Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/emerging-endpoints-treatment-benefit-plgg/57103/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Emerging Endpoints for Evaluating Treatment Benefit in pLGG

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Day One Biopharmaceuticals. Here's your host, Dr. Shelina Ramnarine.

Dr. Ramnarine:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Shelina Ramnarine, and today I'm sitting down with Dr. Mohamed Abdelbaki to discuss how endpoints like time to next treatment and treatment-free interval may complement radiographic progression-free survival when evaluating treatment benefit in pediatric low-grade gliomas.

Not only is Dr. Abdelbaki a Director of the Pediatric Neuro-Oncology Program at St. Louis Children's Hospital, but he's also Professor of Pediatrics at Washington University School of Medicine. Dr. Abdelbaki, thanks for being here today.

Dr. Abdelbaki:
It's an honor to be here, and I'm very excited to be discussing this important subject with you.

Dr. Ramnarine:
Well, why don't we start with some background, Dr. Abdelbaki. For decades, progression-free survival, or PFS, has been a cornerstone endpoint in pediatric low-grade glioma trials. But as we continue to learn more about this disease, what are some of the limitations of relying on radiographic PFS alone, and how have challenges like small lesions, pseudoprogression, and treatment-related imaging changes influenced that conversation?

Dr. Abdelbaki:
So when pediatric low-grade gliomas are completely resected, what we end up doing is following up with this patient, and the tumor typically does not come back except in less than 5 percent of cases. However, more than 50 to 60 percent of the tumors are in locations that are not resectable or require a small resection or biopsy, and therefore, they will require other therapies at certain time points.

So when we share this with families, we always say having a pLGG—as I'm going to refer to it for the rest of the conversation—is like having a chronic disease where the tumor may grow, stop growing, we use a certain medication—either targeted therapy or chemotherapy—things will improve, and then it may grow again. And hence, we care so much about the quality of life and the long-term function of these patients.

The imaging and the criteria that we use for imaging is a problem. And of course, everything has its own limitations, so we're not suggesting that something will solve all the issues that we have. But the problem that we have is that we are relying on imaging to decide whether the patient has progression or not, and in so many cases, you will have radiographic progression that's not associated with clinical progression. And therefore, the patient may have an increase in the size of the tumor, and the symptoms are actually very well controlled.

So what we typically do as neuro-oncologists is we rely on the input of both the imaging and the clinical factors to decide whether to start therapy or stop therapy.

Dr. Ramnarine:
Now, in clinical practice, treatment decisions rarely rely on imaging alone. So how do factors such as neurological symptoms, visual function, endocrine complications, functional status, and quality of life influence your assessment of whether a patient's disease has meaningfully progressed?

Dr. Abdelbaki:
We have to incorporate these factors in our decision-making. As we've mentioned, our patients with pLGGs are patients with chronic disease. We care so much about the visual, neurological, endocrine, and functional outcomes and the neuropsych status. Therefore, our multidisciplinary teams that incorporate all these specialties have to make these decisions regarding our patients.

Outside of a clinical trial setting, we always factor in everything when deciding whether a patient would be considered to have progression or not. So for example, if I have a patient who has seizures that are getting worse and the imaging is stable, that would be considered progression because the seizures that are caused by the tumor are getting worse, and we cannot control it. So this is what is so important about the way we're treating these patients.

Dr. Ramnarine:
So if we bring this all together, the distinction between radiographic progression and clinical progression has led to growing interest in alternative measures of treatment benefit. Specifically, investigators are exploring time to next treatment and treatment-free interval, otherwise known as TTNT and TFI, respectively. With that being said, can you tell us how these endpoints are defined and why they may be particularly relevant in pediatric low-grade glioma?

Dr. Abdelbaki:
I'm glad that we're starting to have these conversations about TTNT and TFI, and it's important for us to make everyone aware of what these mean. So TTNT typically starts from the time that you start one therapy until you start the following therapy. And TFI means that this is the time from stopping this therapy until you need additional therapies.

So these endpoints basically will give you insights into the durability of the response—not relying on imaging only—but relying on other factors that we're going to discuss. So this is extremely important in a chronic disease setting where you have to factor in several decisions, where sometimes the tumors are stable and sometimes there are small changes that may not be meaningful. Sometimes you have to stop therapy or hold therapy because of toxicities. So there are several factors that you have to keep in mind, and that's the benefit of having TTNT and TFI while assessing responses in pLGG.

Dr. Ramnarine:
For those just tuning in, this is *Project Oncology* on ReachMD. I'm Dr. Shelina Ramnarine, and I'm speaking with Dr. Mohamed Abdelbaki about the importance of looking beyond progression-free survival in pediatric low-grade glioma care and incorporating time to next treatment and treatment-free interval into therapeutic assessment.

If we continue analyzing the evolving role of TTNT and TFI, Dr. Abdelbaki, these endpoints have been used in other oncology settings for quite some time. So how have those experiences informed their use in pediatric low-grade glioma, and what additional insights can they provide beyond traditional measures like PFS?

Dr. Abdelbaki:
These terms have been used before in leukemias, multiple myelomas, lymphomas, and even adult gliomas, and they were described in the latest approval for one of the IDH inhibitors. So I think these are important to assess when we expect that survival is going to be prolonged and the treatment burden will be clinically relevant. So they will help capture the timing and necessity of therapeutic intervention rather than radiographic changes alone.

So given that we're talking about pLGG and how we would like, as clinicians, to be incorporating real-world clinical decision-making in our ability to be assessing responses, I think this is where these terms would come into play because they will allow us to incorporate not only radiographic progression, but also the clinical scenarios that may be happening—a patient wants a drug holiday, we have to hold therapy for a certain period of time because of toxicities, or stability that may be associated with some increase in the size of the tumor that's not significant.

So all these factors, I think, when trying to think about TTNT and TFI will be extremely helpful in the near future.

Dr. Ramnarine:
Now, recent retrospective data from studies like FIREFLY-1 have generated considerable discussion around TTNT and TFI. Can you give us an overview of what we're beginning to learn from these early data and what those findings suggest about the relationship between radiographic progression, clinical progression, and the timing of retreatment?

Dr. Abdelbaki:
The FIREFLY-1 study provided the first prospective pLGG data regarding TTNT and TFI outcomes in the progressive/refractory setting. So it was clear that the findings suggest that radiographic progression does not necessarily result in immediate retreatment and that early observations have generated interest in whether TTNT may more closely reflect meaningful progression in some patients.

Of course, as we've discussed, there are limitations to any of these endpoints that we talk about. So similar to the fact that we find that PFS, or progression-free survival, to be not complete, TTNT and TFI have not been validated endpoints. So these are descriptive exploratory analyses that were not powered for subgroup comparisons on that study and are not validated surrogate measures for survival or long-term clinical outcomes. And these are subjective endpoints that may be influenced by non-tumor factors that can vary across investigators and institutions.

So there are limitations, but I think these are very promising endpoints that we should be looking into in our clinical trials.

Dr. Ramnarine:
Before we close, Dr. Abdelbaki, let's look ahead for a moment. As interest in TTNT and TFI continues to grow, what are the most important questions the field is still working through regarding their standardization, interpretation, and validation, and what additional prospective evidence would help clarify their role alongside established measures in future trials and clinical practice?

Dr. Abdelbaki:
There are definitely questions that remain regarding how TTNT and TFI should be standardized across studies and clinical settings. So retreatment decisions may be influenced by physician judgment, institutional practices, or protocol-specific factors. The relationship between TTNT and TFI and long-term outcomes remains an area of active investigation, and further studies incorporating functional outcomes, visual assessments, and quality of life measures and longitudinal clinical data may help define the role of these endpoints moving forward.

As we've mentioned, these endpoints are partially subjective, and they are influenced by treatment-related toxicities, patient preferences, physician judgment regarding whether to and when to intervene, and availability or access to alternative therapies. So if you are in a place where you don't have an available therapy and you may need a longer time to be able to add an additional therapy or waiting for insurance approval, this may prolong your TTNT and TFI. And we haven't used TTNT and TFI in pLGG studies before, and therefore, cross-trial comparisons cannot be made.

However, I think these are very promising endpoints and we should start discussing how to incorporate them in our future clinical trials and think of assessing what we have published before, retrospectively, and look at the TTNT and TFI for all drugs that have been approved or that are undergoing approval in order for us to be able to look at their effectiveness with new factors and new measures like TTNT and TFI.

Dr. Ramnarine:
As those forward-looking comments bring us to the end of today's program, I'd like to thank my guest, Dr. Mohamed Abdelbaki, for joining me to discuss emerging endpoints in pediatric low-grade glioma treatment and how they may help clinicians assess patient outcomes. Dr. Abdelbaki, it was great having you on the program.

Dr. Abdelbaki:
Thank you so much for having me, and I hope everyone will benefit from this conversation.

Announcer:
This episode of *Project Oncology* was sponsored by Day One Biopharmaceuticals Inc. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!