outcome. A recent integrated genomic analysis of 1000 pediatric HGGs and DIPGs has added texture to the above classification.
calling attention to the existence of recurring genomic anomalies within the above subgroups, which may further refine subgroup classifications. Taken together, these data highlight the genomic and prognostic diversity among these tumors, provide insights for therapeutic stratification of patients into risk groups, and suggest molecular targets for therapy.

In this context, the $K27M$ mutation has been targeted through the use of histone deacetylase (HDAC) inhibitors in DIPGs because of their high incidence of $K27$ mutations. At present, the PBTC is conducting an ongoing study of panobinostat, an HDAC inhibitor that has shown efficacy in DIPG preclinical models. COG studies of $BRAFV600E$ and MAPK inhibition with dabrafenib and trametinib are also under development for the subset of HGGs with $BRAF$ mutations. For the subsets of tumors lacking $IDH$, $K27$, or $BRAF$ mutations, a protocol is under development using ABT888, a poly (ADP-ribose) (PARP) inhibitor, as a radiosensitizer. In addition to the above studies, trials of novel therapeutic strategies are in progress (Table 4). The Pacific Pediatric Neuro-Oncology Consortium is testing a peptide-based immunotherapy for patients with $K27$-mutated tumors, based on encouraging preclinical data. A PBTC study of convection-enhanced delivery of a radio-immunoconjugate is under development based on encouraging pilot data by Souweidane et al., and the PBTC is also conducting studies of immune checkpoint inhibition, which holds particular promise in gliomas with a hypermutated phenotype secondary to constitutional mismatch-repair deficiency or Lynch syndrome (NCT02359565).

**Conclusions**

Advances in neuroimaging, surgical technology, conformal RT delivery, and conventional chemotherapy have improved outcomes for children with several types of brain tumors. Recently, the improvement in these modalities has been complemented by advances in the molecular characterization of virtually every type of childhood brain tumor. This has formed the basis for risk-adapted treatment strati-
fication and revealed new classes of molecularly targeted therapeutic agents. Such insights are already beginning to influence the spectrum of first-line treatment options for LGGs; however, progress has been slower for other tumor types, for which the drug development field has not kept pace with the elucidation of new molecular targets. This situation will likely resolve itself in the coming years as new agents are developed, although one challenge that will remain is the molecular heterogeneity of most high-grade tumors as well as their tendency to develop resistance to initially effective therapies. Whereas an LGG is likely to have prolonged sensitivity to MAPK inhibitor therapy, an SHH-activated medulloblastoma may rapidly develop mutations that render it resistant to a promising inhibitor. For these high-grade tumors, it is unlikely that we will find a single magic bullet; rather, we will need to apply an arsenal of agents and strategies in order to achieve meaningful improvements in disease control.

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