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Growth Recovery After Tovorafenib in Pediatric Low-Grade Gliomas: New Data

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:
Welcome to *Project Oncology* onReachMD.I'mDr. Alexandria May, and today,we'rereviewing new data presented at ASCO 2025 on growth recovery in children with BRAF-altered low-grade gliomas following tovorafenibdiscontinuation. Joining me in this discussion is Dr. Daniel Landi,who'sone of the investigators behind this analysis.He'salso 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, thanks for being here today.

Dr. Landi:
Oh, thanks, Dr. May. It's my pleasure.

Dr. May:
To start us off, Dr. Landi, why was it important to explore growth recovery in this patient population after treatment with tovorafenib?

Dr. Landi:
So I think the question of growth with tovorafenib is something that's really become relevant. I think people identified early on that tovorafenib was a potent and effective medicine for pediatric low-grade gliomas with BRAF alterations. These are the most common tumor types that occur in children. They are characterized by clinical behavior that might not be imminently life threatening, but they certainly cause all sorts of problems.

As we were studying tovorafenib in three sequential studies—first in PNOC014, then in the pivotal FIREFLY-1 study, and then safety and tolerability data were also compiled through an expanded access program before the drug was launched commercially—I think people began to understand and recognize that some children weren't growing as swiftly during tovorafenib. This triggered an immediate concern and investigation by people like me, the investigators in the study, and the sponsor of the trials to try and understand what was going on.

Tovorafenib is a type II RAF inhibitor, so the mechanism of the drug is to inhibit CRAF in maturing chondrocytes, which leads to reversible inhibition of linear bone growth. It's really relevant for this patient population because they're kids and they're supposed to be growing, and it's a patient population that's intrinsically high risk for growth dysfunction. Many of these patients have disrupted growth axes because of where the tumor is. Due to prior treatments they've had, they might not grow normally relative to peers who haven't had to go through a brain tumor diagnosis or these treatments.

So as people gained understanding and recognized that growth suppression was occurring in some patients, immediately the question turned to: was there anything that impacted the character of the bone long term? Were these effects reversible? What was the exact mechanism whereby some patients weren't growing? So this piece becomes a very important and relevant analysis and topic for patients treated with tovorafenib.

Dr. May:
Can you walk us through the design of this post hoc analysis, including how data from FIREFLY-1, PNOC014, and the expanded access program were combined to evaluate growth in pediatric low-grade glioma?

Dr. Landi:
The PNOC014 trial was really the first clinical trial for tovorafenib in a prospective sense. FIREFLY-1 was the registrational study. And then there was a safety expansion cohort. And after those cohorts filled—or at different points if it wasn't enrolling—then the sponsor allowed an expanded access program. Tovorafenib is a really important, impactful drug that seems to help many of these patients. So preserving access to the medicine is something that's often done, and it's still really relevant. You can collect safety tolerability data around things like growth suppression or growth recovery in these different clinical contexts, with all the caveats that it is retrospective and ad hoc.

But I think if you look at something like growth suppression or growth recovery, it makes a lot of sense, and it's probably prudent to look at all these different patients because to get that many patients with a rare pediatric cancer is difficult. That's true of all pediatric cancers. And I think we owe it to the patients and families to get as much information out of each patient experience as we can.

Dr. May:
If we look more closely at the methodology, how was growth suppression defined? And how often did it occur among patients included in the analysis?

Dr. Landi:
So I think again, being cognizant that the safety data, particularly around growth, is pooled from these different studies—being PNOC014, the pivotal FIREFLY-1 study, and then the expanded access program—it appears that probably slightly less than half of patients exhibited growth suppression.

There are different ways you can define growth suppression. For the purpose of the ASCO paper, growth suppression was defined in terms of the z-score, which takes the rate of growth relative to norms for age and gender, and growth suppression here was defined as greater than 0.1 per year decrease in height-for-age z-score. So using in the statistical analysis a piecewise linear mixed model, 64 patients pooled across these different cohorts showed growth suppression in these terms during treatment.

Dr. May:
For those of you just tuning in, this is *Project Oncology*onReachMD.I'mDr. Alexandria May, andI'mspeaking with Dr. Daniel Landi about research on growth recovery in children with BRAF-altered low-grade gliomas after discontinuation of tovorafenib.

So,Dr. Landi,if we turn now to the findings, can you tell us what the data revealed about growth recovery and catch-up growth after treatment ended?

Dr. Landi:
So in the abstract, 91 percent of patients who exhibited growth suppression exhibited growth recovery after stopping tovorafenib, and 80 percent of patients exhibited catch-up growth. So not only did they start to grow, but the rate of growth accelerated in a way that regained or approximated their initial growth trajectory before they started.

The rebounds were different depending on the age and, to some extent, the gender of the patients, and the most notable rebounds were in patients who were younger and in patients who were male.

Dr. May:
So you mentioned a couple ofdifferent characteristicsof the patients that may affect growth recovery.Can you talk a little bit more about what patient-specific factors were associated with differences in growth outcomes?

Dr. Landi:
I think age and sex were significantly associated with changes in growth velocity. Males, by and large, tended to exhibit a steeper drop during treatment, but then they also, across the board, seemed to have a slightly stronger rebound growth after treatment. Older patients tended to exhibit a slower recovery, which might reflect expected age-related declines in growth rate.

One of the things that people have considered with tovorafenib is it doesn't seem that tovorafenib impairs bone metabolism or changes the way the bone is formed or bone density. It doesn't accelerate bone maturation or development. Patients on study have had bone ages and skeletal assessments, but it does look like if you naturally were to go through puberty—let's say that you were to start tovorafenib as a teenager who's naturally approaching puberty—if you did exhibit growth suppression and then your bones fused through part of the natural pubertal process, apparently irrespective of the mechanism of tovorafenib—this transient inhibition of CRAF—you wouldn't be able to exhibit this catch-up growth.

Dr. May:
Looking ahead, what do you see as the clinical implications of these findings, particularly when it comes tomonitoringpatients and counseling their families?

Dr. Landi:
I think the implications around the story of growth with tovorafenib are really relevant to how we counsel patients and how we weigh different treatment options for this patient population. Knowing that tovorafenib doesn't seem to permanently damage the bones or the capacity of bones to grow and form normally and that the growth suppression tends to be reversible—meaning when you stop the drug, the vast majority of patients start to grow, and furthermore, many exhibit catch-up growth—I think this allows us as clinicians that look after these patients to truly say, ‘look, these are the things that we’ll monitor for.’

I think the efficacy piece is known, and it's clear that this is an effective medicine for controlling these tumors. But the safety and tolerability piece, as we've talked about, is so relevant. We know that males might rebound more steeply and that older patients across the board might not rebound or grow as quickly when they come off. And this cognizance that the growth axis of the patient intrinsically is relevant. What I mean by that is you really need to know the growth potential of your patient. Is the growth axis disrupted in this patient such that they won't grow, whether they're on tovorafenib or not? How much time might they have to grow when you stop? I think consultation with an endocrinologist who can really answer these questions in as specific a way as any of us as providers can is helpful. Certainly, I've found that to be very relevant for our patients around growth with tovorafenib.

Dr. May:
With those key takeaways in mind, I want to thank my guest, Dr. Daniel Landi, for joining me to review growth recovery data in BRAF-altered pediatric low-grade gliomas following discontinuation of tovorafenib. Dr. Landi, it was great having you on the program.

Dr. Landi:
No, likewise. Thanks for having me and for this discussion. I really enjoyed it.

Announcer:
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