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Clinical Stability Post-Tovorafenib in Pediatric Low-Grade Glioma: FIREFLY-1 Results

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

Dr. May
This is *Project Oncology* on ReachMD, and I'm Dr. Alexandria May. Joining me to review the results from the phase 2 FIREFLY-1 trial that evaluated clinical stability following treatment with tovorafenib in patients with relapsed and refractory pediatric low-grade glioma is Dr. Nicholas Whipple. Not only is he an Associate Professor of Pediatrics in the Division of Pediatric Hematology and Oncology at the University of Utah, but he's also the Medical Director of Pediatric Neuro-Oncology at Primary Children's Hospital. Dr. Whipple, welcome to the program.

Dr. Whipple:
Thank you. It's great to be here.

Dr. May:
To begin, Dr. Whipple, could you briefly describe how our growing understanding of BRAF alterations in pediatric low-grade glioma has influenced the development and use of targeted therapies like tovorafenib?

Dr. Whipple:
This is a really great question and one that I think is on the forefront of providers' minds. Low-grade glioma in the pediatric space has really advanced significantly over the last couple of decades.

In the early days of treating pediatric low-grade glioma, we really weren't aware of the molecular drivers. And through wonderful research that's been performed by scientists and through clinical trials, we have learned that BRAF alterations constitute a majority of the molecular drivers present in pediatric low-grade glioma. For example, approximately 75 to 80 percent of all pediatric low-grade glioma have alterations in BRAF; the most common of those being BRAF fusions, and the second most common being BRAF V600E point mutations. There are others. So in learning that there are these BRAF drivers, it's opened up our portfolio of interventions we can offer to families. With advances in pharmacology and medications that are now available, we're able to target these tumors in a more precise and unique way than we have been before.

While cytotoxic chemotherapy has produced meaningful outcomes for many patients and should still be considered in our toolboxes of how we treat these tumors—without doubt, that should not go away—what we've learned is that there are other medications which can be employed to help patients, and that's an exciting part of this therapy. With MEK inhibitors, combined BRAF plus MEK inhibition, NTRK inhibitors in some instances, and now tovorafenib with its pan-RAF inhibition, we know that these target these alterations in different and unique ways, and we're seeing that. BRAF presence does influence our treatment selection, and it also influences the ongoing research in the basic science arena and in how clinical trials are developed.

Dr. May:
With that background in mind, let's turn to the FIREFLY-1 trial. This study included a planned treatment pause after 26 cycles with the option to restart upon clinical or radiographic progression. So what insights does this design offer for balancing treatment exposure with

long-term disease control?

Dr. Whipple:
I think one benefit of this study is that it follows patients long term, whether they're on treatment or off treatment. So not only do we get representation of how patients are responding actively to this therapy, but we're going to be able to track how they perform once they have discontinued therapy and, for many patients, even once they restart therapy.

So here we're going to be able to balance the clinical effectiveness of treatment, all of the side effects potentially associated with the treatment, and how long these patients are in a state of disease stability once they're off treatment. So we're excited about the long-term trajectory of what we'll be able to learn from this study.

Dr. May:
Now, in terms of the findings, the registrational arm of FIREFLY-1 reported a 53 percent objective response rate, with a median duration of response of 18 months. How do these efficacy outcomes compare with historical benchmarks in this population? And what stands out to you in terms of long-term disease management?

Dr. Whipple:
Historically, we have not always had the benefit of knowing the molecular alterations associated with a tumor. Earlier trials, for example with cytotoxic chemotherapy, did not always know the BRAF status and whether there was a V600E mutation, a point mutation, or not. That's important to know, and these newer trials are telling us that. It's important to note that there is a difference in biology and tumor growth because of the presence or absence of neurofibromatosis type 1.

We know that outcomes for patients with optic pathway tumors may be slightly different or have different growth patterns and trajectories than patients with gliomas that are not in the optic pathway. We know that the presence of BRAF V600E tends to suggest a slightly more aggressive disease course with a slightly higher potential for metastatic disease and earlier recurrence.

So with that very lengthy caveat, one thing that we need to pay attention to as closely as we can going forward is obtaining this information in a consistent way across all disease cohorts: objective response rate, median duration of response for patients with this mutation or for patients with that mutation, in the front line, in the recurrent setting, in patients who have received one prior line, two prior lines, four prior lines, etc.

So with that said, it's difficult to compare with historical controls, but these early data, I would say, are encouraging. We know that percentage objective response rates have not been equally as high across all of these studies. And to the best of our ability, we need to look closely at what makes up those differences and what accounts for those differences, and we can't do that perfectly in hindsight, so we do need to look at that going forward.

A median duration of response of 18 months, I think, is promising in that it's hopeful that we're not seeing a significant rebound in these patients or a significant need to transition therapies or reinitiate therapy in an unacceptable, unreasonable, or surprising amount of patients who have been treated with tovorafenib. So compared to historical controls, I think this is encouraging.

I think it's important to make a note here about the clinical benefit rate. Sometimes we get hung up on objective response rates and needing, having, and wanting to see a shrinkage in tumor. And while that's a wonderful goal, we know that some patients historically have never had significant decrease in tumor size and that for those patients, disease stability is meaningful, valuable, and wonderful.

And one thing that's encouraging to me from the FIREFLY-1 data are that we see a good clinical benefit rate; even though the objective response rate is noted at 53 percent, the clinical benefit rate is reported as higher. That takes into account those who have a percentage response that's less than 25 percent and also takes into account patients who just have disease stability. Said another way, clinical benefit rate takes into account everyone who did not have progressive disease. And for many patients, that is a win; that is a success. Stable disease can be a success. So in addition to following along for objective response rates in this trial and others, I'm always trying to pay attention to the clinical benefit rate.

Dr. May:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Nicholas

Whipple about the updated results from the phase 2 FIREFLY-1 trial in relapsed and refractory pediatric low-grade glioma.

So, Dr. Whipple, if we continue exploring the key findings, a large proportion of patients who completed 26 cycles of tovorafenib opted into a drug holiday, and a high proportion of patients remained clinically stable off therapy, even when there were radiographic changes. How do you interpret these findings in the context of relapsed pediatric low-grade glioma?

Dr. Whipple:
One interesting piece of information that we've learned from this trial is that in many patients who completed 26 cycles of tovorafenib, they had some radiographic changes after they discontinued therapy. But despite that, they remained clinically stable off therapy, meaning there weren't neurologic changes, deficits, or decline. There weren't visual decline events that happened.

This is really reassuring and helps confirm a lot about low-grade glioma; when we discontinue therapy, there may be a brief period of slight rebound growth. And for a long time, providers have wondered: When do I need to restart therapy when there is rebound growth? Do I need to jump on this quickly and restart at the first sign of radiographic progression? Do I have to wait until it hits a certain threshold of being 25 or 50 percent larger? When do I need to intervene again?

And what this data is suggesting to us is that even when there is radiographic progression—when a tumor enlarges by measurement dimensions—patients tend to remain clinically stable. And that is encouraging in that we may not need to jump on retreatment as quickly as we have thought that we may need to in times past. Said another way, on this trial, there were about 31 percent of patients who, once they entered a period of observation, had some rebound growth, which was defined as greater than a 25 percent increase in tumor size within 6 months of the last dose of tovorafenib.

So what this data suggests to me is that with close serial surveillance and physical examination, if patients are doing well clinically, we can watch this. There may be slight regrowth after discontinuation of tovorafenib, as we have seen with other targeted agents in the past, but we may then hit a stride where they are no longer increasing in size. In other words, even though there may be slight regrowth after stopping treatment, we may be able just to watch; that tumor may become senescent—not grow anymore—and we would have never had to restart treatment.

This helps us prevent starting treatment prematurely in this setting. It helps us decrease the likelihood by understanding this better that even though tumors may regrow slightly, we don't have to reinitiate treatment right off the bat. We don't have to reintroduce toxicities again right off the bat, but we can safely watch this via MRI surveillance and physical examination.

Dr. May:
Now, the data also showed that nearly 75 percent of patients remained off therapy for 12 months or longer. Can you tell us what these results suggest about the durability of disease control and the potential for integrating planned treatment-free intervals into routine care?

Dr. Whipple:
I think these are the types of data that people are asking and that they want to know. So I'm very happy that we have this first glance at what percentage of patients have remained off therapy at this time interval. I think this percentage at this time interval is encouraging, and all of us look forward to the next time interval and the next time interval. I think when we talk about the amount of time that patients are able to remain off therapy after being treated, it's a characteristic that hasn't always been discussed widely in the past with other trials, so I'm glad we're discussing it now.

Although patients expect to receive therapy for pediatric low-grade glioma more than once in their life—perhaps even as many as three, four, five, and more times of dedicated treatment periods—treatment-free intervals represent how long of a break patients can have in between treatments where they can rest, where they don't need treatment, and where they can have a reprieve of taking medication, visiting the hospital as much, and experiencing some treatment-related toxicity. This is important.

It seems that different therapies may provide a longer treatment-free interval for some patients. I think patients will agree that they prefer as long of a treatment-free interval as possible. I think that when we talk about treatment-free intervals, the goal is to increase quality of life while maintaining good disease control. And it's the goal of every treating clinician to not treat longer than we have to and to treat for a period of time that allows true benefit, radiographic regression of disease if possible, and improvement in clinical symptoms and

clinical trajectory.

Also, the goal is to put this tumor into a quiescent state as soon as possible and for as long as possible. It's generally considered that most patients enter a biologic senescence in perhaps their early to mid-20s. That doesn't hold true for 100 percent of patients, but it's something that we're able to tell patients and families that's encouraging, that they can hope for and look forward to. But until that time, when biology helps us to achieve a natural senescence, if you will, we need to use the therapies that we have available to us that best achieve control and allow for these treatment-free intervals.

When we think about patient selection and which treatment to use in order to provide the longest treatment-free interval possible, there's just so much that we do not know there. We have learned that certain molecular features probably allow for a longer or shorter period of treatment break than others. One example that I think about is the presence of a BRAF V600E mutation seems to predict, for many patients, a shorter treatment-free interval period than others. The presence of that mutation may suggest a slight increase in biologic aggressiveness and metastatic potential. That seems to be the case. All these pieces of information are important to consider and to inform families about.

Dr. May:
And if we take a look at one more finding, some patients experienced disease progression after stopping therapy, but 21 percent were successfully retreated and remained on tovorafenib at the time of the latest data cut. What do these outcomes suggest about tumor biology and the potential for retreatment?

Dr. Whipple:
When we think about malignant tumors in general, I think we consider that once a patient has progressed after one line of therapy, we often need to intentionally change that therapy to something else to try to achieve a different outcome.

With low-grade glioma, what we're seeing with tovorafenib is that a patient can restart tovorafenib and still have an expected measurable clinical radiographic benefit. These patients are able to be successfully retreated again; that tumor is again responding and becoming consistently smaller than it was at the time of initiation of retreatment. So this keeps this medication in our toolbox.

What's important to remember is that side effects for this medication—and all medications—may be very different for patients. And it's nice to know that as long as a patient responded well to tovorafenib and as long as toxicities were acceptable, at the time of future disease progression, they can reengage and reinitiate tovorafenib and seem to still have a really positive response again a second time. So very exciting data.

Dr. May:
Before we close, Dr. Whipple, there is an upcoming 36-month follow-up that’s expected to provide more data on long-term outcomes, including duration of response and time to next treatment after drug holidays. So what metrics will you be watching for to better define durability of benefit and guide future clinical decisions in this setting?

Dr. Whipple:
So a primary point that I'll be watching for is the median duration of response. What percentage of patients are having duration of response for what length of time? Obviously, the higher percentage and the longer duration of response is what we want. These preliminary data are encouraging, and I'll be excited to see what's reported in future iterations of these outcomes data. And I think everyone's very hopeful, and this is encouraging.

I think a lot of people are asking themselves, is use of tovorafenib going to produce a longer treatment response or duration of response than other therapies? So in selecting what treatment to use—tovorafenib, dabrafenib plus trametinib where appropriate, MEK inhibition, cytotoxic chemotherapy—there are so many variables to weigh: duration of response, disease toxicity, etc. This is what families want to know; this is what patients want to know.

I'm going to also be looking for visual outcomes. This is really one of the first clinical trials that's tracked this in a meaningful and systematic way. So I'll be eagerly awaiting more data on how vision is faring. Are we seeing an improvement in vision? Are we seeing stability in vision? Is it having a significant impact compared to other therapies? I think that this is an exciting and important point to look at. We don't just care about what something looks like on an MRI, though that's critically important; we want to know how patients are

doing. However this tumor is affecting them—whether it's neurologically with physical deficits, vision, seizures, and a multitude of other possibilities—how are those key characteristics of the patient being affected? How are they being changed and improved by this medication? And I think that's what I'll be watching out for.

Dr. May:
With those forward-looking comments in mind, I want to thank my guest, Dr. Nicholas Whipple, for joining me to review the updated results from the phase 2 FIREFLY-1 trial. Dr. Whipple, it was great having you on the program.

Dr. Whipple:
Thank you so much for this opportunity.

Announcer:
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