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Consensus framework for conducting phase I/II clinical trials for children, adolescents, and young adults with pediatric low-grade glioma: Guidelines established by the International Pediatric Low-Grade Glioma Coalition Clinical Trial Working Group

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Abstract

Within the last few decades, we have witnessed tremendous advancements in the study of pediatric low-grade gliomas (pLGG), leading to a much-improved understanding of their molecular underpinnings. Consequently, we have achieved successful milestones in developing and implementing targeted therapeutic agents for treating these tumors. However, the community continues to face many unknowns when it comes to the most effective clinical implementation of these novel targeted inhibitors or combinations thereof. Questions encompassing optimal dosing strategies, treatment duration, methods for assessing clinical efficacy, and the identification of predictive biomarkers remain unresolved. Here, we offer the consensus of the international pLGG coalition (iPLGGc) clinical trial working group on these important topics and comment on clinical trial design and endpoint rationale. Throughout, we seek to standardize the global approach to early clinical trials (phase I and II) for pLGG, leading to more consistently interpretable results as well as enhancing the pace of novel therapy development and encouraging an increased focus on functional endpoints as well and quality of life for children faced with this disease.

Keywords

Low grade glioma | Consensus recommendation | Early phase clinical trial

Traditionally, the generalizability of phase I and II outcomes for pediatric low-grade glioma (pLGG) has been hindered by the utilization of different inclusion criteria and outcome measures. These measures include progression-free survival (PFS), overall survival (OS), response rate (RR), and, more recently, functional outcomes such as visual acuity and motor function.[1–6] The inconsistency in these measures has made it challenging to meaningfully interpret these outcomes and assess how they may apply to other cohorts or be combined with other trial results for the purpose of designing future studies. Harmonizing endpoints enables effective interpretation of outcome data and informs future studies. By providing guidance on the specific data collected for all trial patients, it becomes more feasible to interpret outcomes across studies.

To enable uniformity in trial design across phase I/II pLGG studies, it is crucial to establish consistent eligibility criteria and outcome measures. The term "pLGG" includes circumscribed CNS WHO grade 1 (eg, pilocytic astrocytoma) and grade 2 (eg, pleomorphic xanthoastrocytoma) gliomas and glioneuronal tumors (eg, ganglioglioma), as well as CNS WHO grade 1 diffuse gliomas (eg, MYB/MYBL1-altered astrocytomas). Given pLGGs are principally driven by the MAPK pathway,[7] several trials investigating MAPK-targeting small molecule inhibitors have been conducted, demonstrating promising activity and

reasonable safety profiles of these agents in the relapsed setting, and more recently also in primary pLGG.[1–4]

Considering that the mode of action, safety profile, and clinical behavior of molecular-targeted drugs in pLGG differ significantly from classical cytotoxic drugs, it is imperative to adapt the design of trials accordingly. The objective of this consensus paper, developed by the clinical working group of the international pLGG coalition (iPLGGc), is to provide recommendations on phase I/II trial designs in pLGG in the emerging era of precision neuro-oncology. The members of this group met monthly over 1 year to build concordance around these consensus recommendations, and the final version was agreed upon by all members of the committee. Investigators with specific content expertise were included as deemed appropriate by the committee as well as involving experts from North America as well as Europe.

Clinical Trial Eligibility Criteria Considerations

In this section, we present our recommendations for eligibility criteria of early-phase pLGG trials, considering the distinction between trials for newly diagnosed patients and recurrent or progressive disease. For the latter, and depending on the trial endpoint, we advise enrolling patients with either clear evidence of disease progression on imaging (for trials focused on imaging endpoints) or clinical progression (for trials focused on functional endpoints) as the eligibility criteria. We recommend against including patients with stable disease under the classification of "refractory"—this significantly affects outcome measures and complicates the interpretation of endpoints across studies.

Age

Historically, most trials dedicated to pLGG employed age-based inclusion criteria from 3–18, less than 18, or 3–21 years.[1,8–10] Regulatory agencies have issued guidelines for pediatric development that emphasize the importance of pharmacokinetic assessments utilizing age-defined cohorts: 0–2, 2–11, or 12–18 years. These guidelines recognize that drug metabolism is dependent on age. Additionally, age limitations may be influenced by the available drug formulation. For instance, orally administered drugs often come in capsule or tablet forms that must be swallowed whole, posing limitations for patients who are young, developmentally delayed, or experiencing swallowing difficulties.

Given classification of pLGGs is now based on molecular characteristics according to the newest 2021 World Health Organization (WHO) classification system, we must appreciate that some LGGs predominantly observed in pediatric cases can also occur in adolescents or adults, and vice versa.[11,12] However, what remains unclear is whether age at onset influences the biological behavior of these WHO grade I tumor entities, despite sharing similar molecular features. For example, infants less than 1 year of age with hypothalamic-chiasmatic located pLGGs are at particularly high risk of succumbing to their disease in contrast to older children.[13] Thus, novel treatments should also be investigated in this younger age cohort as appropriate, and every effort should be undertaken to also include this youngest age group in phase I/II trials.

Enrollment in trials for pLGG should be driven by the molecular subtype rather than specific age restrictions unless there are safety issues, formulation concerns, or the need to establish a safe dose, and/or pharmacokinetic characteristics in a specific age group. However, we further recommend an upper age limit of 25 years due to logistical challenges associated with enrolling older patients, and the potential for a different side effect profile in new combinations, as young children often require and tolerate higher doses compared with adult patients.[14,15]

Previous Therapy and Considerations for Appropriate Washout Periods

Although the number and types of prior therapies do not concern newly diagnosed patients, they must be navigated for trials in the recurrent setting. For example, MEK inhibitor trials for recurrent pLGG have historically not allowed prior MEK inhibitor therapy. However, the assessment of the type II RAF inhibitor tovarafenib within the Firefly1/PNOC026 trial was conducted without limitations on prior targeted therapies involving the MAPK pathway. These subtle differences in trial eligibility must be considered when evaluating observed RRs across studies.

We acknowledge there is currently limited data on how prior therapy affects outcomes in the pLGG population. Nonetheless, we recommend against limiting the number of prior therapies. Instead, we advise prioritization of an appropriate washout period from prior therapies to avoid overlapping toxicities, such as a minimum of 28 days from the administration of classic myelosuppressive chemotherapy and 42 days for nitrosureas. For previously administered biologic agents, we recommend the patient be removed from the medication for a minimum of 7 days, and for monoclonal antibodies at least 21 days. In the case of Radiotherapy (RT), we recommend at least 3 months after RT including craniospinal RT, and pseudoprogression needs to be ruled out prior to enrollment. However, we acknowledge that certain agents, like tovarafenib, may necessitate extended washout periods due to prolonged half-lives. Appropriate washout periods for cellular therapies are currently not known and will be the topic of ongoing investigations.

However, the pLGGc endorses consideration of a scientifically based approach to washout periods (such as basing the washout period on plasma half-life or toxicity recovery) over traditional historical time-based washout periods in order to minimize delays in enrollment.[16] In any case, the risk for overlapping toxicity and/or efficacy with previous treatments should be minimized to reduce confounded endpoints.

Special Considerations for pLGG and Neurofibromatosis Type-1 (NF1).—Approximately, 20%–30% of patients with NF1 will develop a pLGG during childhood, most

commonly in the optic pathway, but also in other brain regions, such as the brainstem.[17–19] We recommend that treatment be initiated when patients develop symptoms that affect function, such as vision abnormalities resulting from an optic pathway glioma (OPG) or neurologic/motor deficits resulting from a brainstem glioma. In NF1-associated pLGG, treatment is rarely initiated based on tumor growth alone with the rare exception of the very young child, as visual exams are not reliable. In fact, some data indicate tumor growth or response does not consistently coincide with functional response.[20,21]

Given that the trajectory of NF1 and non-NF1 patients is unique, both in terms of survival outcomes and toxicities, stratification by NF1 status is necessary when both NF1 and non-NF1 patients are included in a single trial.

As the most common indication to initiate treatment for patients with NF1-associated OPGs is visual impairment, there must be consistency in the assessment of this eligibility criterion. We recommend the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Visual Outcomes Committee[22] as well as expert recommendations regarding visual criteria for treatment as outlined below.[23] These criteria have been adopted and incorporated into recent Children's Oncology Group trials such as ACNS1831 (NCT03871257) as follows: visual worsening is defined as worsening of visual acuity (VA) and/or visual fields documented within the past year (by examination or history). In addition, patients with significant visual dysfunction, which is defined as VA worse than normal for age by 0.6 logMAR (20/80, 6/24, or 2.5/10) or more in 1 or both eyes, would be eligible if treatment were indicated. These same criteria should be applied to non-NF1 patients with OPG being enrolled in a trial based on visual dysfunction.

Other Trial Eligibility Considerations

Disease State

There has been inconsistency across studies regarding whether patients with disseminated disease are eligible for enrollment. We advocate for the inclusion of all patients including focal, multifocal, and disseminated disease in clinical trials. We recommend conducting separate efficacy analyses for patients with distinct disease states. However, the overarching trial sample size should primarily be determined based on the primary cohort and primary objective. Ideally, patients with disseminated disease would be enrolled into separate strata. Nevertheless, the feasibility of this approach may be constrained by the trial's size, particularly given the limited patient numbers with disseminated disease.

Organ Function Requirements

We recommend standardizing baseline organ function requirements across trials to enable consistent assessment of toxicity and safety maintenance. Specifically, the following criteria are recommended: adequate renal function, adequate liver function, absolute neutrophil count ≥1,000/μL (unsupported), platelets ≥100,000/μL (unsupported), and hemoglobin ≥8 g/dL (may be supported). Some agents may require specific eligibility requirements such as electrocardiogram or echocardiogram.

Clinical Status

Patients enrolled in a trial should have a baseline functional score on the Lansky/Karnofsky scale greater than 50. Symptoms related to tumor location and resulting in lower scores should be considered appropriately. For example, patients who are unable to walk because of paralysis, but who are up in a wheelchair, should be considered ambulatory for the purpose of assessing their performance score.

Pathology Requirements and Molecular Characterization for pLGG

The purpose of tissue diagnosis is 2-fold: to define the histological-molecular subtype of the tumor and to define its genetic drivers, which might inform targeted treatment.

The consensus recommendation for future trials is to mandate definitive pathological diagnosis and tissue submission for all trial patients, however, the iPLGGc acknowledges that there are specific scenarios, such as NF1-associated tumors isolated to the optic nerve or brainstem, where a tissue requirement may be deemed clinically inappropriate and need to be waived.

Tissue or relevant molecular data that was previously generated in an accredited laboratory, for trial participation should be accepted and not duplicated. Tissue from any prior surgery should be accepted for trial enrollment, although more recent tissue will be more informative on the presence of additional molecular changes. Fresh frozen tissue collection as part of eligibility for exploratory biomarker studies is critical and should be collected whenever feasible, aiming to establish a repository for the development of innovative predictors regarding patient response and stratification in upcoming trials. This approach is particularly crucial given the emerging recognition that responses to treatments such as MAPK pathway inhibitors exhibit heterogeneity, even among pLGGs bearing identical underlying genetic alterations.[24]

Consideration should be given to the planned collection of on-treatment or post-treatment tissue, whether on an ad hoc basis for patients who require tumor resection during or after trial participation, or more formally by inclusion of a surgical/target validation arm.

Central Pathology Review Requirements

The diagnosis should be reviewed by pathologists with appropriate accreditation in neuropathology and demonstrable expertise in pediatric neuropathology. There should be a minimum set of molecular data as outlined in (Figure 1). The diagnosis should be provided as an integrated diagnosis using the categories and grades indicated in the fifth edition of the 2021 WHO CNS classification of tumors, also taking into account interim updates from the

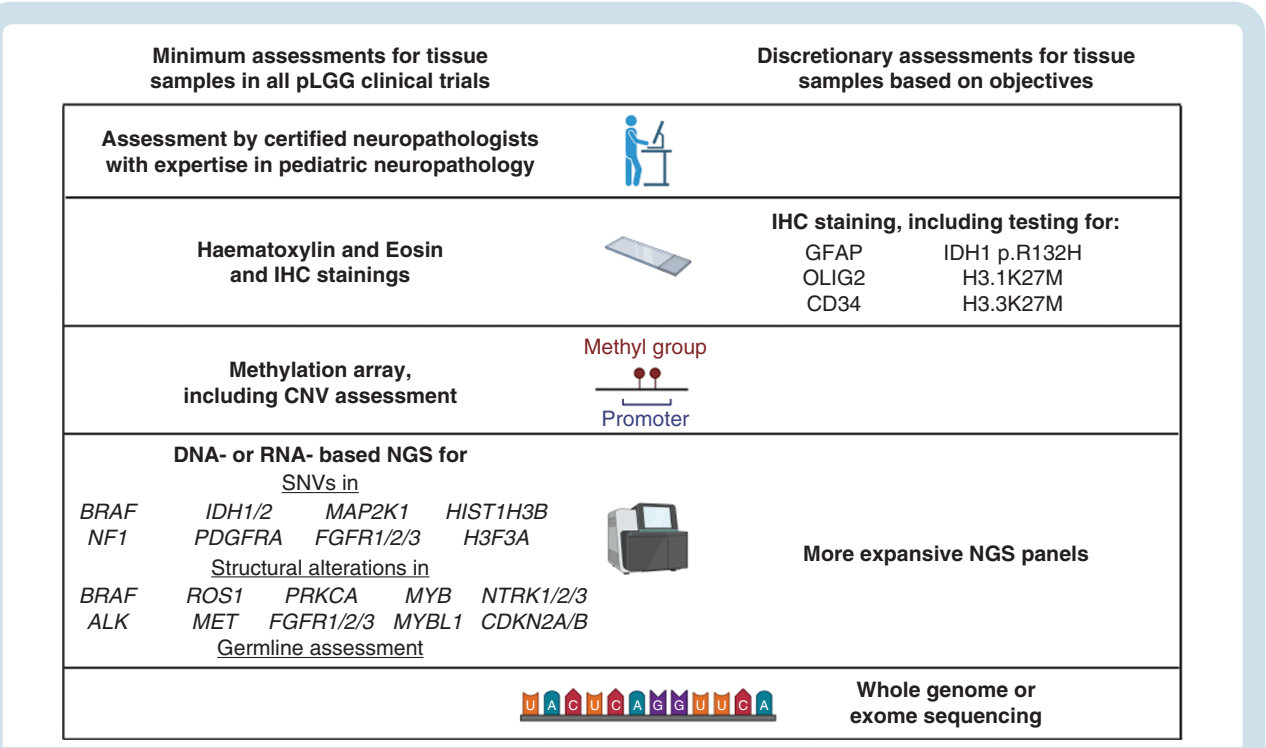

Figure 1. Minimum and discretionary assessments in pLGG clinical trials. H & E, haematoxylin and eosin. CNV, copy number variation. IHC, immunohistochemical., NGS, next generation sequencing (such as RNA sequencing). SNV, single nucleotide variation. Created with BioRender.com.

Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW). There should be more than one pathologist undertaking a central review to offer inter-pathologist quality assurance and consultation on difficult cases. Laboratories providing diagnostic genomic testing should be accredited by appropriate national or international agencies (eg, CLIA, UKAS, and ISO 15189) and consideration should be given to providing data on interlaboratory comparisons. If there is a discrepancy between the histological and molecular information, the iPLGGc recommends a real-time central pathology review, otherwise central pathology review can be postponed until the final analysis of the trial. A recommended workup for tissue is shown in Figure 1, with the aim to identifying key drivers of pLGG. Growing data suggests a subset of pLGG patients carry germline genomic alterations, and accordingly, we must evaluate the impact on therapy response of these germline variants across trials.

Cerebrospinal Fluid (CSF) Assessments

There is value in obtaining CSF for further biomarker development, such as circulating tumor DNA. Prior studies using blood serum have been mainly negative and therefore there is an urgent need for future development. The acceptance of collecting CSF on pLGG studies by patients and families is currently being evaluated through surveys developed by the iPLGGc coalition and will be reported separately. Other considerations can be given to microbiome studies as exploratory investigations as well as collections of viable tumor tissue to allow pLGG model generation which is largely lacking to date. It will be important that the community harmonizes the collection and storage of these specimens to allow for meaningful interpretation across studies.

Considerations for Clinical Trial Endpoints

The current standard focuses on imaging-based endpoints, such as RRs and PFS. As we learn more about novel agents, the iPLGGc believes in the inclusion of functional, motor, and neurocognitive assessments at baseline and throughout a trial. Most patients will live well into adulthood, and therefore maximizing their quality of life (QOL), functional outcomes, and patient-reported outcomes (PROs) must be a top priority.[25]

Imaging

We recommend incorporating RANO-LGG criteria in addition to the newly developed RAPNO guideline for response assessment in pLGG in any future clinical trial protocols.[26] As the disease has a chronic nature, there was extensive discussion regarding the routine use of contrast-enhanced agents for imaging assessments in pLGG. Concerns were raised about the known side effects and potential long-term affects associated with the use of contrast agents.[27] However, the committee determined that there is currently insufficient data to recommend a change in the use of

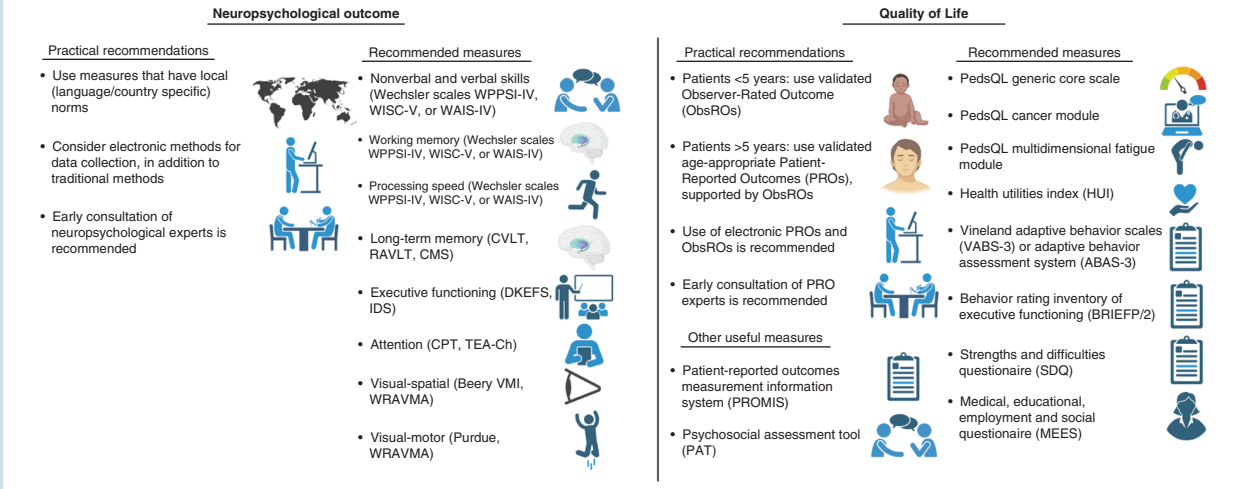

Figure 2. Practical recommendations and recommended measures for neuropsychological and quality-of-life (QoL) assessment (Created with BioRender.com).

contrast enhancement for monitoring pLGG, in particular, in early-phase clinical trials with typically limited durations and aligned with the RAPNO LGG guidelines.

Controversy exists regarding the interval of MRI assessments to monitor response assessments in pLGG. The RAPNO guidelines currently recommend a 3-month interval, which has been the standard practice in most trials in the United States and Europe. However, there is a growing recognition of the potential utility of performing imaging assessments at earlier time points, particularly depending on the mode of action of the clinical trial therapy strategy. The iPLGGc advocates for the integration of more frequent imaging time points in clinical trials if warranted by a specific research question, such as changes in metabolic activity or perfusion, or mode of action of a proposed study regimen, with a focus on children who do not require sedation for their MRIs. This recommendation aims to balance the potential toxicity associated with increased imaging frequency with the valuable knowledge gained from characterizing the response patterns and dynamics of pLGG.

In summary, while the current standard interval for MRI assessments in pLGG trials is 3 months, we consider more frequent time points, particularly at treatment initiation and discontinuation, to improve our understanding of treatment response and rebound or (pseudo)progression dynamics in pLGG patients (see manuscript on rebound and resistance).

Functional and Quality-of-Life Outcomes

Fortunately, most children with pLGG will live well into adulthood; thus, maximizing their functional outcomes and QOL should be included in the assessment of novel agents in trials. Changes in tumor size often do not correlate with functional outcomes.[28,29] However, a recent review showed that only 8% of registered trials include QOL endpoints in their study protocol.[30] Therefore, we recommend the inclusion of functional endpoints, including those pertaining to visual, motor, neurocognitive outcomes, and QOL assessments at least as secondary or exploratory endpoints in phase I/II pLGG trials. However, when selecting a variety of tests, one needs to take into account the burden for families as well as appropriate reimbursement for the study team to ensure adequate compliance and to balance feasibility with data quality, which may suffer if a study protocol includes too many endpoints. Such measures may be PROs, observer-reported (ObsRO; parent/caregiver or clinician), or performance-based (eg, cognitive tests).[31]

QOL Assessment.—The ISPOR PRO task force for good research practices for the assessment of children and adolescents recommends the use of ObsROs in children below 5 years of age and age-appropriate PROs in children above the age of 5 years.[32] Depending on the child's ability to self-report, PROs may be supplemented or substituted by ObsROs in this latter group. PRO/ObsRO measures in trials should be validated prior to inclusion and endpoints should be clearly defined. Additionally, the use of electronic PROs (ePROs) is encouraged. These facilitate the implementation of longitudinal assessment in the hospital and at home, with easy monitoring of questionnaire completion and thus improved data quality.[33,34]

The assessment of QOL should focus on positive and negative biopsychosocial aspects related to the disease and its treatment as experienced by the patients themselves (Figure 2).[35,36] This includes the assessment of physical health, including both functions (dexterity, physical activity, strength) and symptoms (nausea, pain, dizziness, fatigue, problems with concentration or attention); psychological health, including functions (self-esteem, benefit finding, satisfaction) and symptoms (general or treatment-related anxiety, worries, sadness); and social health, including functions (positive interactions with peers, family, in school) and symptoms (social withdrawal).

Frequently used questionnaires are the PedsQL generic core scale and the PedsQL cancer module.[37] The SIOP-E Brain Tumour Group additionally recommends the use of several other questionnaires,[38,39] including the Health Utilities Index (HUI),[40] the PedsQL Multidimensional Fatigue module,[37] the Vineland adaptive behavior scales (VABS),[41] and the Behavior Rating Inventory of Executive Function (BRIEF).[42] However, recent research has questioned the content validity of the PedsQL.[43,44] In addition to the above-mentioned questionnaires, the generic Patient-Reported Outcomes Measurement Information System (PROMIS) by the National Institutes of Health (NIH) offers several valid and reliable scales to assess QOL in children with cancer.[45,46] The Psychosocial Assessment Tool (PAT) is a broadly used and well-validated parental report to assess psychosocial risk factors in pediatric cancer patients and their families.[47] To allow a comparable assessment of demographic, endocrine, and general medical information, it has been recommended to use the Medical, Educational, Employment and Social Questionnaire (MEES).[48]

Since the choice of adequate measures strongly depends on the trial design and specific trial endpoints, it is recommended to consult with PRO experts during the trial planning phase.

Neuropsychological Outcomes.—In addition to PROs, it is important to include a direct assessment of neuropsychological function with consideration of resources as noted below. Patients and survivors of pLGG experience multiple neuropsychological challenges, including memory and cognitive speed deficits.[49] Recently, colleagues from COG and SIOP-E described their set of tests that can be used across various languages and countries in pediatric oncology groups, such as the Wechsler scales for nonverbal reasoning, verbal comprehension, working memory, and processing speed.[37–39] This includes using a "core" set of measures that can be completed within a relatively short time (<2 hours), and a "core plus" set of measures where resources are possible. Some pediatric oncology trials have used computerized assessments, including Cogstate (https://www.cogstate.com/), to help with harmonizing across languages and centers meanwhile reducing the need for clinicians. These measures can be considered for pLGG trials, but they need further development to be clinically relevant at an individualized level. Finally, the timing of these assessments should be considered in the context of the phase of the trial and patient. Although an early time point (especially before treatment) is considered ideal to assess for baseline differences, this is not consistently feasible given the functioning of the patient and their family. Follow-up time points, for example, every 2 years, should align with the broader QOL assessments, as described below.

Performance-based measures should use standardized approaches to measurement, consider baseline characteristics of patients that may affect outcomes (eg, patients with very poor vision may not have the potential for visual improvement with tumor-directed therapy), and have validated and clinically meaningful endpoints. In order to increase completion rates, researchers can embed these measures directly into the trial, advocate for dedicated centralized staff, and ensure there is local staff for implementation. Well-developed measures may be included as co-primary endpoints, such as visual endpoints for OPGs. Less validated measures should be included as secondary or exploratory endpoints, thereby evaluating their utility for pLGG management. Inclusion of such outcome measures provides crucial information on the impact of novel therapies on patient outcomes and can show benefit during regulatory reviews.

Visual Outcomes.—Visual outcomes should be included as outcome measures in all trials for OPG and are currently included in ongoing prospective trials that include OPG patients (NCT03871257, NCT04166409, NCT04576117, NCT04775485, NCT05566795, NCT02840409, and NCT04544007). Evidence-driven, consensus recommendations for visual endpoints have been offered by the REiNs Visual Outcomes Committee and adopted by the pLGG RAPNO working group.[22] The iPLGGc recommends the inclusion of these measures, including VA outcomes using Teller Acuity Cards (TAC) as the primary visual endpoint and, once the patient's age allows, with HOTV charts as a secondary endpoint. Preliminary data reported from the ongoing NF1-OPG Natural History study suggests that close to 90% of patients can perform TAC at the time of treatment initiation, while less than 50% can perform HOTV.[50] In trials that include a large number of OPG participants, VA outcomes should be considered as a co-primary endpoint alongside imaging outcomes, preferably measures with TAC, whereas HOTV could be considered as a secondary endpoint. If visual function is used as a (co)primary endpoint, the magnitude of improvement should be at least 0.2 logMAR. Although visual field deficits can affect function in children with OPG, they are still an exploratory endpoint given the challenges of measuring them reproducibly in young children.

Neurologic/Motor Outcomes.—Neurologic, and specifically, motor, function is commonly affected by pLGG and may be influenced by tumor location and prior therapies, such as neuropathy following vincristine treatment.[51] There are also confounding variables, including developmental differences in the acquirement of motor skills and the motor weakness associated with NF1. Altogether, there are currently no standardized assessment measures of neurologic or motor function for pLGG. The Neurologic Assessment in Pediatric Neuro-Oncology (pNANO) was recently created to evaluate 10 specific domains of neurologic function, including gait, strength, cerebellar function, facial strength, level of consciousness, dysarthria, dysphagia, extraocular movements, visual fields, and VA. These are specifically for pediatric brain tumor patients based on both patient/caregiver reports and direct examination.[52] This scale is currently undergoing prospective evaluation for its validity, reliability, and feasibility.

Performance-based tests of motor function are dependent on patient effort and the consistency of the testing procedure (eg, hand-held dynamometer), are confounded by other factors (eg, pulmonary/cardiovascular function and the 6-min walk test), and suffer from test–retest reliability (eg, manual muscle testing). The International

Cooperative Ataxia Rating Scale has been validated for use in focal cerebellar lesions, spinocerebellar, and Friedrich's ataxia, and has been used to report outcomes for children with cerebellar tumors.[53–56] However, it is unknown whether it is sensitive to change over time. The third edition of the Vineland-3 Motor Scale from the VABS is a parent rating form that enables the detection of change in both fine and gross motor function; importantly, this is available in multiple languages and has previously been used for the assessment of children with brain tumors, including pLGG in an earlier version.[57–61] Although validated for children less than 10 years of age, this questionnaire is recommended for all ages and has been integrated into several large pLGG clinical trials (NCT03871257, NCT04166409, NCT04775485, and NCT05566795).[62]

Length of Therapy for New Targeted Agents

The ideal duration of therapy for novel targeted drugs remains unknown. Whether these agents induce tumor senescence, or temporary suppression of the targeted pathway with feedback-loop activation is an area of investigation.[63] Other papers in this series address this topic in further detail. Recent trials have arbitrarily defined 2 years as a common duration of therapy in both up-front and recurrent pLGG (NCT04201457, NCT04923126, NCT04485559), although shorter durations have also been used (NCT02285439).[1,4] In trials employing a MEK inhibitor (MEKi), patients who ultimately benefit from the therapy typically show an initial clinical or radiographic response within the first year.[64] Time to treatment responses and response duration to targeted inhibitors can range from months to years. Recently, responses according to RANO criteria have been reported in the first 3 months using a brain penetrant second generation RAF inhibitor[65] and for pLGG with *BRAF*^{V600E} alterations treated with BRAF^{V600E} inhibitors and MEKi combination.[2] However, a subset of pLGGs have been observed to respond late in therapy, motivating a longer duration.[1] Durability of response is variable, and tumor rebound following discontinuation of MAPK inhibitor therapy is described.[66] A common 2-year duration for targeted agents given as monotherapy is recommended, which will ensure that future agents are comparable in tumor response, toxicity, and durability of treatment effect. Trials of targeted agents in combination with traditional cytotoxic agents may require a shorter treatment duration, and other novel trial designs may suggest alternative treatment durations. However, the pLGGAc acknowledges that some children might require longer therapy duration, for example, infants with diencephalic syndromes. In tumors that progress or recur after discontinuation of BRAF- or MEK-targeting therapies, re-treatment with these agents has been effective at achieving response or prolonged stable disease.[66] Unfortunately, the ideal duration of re-treatment and potential for successful discontinuation is currently unknown. Therefore, incorporating a re-treatment arm in trials of targeted agents as included in PBTC-029 (NCT 01089101) or NF108/PNOC010 (NCT03231306) may guide the optimal overall duration of treatment and provide insight on the rebound. We recommend re-treatment be offered to patients who responded to treatment then progressed or recurred after discontinuation. Criteria for re-treatment should be built around distinctions between rebound and natural progression, standardizing the protocol to reduce variability in the re-introduction of these agents.

Toxicity Management

Guidance for reporting and managing anticipated toxicities should be included in all pLGG clinical trial protocols, with clear criteria for dose interruption, permanent discontinuation, or rechallenge. This is especially important for pediatric-specific toxicities, such as growth and skeletal or endocrinologic maturity, which may not be captured by standard adverse event reporting definitions such as CTCAE. Additionally, when defining dose-limiting toxicities (DLTs) for dose-finding studies, it must be considered that tolerance for moderate toxicities may be lower than in other more acute oncologic settings, and typical DLT definitions may be inappropriate.

Designs Based on External Controls

The use of external controls is under investigation. Most early-phase efficacy studies for pLGG have used fixed efficacy thresholds for binary endpoints, such as radiographic objective RR, assessed via common group-sequential approaches, such as Simon's 2-stage design. Success thresholds for efficacy are derived from values reported in the literature and deemed clinically meaningful. To increase these endpoints' utility, radiographic responses are often required to be sustained for 8–12 weeks, corresponding to the specified MRI schedule. Similar designs have been used for dichotomized time-to-event endpoints, such as 6-month PFS (PFS6). While such designs are efficient with sample size, the binary endpoints use minimum information for primary decision-making. The design thresholds may be hard to establish or affected by the time points to which they are tied: PFS6 may be arbitrarily high due to measurement intervals or physician bias, leading to poor estimates of efficacy, since it is a relatively early time point for pLGG.

An alternative approach is to incorporate efficacy endpoints that more closely represent benefits for patients, such as PFS even in early-phase studies, and use external datasets with detailed patient-level data as the comparison cohort. These designs would then use log-rank/Cox model type analyses comparing the PFS distribution of the trial cohort to the identically defined PFS distribution of the external cohort with appropriate adjustment for important covariates. The most suitable external comparison cohorts are constructed from large, contemporary datasets that include adequate detail to enable the matching of patients based on the eligibility criteria used in the study. Additionally, similar disease assessment intervals with consistent radiologic and clinical disease assessment criteria would help reduce bias. It is also important to ensure

that the external data set is mature without too many censored patients. Approaches that utilize propensity scores or multivariable Cox models can be used to formally incorporate important covariates into the outcome comparisons. Even when all these criteria are satisfied with an attempt to balance or control for all known covariates that can potentially affect the outcome, the primary concern in such designs is the inability to control for unknown confounders, including differences in supportive care or biases in patient populations that enroll on trials versus registries, and differences across geographic regions. To reduce this concern, an important design recommendation is to use relatively small type I errors, for example, 5% with a larger effect size to help rule out false positives. Jahanshahi et al. (2021) provide an excellent summary of the important considerations of such designs and the subsequent outcome analyses.[67]

In the case of pLGG, the recommendations outlined in this manuscript are an attempt to help create relatively uniform criteria for conducting clinical trials by various academic and industry groups which can then be used as external controls for future trials.

Considerations for Patient's Informed Consent

The ICF of any trial in pLGG should include appropriate wording to allow data and tissue sharing for secondary use amongst academic groups. It should be considered to include opting-in for sharing data and tissue with pharmaceutical firms for the purpose of developing biomarkers, therapies, and diagnostics.

Conclusions

Major advances in the molecular underpinnings and therapies for pLGG have been made. However, the need to refine trial methodologies and optimize the duration of targeted therapies and dosing schedules persists. Incorporating functional endpoints into early-phase trials is vital. To speed up progress, we must harmonize eligibility and assessment criteria. This extends to on-study assessments, spanning imaging procedures, tissue analyses, QOL measurements, and correlative investigations. Access to on-treatment tissue continues to be a challenge in pLGG research and limits our ability to understand treatment responses and failures that would facilitate the development of better therapeutic strategies. Assessment of potential surrogates, such as CSF, will be critical to advance future therapies. Further, the majority of these recommendations are currently only applicable to phase I/II clinical trials conducted in resource-rich countries and steps should be taken to develop tools for low-income countries.

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Conflict of interest statement

None declared.

Affiliations

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