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3-Year FIREFLY-1 Findings in pLGG: A Look at Long-Term Outcomes

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. Today, we'll be reviewing the three-year follow-up data from FIREFLY-1 and exploring how the findings on treatment-free interval, post-treatment stability, and retreatment may inform our understanding of pediatric low-grade glioma care.

Joining me for this discussion is Dr. Daniel Landi. He's an Associate Professor of Pediatrics and Neurosurgery, the Associate Program Director of the Neuro-Oncology Fellowship, and a member of the Pediatric Brain Tumor Program at the Preston Robert Tisch Brain Tumor Center at Duke University. Dr. Landi, welcome to the program.

Dr. Landi:
Thanks, Dr. May. I'm excited to be here and to talk with you today.

Dr. May:
So before we dive into the long-term findings, Dr. Landi, let's start with some background. FIREFLY-1 enrolled a pretreated population with relapsed or refractory BRAF-altered pediatric low-grade glioma. That being said, can you walk us through how the trial was designed to capture long-term outcomes like treatment-free interval, post-treatment stability, and retreatment?

Dr. Landi:
Sure, that would be my pleasure. I think the FIREFLY-1 study has been an impactful study for the most common disease that we treat as pediatric neuro-oncologists.

This was a registrational, multi-site, phase two study, and the primary objective was to see how effective tovorafenib is at controlling tumors through RAPNO criteria. It was a positive study; we know that it led to the FDA accelerated approval of tovorafenib in relapsed/refractory BRAF-altered pediatric low-grade glioma. So this has really changed the way many of us approach and treat the disease, and now, post-approval tovorafenib is something that's available everywhere.

I think that as these data have matured, one of the things that's been really important for the FIREFLY-1 study is the fact that treating providers had the option for patients to enter a drug holiday or to stop taking tovorafenib. The majority of patients who were still receiving treatment at two years, more or less, entered this drug holiday. And what you're alluding to and what's been really interesting to follow is what happens to these patients from there.

Dr. May:
Turning to the three-year follow-up data, 39 patients entered the post-treatment observation period—most after completing their planned treatment course—and notably, 77 percent of them remained treatment-free for at least 12 months. From your perspective, what do these findings tell us about the durability of disease control after completion of treatment and the long-term disease course in pediatric low-grade glioma?

Dr. Landi:
I think the data are encouraging. This is a pretreated patient population, many of whom had multiple lines of treatment to that point. And like you said, the majority—close to 80 percent in this initial cohort that reached the 12-month period—remained off drug. So I think

what that tells you is that there's clinical stability, and these patients are able to not be on treatment. I think the goal is always that you use as few medications or any intervention, regardless of what that is, for any child. So the data are encouraging.

Dr. May:
Absolutely, and that's a great transition to what I want to ask you about next because another notable finding was that the median progression-free survival was 16.6 months, while median time-to-next treatment was 42.6 months. How should we think about this discordance, and what does it suggest about the relationship between radiographic progression, clinical progression, and treatment decision-making?

Dr. Landi:
For some of the patients, and this was true in the pivotal cohort and the expansion cohorts for patients treated on FIREFLY-1, let's say you had a tumor that started at a certain size, and then maybe it responded, but then it increased a little bit. If you have an increase from the lowest point in your MRI of at least 25 percent, then that's flagged as progressive disease.

There were a number of patients in the FIREFLY-1 study where investigators or doctors like me had the option to continue protocol treatment to keep kids on study if we thought they were deriving clinical benefit. You try and treat the patient. If that patient's clinically stable and tolerating the drug, just because the MRI has grown and triggered your radiographic PD definition, that doesn't mean that's an ineffective treatment. There's actually some data that's been shown in the FIREFLY study previously that many of those patients who had radiographic PD—progressive disease—that continued on treatment went on to have deeper durable responses.

The same is true for patients who have stopped the drug and have radiographic progressive disease. They've had over 25 percent growth. Some of the nuances of this data indicate that in many cases, even if you have that progressive disease, the size of the tumor is still below where you started or it doesn't continue in a way that portends the need to retreat.

Dr. May:
For those just tuning in, this is *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Daniel Landi about three-year follow-up findings from FIREFLY-1 in pediatric low-grade glioma.

Now, the observation period data also provided insight into tumor behavior after tovorafenib was discontinued. Although about a third of patients met criteria for rebound tumor growth, most tumors remained below baseline measurements, and many subsequently stabilized or decreased in size without intervention. So, Dr. Landi, how do you interpret these observations, and what do they suggest about how we should be considering post-treatment tumor behavior in this disease?

Dr. Landi:
What we've seen and what you've now described for FIREFLY-1 and the cohort of patients who entered what we call this drug holiday is some of this variability in what the MRI does. There are certainly patients where the tumor will shrink. In some cases, when you stop treatment, it will continue to shrink. In some cases, it will grow or rebound. Sometimes you see a blip at a certain time point—three or six months off—and then it'll plateau. There are some patients where the MRI will continue to grow to the point that the patient progresses or the treating provider decides to restart treatment.

But it's difficult to predict. I think in the FIREFLY cohort at least, you have the different alterations—predominantly BRAF fusion or the BRAF point mutations—but across the board, I think you still have to approach each patient in the clinical scenario as an N of one, meaning you have to see how it goes. I think you stop the drug, or you decide with the family you're going to enter a drug holiday. I think it's helpful to set parameters in terms of when you might consider retreatment, which again, in my view, are always based on the clinical symptoms of the child, not so much the MRI.

Dr. May:
Let's focus in on that retreatment aspect for a second too. When it came to retreatment, the patients who required additional therapy during observation were largely those who had shown signs of tumor rebound, and all of them were retreated with tovorafenib. What can you tell us about how that retreatment played out, both in terms of tumor response and durability?

Dr. Landi:
As we've talked about, the majority of patients, at least at the 12-month post-treatment interval, aren't back on the drug. But certainly, there are patients where their tumors grow, they become clinically worse, their hemiplegia gets worse, or their vision is threatened. And for those patients who go back on tovorafenib, at least in the early junctures, it looks quite likely they'll respond similarly to how they did in their initial treatment, which again, I think is pretty consistent with other oral agents that have been looked at in this space.

So it's not surprising, but it's still reassuring. And I think it is a comfort for families when you talk to them that whenever you're going to enter a drug holiday, especially if they've had a very difficult course to that point, this is the first medicine that's worked. They always feel

better knowing that for patients who have needed to go back on, number one, this would be an option, and number two, your child's likely to respond.

Dr. May:
The longer follow-up also provided additional safety data. The overall profile remained largely consistent with what's been previously reported, though intratumoral hemorrhage was observed, and decreased growth velocity that occurred during treatment appeared to reverse in most patients after discontinuing therapy. How should we interpret these longer-term safety findings, and what do they mean for our understanding of tolerability over the course of a chronic disease like pediatric low-grade glioma?

Dr. Landi:
I think the hemorrhage piece is something that certainly is in the label. The way that I typically counsel families is that this is one of the things we'll monitor for. If a patient has a bleed, it's not a contraindication to receive tovorafenib. There's guidance now in the prescribing information for what you should do if you see a bleed.

The growth velocity piece is something that's hugely important because, again, these are young children; they're growing, and the incidence or the likelihood of developing growth suppression while taking tovorafenib, as you mentioned, is quite high. I think whenever you evaluate a patient to see if they're a child who develops linear growth velocity suppression on tovorafenib, it just takes a bit of time to see that.

I think as the FIREFLY pivotal cohort matured, you saw investigators like me and others start to look at the height of the child over time and identify that this was occurring. It was hugely important, I think, to identify the mechanism and establish, number one, does this affect bone maturation or growth kinetics? Are we causing premature closure of the growth plates? That doesn't occur with tovorafenib. And what you see, like you mentioned, is the majority of patients who stop tovorafenib who have growth velocity suppression then start to grow.

The way that this impacts my counsel and my practice is, number one, we talk about this very prominently, and I'll usually pull up the growth curve and explain how we'll monitor this. I think seeing the data and the likelihood of growth recovery off drug is really important. We have to be a little cognizant of the timing, and what I mean by that is, let's say a patient develops growth velocity suppression on tovorafenib. We anticipate they'll catch up off drug, but only if they are still able to grow. I think where this impacts my clinical practice, at least in a discussion with the families or for the peripubertal patients—patients who are going to naturally stop growing on their own—it doesn't look like tovorafenib interacts with endocrine function growth of the bones otherwise. But if you have a patient who has growth suppression and they go through puberty and fuse their growth plates, they might not be able to catch up.

Dr. May:
Before we close, Dr. Landi, let's place these findings into the broader landscape of pediatric low-grade glioma care. As encouraging as these results are, no single study tells the whole story. So how should we think about treatment-free interval, post-treatment stability, and retreatment in that context? And what additional prospective evidence would help refine our understanding of long-term management moving forward?

Dr. Landi:
I think all of us in this space or those who look after these kids would love it if you could compare. And I think in pediatric oncology more broadly, this is often difficult to do. Even though this is the most common type of tumor we treat, it's still relatively rare, and it's difficult and certainly fraught to draw comparisons between the tovorafenib experience through the FIREFLY studies with other agents. So it's very difficult to say tovorafenib is better, worse, or similar to other agents.

But I think the things that are encouraging and at least give us recourse in how we manage and approach patients in our discussions with families are some of these data. You can say, “Look, at least at 12 months, the vast majority—close to 80 percent of patients—that reached 12 months off treatment weren't back on something, that at least helps you feel like this medicine works a good bit of the time.” I think similarly, seeing that it's not just necessarily that in many cases these tumors don't need treatment, but in many cases, they continue to shrink or plateau and you might still achieve biologic senescence. Perhaps, based on at least some of the patients in this study, the tumor which you're hopeful will stop growing on its own still does so.

Again, what you would love is a drug that's perfectly safe, perfectly well-tolerated, a good quality of life, controls the tumor, and then when you stop it, you don't need more treatment. I think with tovorafenib, you're seeing that the safety and tolerability are good, the efficacy on drug are good, and at least there's recourse to stop it in a way that there's a good chance you won't need more treatment in a year when you do, and if you do retreat, there's a good chance you'll respond.

Dr. May:

With those final comments in mind, I want to thank my guest, Dr. Daniel Landi, for joining me to review the three-year FIREFLY-1 findings and their implications for our clinical understanding of long-term outcomes in pediatric low-grade gliomas. Dr. Landi, it was great having you on the program.

Dr. Landi:
My pleasure.

Announcer:
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