

Clinical trial challenges, design considerations, and outcome measures in rare CNS tumors

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Abstract

Clinical research for patients with rare cancers has been very challenging. First and foremost, patient accrual to clinical trials typically requires a network, cooperative group, or even international collaboration in order to achieve the necessary numbers of patients to adequately evaluate a new treatment or intervention. Similar limitations in preclinical models and in the understanding the natural history of the disease or pertinent prognostic factors further impede the development of hypothesis-based, appropriately powered clinical trials. However, despite these challenges, several studies in rare cancers, including ependymoma and subependymal giant cell astrocytoma, have helped to establish new treatment regimens. Importantly, in these seminal trials, patient outcomes measures were critical in describing the clinical benefit derived from the therapy, underscoring the need to incorporate these measures in future trials. While obstacles still remain, novel and creative approaches to clinical trial designs have been developed that can be used to study new treatments for patients with rare cancers, thereby addressing a significant unmet need.

Keywords

clinical trials | novel clinical trial design | patient-reported outcomes | rare cancer

Developing new treatments for patients with rare diseases, including cancer, has many challenges. As has been well recognized, rare cancers typically do not get the same public attention and awareness as well as grant or philanthropic funding as more common cancers. With a very small patient population, investment by pharmaceutical and biotech companies is often limited as there are concerns about the financial return on their resource investment. Fortunately, there are some sources of support for research in this area, including the FDA Orphan Disease Program. There are some other bright spots, including support from the Beau Biden Cancer Moonshot Program which provided funding to create the NCI-CONNECT (Comprehensive Oncology Network Evaluating Rare CNS Tumors) rare CNS Cancer Program. With this support, the NCI-CONNECT Program has developed an infrastructure for collecting, analyzing, and sharing data with the goal to translate these discoveries into new therapies. The NCI-CONNECT has a national network

comprised of 33 sites across the United States and an outstanding website and prominent social media presence to help get the word out to advocacy organizations and to reach patients (Figure 1).

Despite these important efforts, the study of rare cancers of the central nervous system (CNS) in the broader landscape continues to be hampered by limited research funding and a consequent lack of suitable preclinical models. However, as serious as these limitations are, the biggest challenges in designing and conducting clinical trials are related to patient accrual. In many if not most cases, there simply are not enough patients with a particular tumor type either eligible or both willing and logistically able to participate in clinical studies. In addition, investigators may have difficulty with supporting the necessary infrastructure for a trial with accrual that will often be slow or limited in rare cancers. Paradoxically, the more these rare cancers are studied, the challenge of accrual becomes even greater as trials must compete amongst one

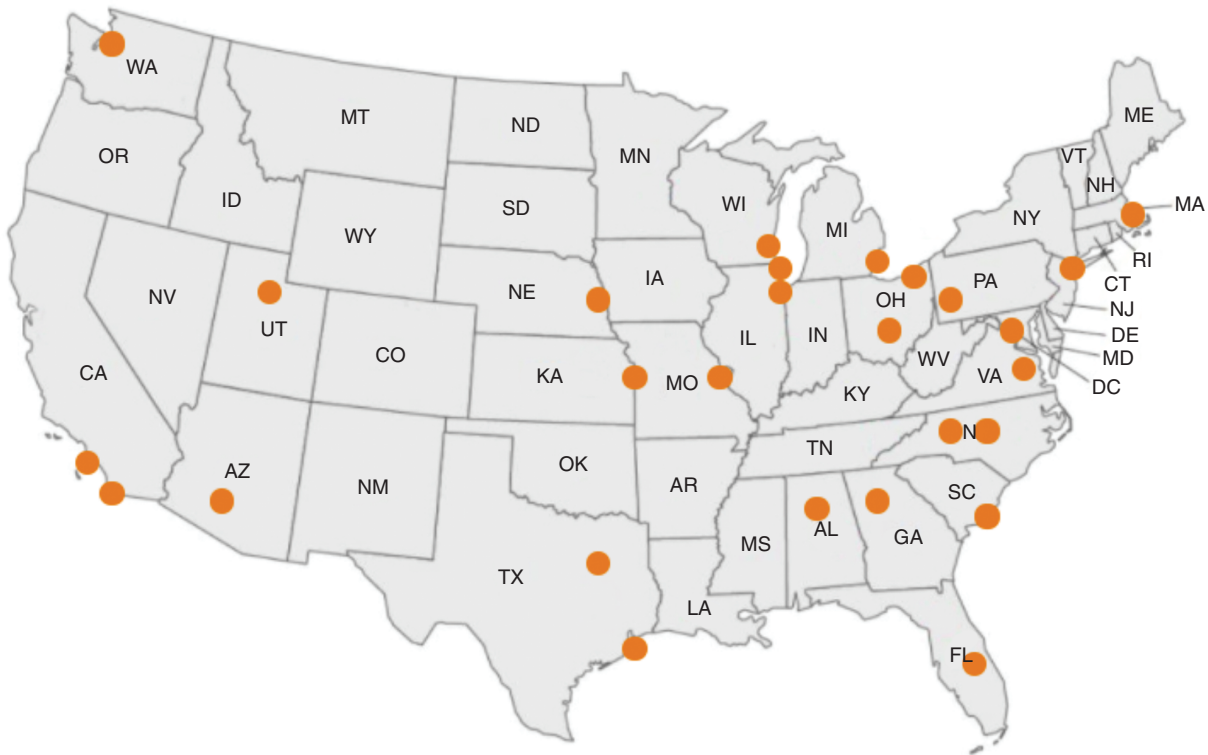


Fig. 1 NCI-CONNECT clinical network sites.

another for participants. The ever-increasing sophistication of molecular technologies enabling more in-depth genomic analysis also has led to the recognition of many more distinct molecular subtypes of these rare cancers. In other words, on the basis of distinct molecular findings, these rare cancer types are being further divided into even rarer subtypes. These individual differences in identified alterations and newly recognized subtypes, while informative, further complicate clinical trial design and implementation and therefore progress in targeted approaches to therapy. Additionally, access to advanced molecular profiling, often essential for identifying these rare subtypes, is not easily obtained at many centers.

Ependymoma, a rare type of tumor that can form in the brain and spinal cord arising from ependymal cells that line the passageways through which cerebrospinal fluid flows, is an excellent example of how molecular analyses have defined newly recognized, distinct subtypes that vary in both prognosis as well as underlying tumor biology. Historically, ependymoma was a diagnosis based on histologic features, most notably perivascular pseudorosettes and true rosettes. However, as a result of recent international collaborative efforts, 9 distinct subtypes of ependymoma were defined on the basis of both their molecular characteristics and tumor location (Figure 2).¹ These 9 distinct subtypes have been amended to include a tenth histologically defined ependymoma that has completely unique clinical and molecular characteristics. This subtype is characterized by a primary spinal cord location, typically within the dura (intradural) but outside of the spinal

cord (extramedullary). This cancer is very commonly disseminated in the spinal canal and is characterized by an aggressive disease course. Molecular analysis has defined this subtype by the amplification of the *MYCN* gene, which is unique in ependymoma.^{2,3} To further underscore the challenge in clinical trial accrual in rare cancers, only 27 cases of *MYCN*-amplified ependymoma have been reported in the world's literature, thereby necessitating a large collaborative effort to enable adequate identification and enrollment in any therapeutic clinical trials.

There are many other practical considerations as well when it comes to patient accrual in clinical trials for rare CNS cancers. Given the rarity of these cancers, awareness of these opportunities is a challenge. Both patients and health care providers are often less informed on rare cancers and associated clinical trial opportunities. With patients distributed across a wide geographic area and data demonstrating that the majority of patients are not followed at major academic centers, it may be difficult to find and reach these patients to inform them of ongoing clinical research activities for their rare cancer. However, this does not diminish the importance of having both national and international centers of excellence where there is expertise and ongoing research for these diseases. In this context, several approaches may help overcome the limited access to knowledge and the logistical and geographic challenges. Social media and philanthropic and patient advocacy organizations can be helpful in providing connections and information about ongoing clinical trials.

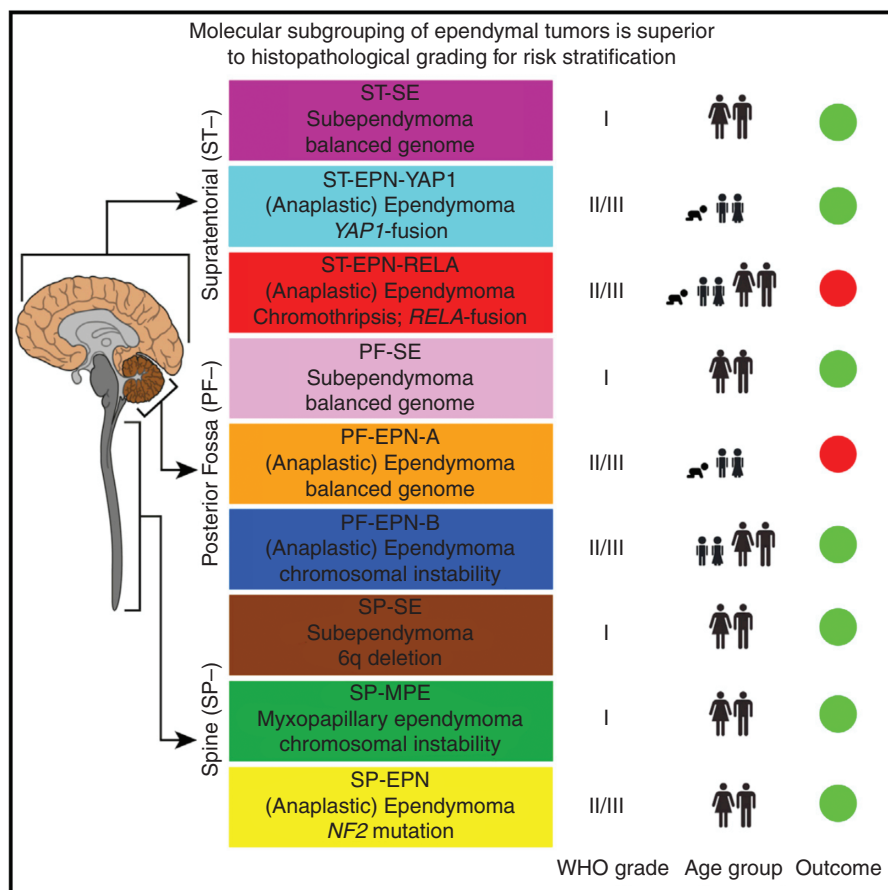


Fig. 2 Molecularly defined subtypes of ependymoma.

However, online efforts cannot reach everyone and a lack of easily accessible information and the difficulties in reaching patients where they continue to present obstacles in conducting clinical trials for rare cancers.

Adapting the Clinical Trial Path for Rare Cancers

Given these logistical challenges, the question becomes: How do we adapt and apply clinical trial for rare cancers? One aspect to consider is the traditional clinical trial path itself. This path has traditionally gone from phase 1 to phase 2 and, if there is a strong efficacy signal, to a phase 3 randomized study. Notably, and what may be particularly germane for rare cancers is that there has been an increasing interest in preclinical and early clinical trials including the “window of opportunity” or phase 0 trials. These require fewer patients than the traditional studies and, in the case of rare cancers, may provide early metrics of treatment success or failure by determining if the therapeutic agent has adequate tumor delivery (tumor pharmacokinetics) and whether it hits the intended drug target (tumor pharmacodynamics). These measures are particularly important, for instance, in brain tumor research,

where drug delivery is an issue because of the blood-brain and blood-tumor barrier.

For rare diseases, data from prior studies and other cancers can often inform phase 1 trials and—if done in brain tumors—phase 0 trials testing drug delivery (tumor pharmacokinetics) to the tumor. As originally conceived, the phase 0 paradigm relies heavily on preclinical modeling before patient testing.⁴ This provides critical preliminary data on delivery and pharmacodynamic assays before enrolling patients. A treat and biopsy or treat and resect approach is most commonly used in this context, although a biopsy prior to treatment is optimal, enabling a comparison of contemporary pretreatment and posttreatment tumor tissue.⁵ However, while preclinical modeling is important as a preliminary step for phase 0 trials, there are fewer preclinical models for many of the rare cancers underscoring the utility of using data about drug delivery from studies in other brain tumors, thereby enabling eliminating drugs with poor delivery from further development and focusing on agents demonstrating adequate tumor delivery. While these studies in other brain tumors may address this fundamental issue of delivery, tumor pharmacodynamic testing is still required for each individual rare cancer.

As an example that demonstrates the utility of this approach, Dr. Richard Gilbertson and colleagues published a seminal paper in 2014 describing the C11orf95-RELA

fusion in supratentorial ependymoma that leads to the constitutive activation of NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells).⁶ Proteasome inhibition decreases the clearance of I κ B kinase (IKK), which is the natural inhibitor of NF- κ B. Although proteasome inhibitors such as bortezomib have proven highly effective for systemic cancers such as multiple myeloma, these agents were specifically designed not to cross the blood-brain barrier. In contrast, the proteasome inhibitor marizomib was proven to achieve good penetration in both normal brain and the primary brain tumor, glioblastoma, leading to several clinical trials and providing important evidence that marizomib crosses the blood-brain barrier.⁷ As described in detail by Holland et al (this supplement), a preclinical mouse model (RCAS-TVA) that recreated the C11orf95 (ZFTA)-RELA fusion ependymoma, showed a response to treatment with marizomib. This provided additional rationale for a clinical trial in the NCI-CONNECT program testing marizomib in patients with ependymoma harboring the RELA fusion and comparing it with RELA negative ependymoma.

In addition to providing a novel therapeutic approach to a rare subtype of a rare cancer, RELA fusion ependymoma demonstrated proof of principle that an important laboratory discovery can get translated into a preclinical model, which then provides important rationale and support for a hypothesis-based clinical trial. Furthermore, the need for collaboration is highlighted, whereby the seminal discovery of the underlying cancer driver by Dr. Gilbertson and his colleagues enabled Dr. Holland to create the animal model. These important endeavors which provided critical understanding of the pathogenesis of the cancer and putative therapeutic targets led to the development of the clinical trial within a program, NCI-CONNECT, capable of managing this study in a very rare cancer subtype. It is also worth noting, as described by Holland and colleagues in this supplement, that models of rare cancers can uncover important mechanisms of disease that may have both broad and direct applicability to other cancers or mechanistic implications for therapeutic targeting. In this context, the discovery of a novel gene fusion in ependymoma is one of the earliest examples of chromothripsis—a process in which chromosomes fracture and reanneal leading to novel fusion genes and cancer-driving proteins, which is an area of increasing interest and investigation.⁸

The successful implementation of this paradigm will hopefully lead to similar efforts and breakthroughs in a variety of rare cancers and diseases. The success of such an approach depends on collaborations at every step along the way, beginning with the collection of tumor material and corresponding clinical data. This enables the in-depth analyses necessary to uncover these types of driver alterations in rare cancers, whether they are fusions, point mutations, or other molecular or genetic alterations. In the case of ependymoma, clinically annotated tumor collections, such as the CERN Tumor Tissue Repository, helped contribute to a better understanding of prognosis as well as the molecular testing that uncovered the tumor subtypes.^{1,9} It is only through collaborative, multidisciplinary, and trans-institutional approaches that advances in these rare diseases can be made, a consequence of the rarity of these diseases

and the inherently limited tumor material for analysis and small numbers of patients eligible for participation in clinical trials.

Expanding Patient Eligibility and Novel Trial Design

There are additional strategies that can employ to aid in the design of clinical trials for rare CNS cancers. Phase 1 trials are traditionally used to determine optimal dosing as well as evaluate the spectrum of treatment-related toxicities. These studies commonly include pharmacokinetics based on serial measurement of drug concentrations in blood. Therefore, the results of dose-finding and pharmacokinetics from prior studies can be used to help minimize the number of patients with rare CNS cancers required for safety testing, unless there are specific concerns about the disease or the patient population (ie, in hereditary syndromes). When a treatment is planned where phase 1 data do not exist, expanding the disease eligibility beyond the rare cancer(s) of interest also can help to expand the pool of potentially eligible patients and accelerate patient accrual.

As an example of this strategy, the NCI-CONNECT is conducting a first-in-human study of ONC206, (NCT04541082). Earlier clinical trials showed preliminary activity of the related drug ONC201 in histone mutated glioma.^{10,11} Preclinical evidence suggests that ONC206 is a more potent inhibitor of the dopamine receptor, DRD2. This trial expands eligibility to expedite accrual and accelerate determination of the phase 1 endpoint of maximum tolerated dose by including individuals with a wide variety of CNS cancers. Subsequent studies now planned will concentrate on more specific tumor types.

Phase 2 studies are designed to determine a preliminary measure of treatment efficacy. Unfortunately, there have been many examples where the results of single-arm phase 2 studies, compared to historical controls, have demonstrated efficacy that has not been borne out in subsequent larger, randomized trials. Given the issues with accrual and rarity of many CNS cancers, randomized trials may be impractical in many cases. However, there are examples in which the results of a single-arm clinical trial have been compelling and resulted in regulatory approval of the treatment for the rare cancer. This is best exemplified by the study testing the mTOR inhibitor everolimus in patients with tuberous sclerosis-associated subependymal giant cell astrocytoma (SEGA).¹² In this study, there was both a high rate of objective response and clinical benefits including improved quality of life and decrease in seizure frequency. As a further example, the CERN-08-02 study mentioned above, which combined temozolomide and lapatinib, demonstrated objective responses, disease stabilization and, as described below, clinical benefit in patients with recurrent ependymoma.¹³

Comparative phase 3 randomized trials provide the highest level of evidence of efficacy, but they are also resource-intensive, typically requiring large numbers of patients and take a long time to accrue and complete. As previously mentioned, randomized controlled trials are difficult in rare cancers, but they are sometimes

necessary if the response to the standard of care is variable. For example, in adult medulloblastoma, approximately 70% of these tumors are classified molecularly as being in the sonic hedgehog category. However, given the variable effectiveness of established first-line treatment in medulloblastoma, testing whether the addition of a smoothed inhibitor improves outcome in this sonic hedgehog-positive subpopulation will require a randomized trial. To address this, complementary studies by the EORTC and Alliance Oncology Group are planned.

Novel clinical trial designs also may be helpful. Umbrella and basket designs, which typically focus on targeted therapies, are proving particularly useful.¹⁴ An Umbrella design, which provides treatments for a single tumor type, would include specific treatment arms for subtypes in diseases like ependymoma and medulloblastoma. The Basket design focuses instead on the target and is more agnostic to the disease subtype. For example, a Basket trial could test the targeting of BRAF abnormalities in a variety of different cancer types or the use of immunotherapy in a variety of rare cancers. In the NCI-CONNECT portfolio, there is a Basket immunotherapy trial that is testing nivolumab in all the rare cancers studied in the NCI-CONNECT, stratifying patients by the extent of prior therapy (NCT03173950). Adaptive designs are increasingly being considered which, particularly in a randomized study, enable redistribution of patients to treatment based on real-time determination of results. In the context of rare diseases, multiple treatments can be efficiently tested, and the most effective treatment potentially determined before full accrual is completed.¹⁵

In some cases, logistical challenges may be best addressed by developing clinical trials with pragmatic designs using either oral agents that do not require regular visits for treatment or by otherwise reducing the number and frequency of treatments that a patient must travel to receive. As an example of a pragmatic design, The Collaborative Ependymoma Research Network (CERN-08-02; NCT00826241) study combined the oral agents temozolomide and lapatinib, the latter targeting HER2 and EGFR overexpression that are both found in a high percentage of ependymomas.¹³ For this study, patients were evaluated at the treating facility only every 8 weeks when the next 2 cycles of the medications were provided.

In conclusion, clinical research for rare cancers remains a challenge, but there are ways to adapt and improve on existing methods. Programs such as the NCI-CONNECT are helping to accelerate advances in rare cancer. Although clinical trials in rare CNS cancers are more difficult than comparable clinical trials in common cancers, accrual and progress can be enhanced with the use of existing clinical data or broader inclusion criteria together with early studies of delivery in phase 0 trials or safety in small phase 1 trials. These measures help to reduce the need for patient accrual. In addition, the implementation of novel clinical trial designs, such as an Umbrella, Basket, or Adaptive design, may also accelerate the progress. There should be interest also in implementing pragmatic treatment plans, such as the use of oral agents or infrequent administration, or alternatively, a clinical trial network that will reduce the travel and logistical issues for each patient, making participation easier on patients. The use of social media can enhance awareness amongst patients and health care

providers. The collection of clinically annotated tumor tissue will certainly accelerate discovery, improve our understanding of patient outcomes and potentially inform the development of preclinical models necessary for further novel treatment development. Finally, efficacy studies incorporating clinical outcome assessments (COAs) to help determine true treatment efficacy is a vital part of these clinical trials. By combining many of these strategies, progress will be made in identifying promising new targets and conducting clinical trials of potentially promising new treatments for rare CNS cancers.

Considering Outcome Measures in Rare CNS Tumor Trials

Traditionally, outcomes in cancer clinical trials have primarily focused on measures related directly to the impact of the treatment on the tumor. These measures include objective tumor response, progression-free, and overall survival. Increasingly, however, there has been a recognition that the impact of therapy on how a person feels and functions may be equally if not more important, especially in some contexts (Table 1). These combined outcomes measures highlight the concept of COAs.^{16,17}

COA measures are particularly germane for patients with CNS cancers. Recently published data from a web-based survey of rare tumor patients (ClinicalTrials.gov Identifier: NCT03251989) demonstrated that over 80% of those with high-grade tumors and almost 50% of those with low-grade CNS tumors report an inability to return to work from the time of diagnosis.¹⁸ Within the NCI-CONNECT, we are studying the impact of rare CNS tumors by evaluating life changes in patients who have 1 of the 12 tumor types (Table 2) included in the NCI-CONNECT Program. To date, our findings have demonstrated that 60% of patients report a change in employment, with 31% having to stop work and 10% losing their job because of their brain or spine tumor diagnosis. These findings highlight the significant impact that these CNS tumors, many of which are thought of as “lower grade” or even “benign,” have on individuals (Table 3) and their life quality.

Previous qualitative studies have shown that patients with more common CNS tumors report spending the majority of their time feeling ill and unable to perform usual activities.¹⁹ Other studies have shown that this impact extends to the caregiver and family, notably reporting that there is increased stress, a negative impact on financial status, changes in family rules, and more recently, health effects for the caregiver.^{20,21} Our specific focus on understanding the severity and course of symptoms in patients with CNS tumors has revealed that 50% of patients have 10 concurrent symptoms and 40% report at least 3 symptoms that they rate as moderate-to-severe.²² The moderate-to-severe symptom rating is highlighted because in CNS tumors as well as other cancers, symptoms rated as moderate-to-severe have been associated with lower quality of life and even significant impacts on cancer progression and survival.

Patient-reported outcomes (PROs) instruments, a common form of COA, provide important information

Table 1 Definition of Clinical Benefit

A positive clinical benefit of an intervention, ie, a positive effect on how a person feels, functions, or survives

- How long a patient lives
- How the patient feels or functions in daily life

Can be demonstrated as either:

- A comparative advantage in the treatment of a disease or a condition

Or

- A comparative reduction in treatment-associated toxicity

Clinical outcome assessments (COAs) include:

- Patient-reported outcomes (PROs)
- Clinician-reported outcomes (ClinROs)
- Observer-reported outcomes (ObsROs)
- Performance outcomes (PerfOs)

Table 2 Tumor Types Under Investigation by the NCI-CONNECT Program

- Atypical teratoid rhabdoid tumor (ATRT)
- Choroid plexus tumors
- Histone mutated gliomas
- Ependymoma
- Gliomatosis cerebri (defined by imaging criteria)
- Gliosarcoma
- Medulloblastoma
- Meningioma (high grade)
- Oligodendroglioma/anaplastic oligodendroglioma
- Pineal region tumors
- Pleomorphic xanthoastrocytoma/anaplastic pleomorphic xanthoastrocytoma
- Primitive neuro-ectodermal tumors (CNS embryonal tumors)

directly from the patient related to symptoms and other outcomes and can be administered longitudinally to understand changes in this impact over the course of the disease. Using validated PRO instruments to measure symptom burden in patients with either primary brain (MDASI-BT) or spinal cord (MDASI-Spine) tumors, we found that patients have multiple symptoms that are co-occurring throughout the disease trajectory and regardless of the stage of their disease.²²⁻²⁴ The majority of the symptoms included in these measures are considered to be core symptoms of disease, based on greater than 10% of the population experiencing them.¹⁹ These findings clearly demonstrate that patients are highly symptomatic. However, symptoms vary from patient to patient, and it should be noted that the majority of patients in these studies had malignant gliomas.

To further study the importance of symptom burden on interference in daily life activities in those with more rare CNS tumors, a longitudinal Natural History Study (ClinicalTrials.gov Identifier: NCT02851706) and a web-based study (ClinicalTrials.gov Identifier: NCT03251989)

Table 3 Patients With Rare CNS Tumors Are as Symptomatic as Those With High-Grade Glial Tumors

Scale	NCI-CONNECT Risk and Outcomes Web-Based Study	
MDASI-BT	N = 86	
	Mean (SD)	
	Symptom mean (SD)	2.0 (1.7)
	Symptom mean range	0-6.9
MDASI-SP	N = 121	
	Mean (SD)	
	Symptom mean (SD)	2.7 (1.8)
	Symptom mean range	0-7.9
	Interference mean (SD)	3.5 (3.1)
	Interference mean range	0-10.0
	Interference mean (SD)	4.0 (2.8)
	Interference mean range	0-10.0

are being conducted, which allow participation from patients with rare CNS cancers without geographic restrictions or the need to travel to participate. Early results from this study determined that rare CNS tumor patients are also highly symptomatic. The reported interference in daily life in terms of activity and mood was also quite severe, providing additional evidence that rare CNS tumors affect how patients feel as well as function. These are important findings that extend beyond individual assessment and management because the FDA has defined clinical benefit of a therapy not only as a positive effect on how a person survives, but also how they feel and function.¹⁶ In other words, clinical benefit can be defined in terms of how long a person lives, but it can also be defined in terms of quality of life. The FDA has recommended that standardized COAs are used in clinical trials to define this clinical benefit.^{16,25} This includes PROs that are critically important in patients with these rare CNS tumors associated with significant symptoms and functional limitations. Additionally,

recent data have demonstrated that collecting and evaluating PROs in patients with systemic cancer is associated with improved survival, although studies evaluating this question in patients with CNS cancer have not been completed.²⁶

The development of guidelines for use of COAs in brain tumor clinical trials has been the focus of recent collaborative workshops. In preparation for a 2014 workshop sponsored by the FDA and the Jumpstarting Brain Tumor Drug Development Coalition, which is a group of advocacy organizations, patients were surveyed to identify what they thought the priorities for treatment studies should be.²⁷ One of the questions asked was: In addition to allowing a person to live longer, what would you most like to see future brain tumor treatments do? Patients were then able to rate on a scale from 1 to 5, whether something was “not at all important” ranging to “extremely important.” Patients identified a significant number of symptoms that were important to them to be addressed in clinical trials testing new treatments going forward.²⁷ Recommendations from this workshop included the routine monitoring of the use of concomitant medications, such as anticonvulsants and corticosteroids during trials. Additionally, symptom burden and functional status using PROs as well as clinician-reported observations or testing should both be performed to assess functional outcomes in clinical trials.²⁷ A group with representatives from many agencies including the NCI, RANO, FDA, EMA, and Advocacy organizations then continued this work, culminating in the publication of recommendations for a core set of symptoms and functions to be included in both clinical care and research in those with brain tumors.²⁸ These core symptoms included difficulty communicating, pain, perceived cognition and seizures, in addition to those side effects and symptoms that are specifically associated with the treatment under investigation. Changes in function included physical functioning, including weakness, difficulty in walking, and role functioning, defined as how well the patient performs in their life or work role.

COAs have proven to be critically important in the determination of efficacy in rare CNS cancer clinical trials. In addition to the study of everolimus in patients with SEGA, the phase 2 study of temozolomide and lapatinib for patients with recurrent ependymoma described above underscores the

potential importance of these measures.¹³ While there was direct evidence of tumor response with an overall response rate of 10%, including one complete response, the majority of patients achieved disease stability. Given the variable nature of ependymoma progression, the clinical significance of stable disease is uncertain. However, PRO data were systematically collected using the MDASI-BT for brain tumors and the MDASI-Spine tumor instruments. Over the course of the study, patients who remained on treatment either with objective response or disease stabilization had a striking percentage decrease in moderate-to-severe disease and autonomic symptoms, as well as a marked decrease in significant activity-related interference items (as shown for spine tumors in [Figure 3](#)).¹³ In summary, patients in this study who achieved either disease stabilization or partial tumor response had improvement in how they felt and how they functioned. The impact on function was further identified with the use of the physician-rated Karnofsky Performance Status. In those with spine tumors, there was a 50% improvement, and no worsening in performance status during the course of the study. For those patients who had tumors in the brain, 43% of those patients had stable or improved Karnofsky Performance Status measures. The results of this study were reviewed by the NCCN Committee on the basis of both disease control rates and the improvements in how the patient feels and functions, and this regimen is now included as an option for those with recurrent ependymoma.

To evaluate the importance of these core symptoms in the broader CNS tumor population, a diverse sample of patients with both common and rare CNS tumors utilizing data collected as part of the Natural History Study in the Neuro-Oncology Branch at the Center for Cancer Research at the National Cancer Institute has been analyzed. The study found that the core set of symptoms and functions were more severe among patients with disease progression compared to those with stable disease based on imaging studies. Furthermore, longitudinal assessment of symptoms from the time of no progression to the time of progression was analyzed. It was found that symptoms worsened at the time of disease progression. Collectively, the data support the use of these core symptoms and functions in future studies.²⁹

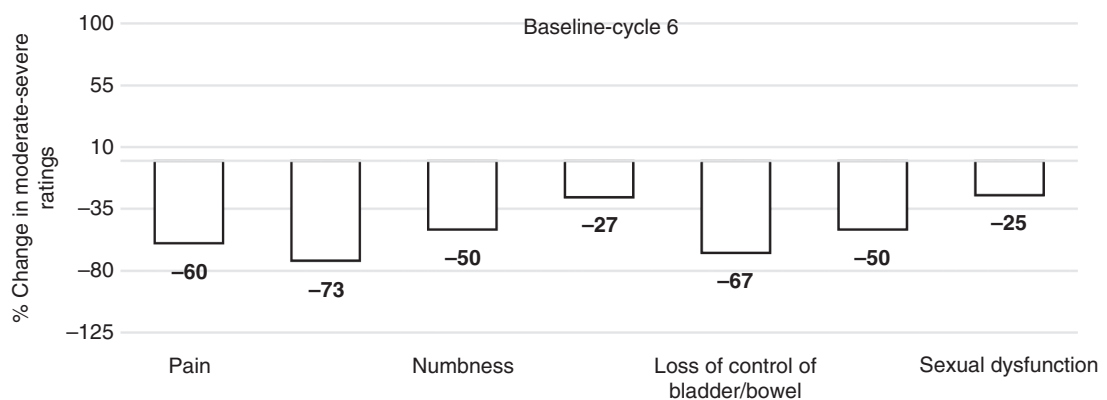


Fig. 3 Comparison of incidence of moderate-to-severe spine symptoms from baseline to cycle 6 of temozolomide-lapatinib treatment (negative change means fewer patients).

It's clear that primary outcomes measures of clinical trials are evolving, and appropriate outcomes will vary according to the specific goals of each treatment and trial. If the trial and the agent being tested are designed to improve symptoms, then using a symptom endpoint should be the priority.³⁰ On the other hand, if the drug is designed to shrink tumor, then the outcomes should be focused on those more traditional clinical trials outcomes, with COAs used to augment the results of the more traditional efficacy measures as highlighted by the ependymoma trial. These patient outcomes measures may be important for enhancing our understanding of the disease and the impact of our treatment on how the patient feels and functions during that period of survival.

In summary, although many rare CNS tumors are considered low grade with an anticipated long survival, patients are often highly symptomatic. In many cases, significant symptoms and functional limitations are present from the time of diagnosis, which can continue through the disease trajectory. By accurately assessing symptoms and function in clinical trials, we can better evaluate the true clinical benefit of a therapy and understand its impact on the clinical trajectory and patient lives. This is important from a patient's perspective, and can help us improve care, quality of life, and the length of life in the future. As such, incorporating COAs into clinical trials, particularly in the limited number of studies possible for patients with rare cancers, is critical. The insights about impact of treatment on symptoms and function provide an important dimension beyond traditional measures of disease response. Furthermore, given that large, randomized studies in rare diseases are typically impractical, incorporation of COAs into early phase studies may provide critically important insights about both worsening and improvements in selected treatment-related and disease-related symptoms, respectively, these early studies are critical to optimal planning of future, definitive clinical trials for patients with rare CNS cancers, addressing a serious unmet need.

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