

### 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/medical-industry-feature/managing-nf1-and-plexiform-neurofibromas-with-the-first-fda-approved-treatment-option/15335/>

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## Managing NF1 PN with this First FDA-Approved Treatment Option

### Announcer

#### INDICATION

KOSELUGO® is indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

#### SELECT SAFETY INFORMATION

**WARNINGS AND PRECAUTIONS** associated with Koselugo (selumetinib) include Cardiomyopathy, Ocular Toxicity, Gastrointestinal Toxicity, Skin Toxicity, Increased Creatine Phosphokinase, Increased Levels of Vitamin E and Risk of Bleeding, and Embryo-Fetal Toxicity.

**ADVERSE REACTIONS** (≥40%) include vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

**DRUG INTERACTIONS** include strong/moderate CYP3A4 Inhibitors or Fluconazole and CYP3A4 Inducers.

Please see additional Important Safety Information throughout and full Prescribing Information for Koselugo (selumetinib) at [bit.ly/KoselugoPI](http://bit.ly/KoselugoPI).

### Sandy

Thank you all for joining us. My name is Sandy Millman, and I work at Alexion on the neurofibromatosis type 1 team. We are excited to have Dr. Prasad with us today.

Dr. Prasad, again, thank you for your time. If you could get us started by, please stating your name, specialty, and your current institution.

### Dr. Prasad

Hi, Sandy. My name is Pinki Prasad, I'm a Pediatric Oncologist by training. I am here at Children's Hospital in New Orleans, and I'm an Associate Professor in Pediatrics at LSU School of Medicine.

### Sandy

If we can transition just to speak a little bit about your practice. Whenever you receive referrals for your neurofibromatosis type 1 patients that come from outside your institution, what specialties tend to refer patients directly to you?

### Dr. Prasad

So, we are lucky. We get a number of different subspecialties who actually refer to us and they include people in genetics, ophthalmology, and neurosurgery. So, in ophthalmology we have patients who have vision issues or optic gliomas, and for neurosurgery, we get referred patients that have different masses.

### Sandy

What testing do you usually perform to help you become informed about if and when the patient should be put on treatment?

### Dr. Prasad

So, for us the most common testing is usually some sort of imaging. So, we recommend MRIs and so, all of our NF1 patients should be getting MRIs of brain and spine fairly regularly, almost annually. And then we also, for those patients that we know have a plexiform

neurofibroma, should get imaging of their primary site at least annually. Our biggest recommendation. If we feel like they are a candidate for Koselugo, then we do perform other testing as well, including, some baseline testing for cardiac function, and some lab work and things of that sort.

**Sandy**

If you could think about a clinical presentation at the time that you decided to treat a patient with Koselugo, and share a little bit about that with us, please?

**Dr. Prasad**

I think the biggest things are, some progression in either pain, disfigurement, those are the big triggers for us, for us to start Koselugo. We always bring up Koselugo pretty early on in our NF1 clinic so families are aware of the drug. They are aware that this is the FDA approved treatment for pediatric symptomatic inoperable NF1 plexiform neurofibromas. So, this is language they hear pretty regularly through our multidisciplinary team.

**Sandy**

How do you define symptomatic for both acute or visible symptoms, and the more subtle or less obvious ones?

**Dr. Prasad**

So, to me symptomatic is any symptom that's important to a patient or a caregiver. And it can be a variety of different things. Sometimes it's visible, but sometimes it's not as visible. So, if it's bothering the patient, I think it's considered to be a symptom and it should be monitored and looked at.

**Sandy**

Now if I can ask you, Dr. Prasad, to think about a specific NF1 PN patient that you chose to start on Koselugo, or selumetinib. Why did you choose this therapy?

**Dr. Prasad**

So, I had a male adolescent who was followed very closely in our NF1 clinic. He had been seen by a number of different subspecialists including orthopedics, neurosurgery and neurology, and he had been diagnosed with scoliosis. We really thought the scoliosis was secondary to a very large plexiform neurofibroma. The scoliosis was causing a lot of pain and so, our orthopedic colleagues, along with our neurosurgical colleagues, performed a number of different surgical interventions. And despite all those interventions, the pain actually continued. So, after 3 years of different surgical interventions, the family was not willing to do any further surgeries, and we realize that these plexiform neurofibromas was inoperable. And so, the patient was referred to me to discuss medical management. And at that time, we decided to talk about Koselugo.

**Sandy**

What are your treatment goals with Koselugo?

**Dr. Prasad**

The goal is stabilization of disease, preferably decrease in PN size - this is how we define treatment success. One of the biggest reasons for starting treatment is also making sure we are doing symptom management for the PN. And it's really a redefinition for us as oncologists. We know that there's no set duration for treatment, and most treatment is going to last at least 6 months in order for us to see any kind of a response. We do discuss with our families that overall response rate in studies that were done, called the SPRINT study, was about 66% in our Phase 2 Stratum 1 for Koselugo.

**Dr. Prasad**

Although the median duration of response was not reached by February 2021, of those patients who had a partial response, 79% of patients remained in response at 24 months and 64% remained in response at 36 months.

**Sandy**

How do you approach conversations with the family on starting treatment with Koselugo? How do you also set treatment expectations, you know, for instance specifically around the anticipated time to response, as well as potential adverse events?

**Dr. Prasad**

So, the expectations are very important to communicate for any of our patients who are going on Koselugo. The expectations that we want to make sure that they understand is, one; this medication is going to take some time to work. We also want to make sure that our caregivers and our patients are armed with information to manage any adverse events that may happen with the medication.

Koselugo adverse events are well characterized, can be managed, and may not require discontinuation or medication.

Most common adverse reactions greater than or equal to 40% include vomiting, all types of rashes, abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritis.

**Sandy**

Going back to the patient that we discussed earlier, how long did it take to observe an initial response?

**Dr. Prasad**

For this particular patient, it took about 3 to 4 months for us to observe an initial response for PN reduction and symptoms.

**Sandy**

How long has the patient been on therapy?

**Dr. Prasad**

Our patient has now been on therapy for 3 years and remains on therapy at this time. Koselugo is dependent on body surface area, so we explained to our family that dosage was going to change as our patient continued to grow and develop.

In literature, we know that in the long-term follow up, the median duration of exposure with Koselugo was 4.4 years. During this time, no new safety signals were found. However, monitoring is still important as known adverse events may occur.

**Sandy**

Over the course of therapy, what changes did you observe in the patient?

**Dr. Prasad**

I think the biggest thing was that our patient's pain went away in 3 to 4 months, and parents noticed that he was taking a lot less pain medicine. With less pain, he was able to help ease into activities of daily living and increase his mobility, and this actually resulted in him having more energy and overall feeling better. He was very excited because for the first time in a long time he was able to participate in physical education and this made him feel like his quality of life had improved.

**Sandy**

Thank you so much for sharing that patient's story, Dr. Prasad. And thank you for all that you do for the patients and caregivers.

**Dr. Prasad**

Thank you so much for having me.

**Announcer**

### IMPORTANT SAFETY INFORMATION

#### WARNINGS AND PRECAUTIONS

**Cardiomyopathy.** A decrease in left ventricular ejection fraction (LVEF)  $\geq 10\%$  below baseline occurred in pediatric patients who received Koselugo in SPRINT with some experiencing decreased LVEF below the institutional lower limit of normal (LLN), including one patient with Grade 3. All patients with decreased LVEF were asymptomatic and identified during routine echocardiography. Decreased LVEF resolved in 71% of these patients. The safety of Koselugo has not been established in patients with a history of impaired LVEF or a baseline ejection fraction that is below the institutional LLN. Assess ejection fraction by echocardiogram prior to initiating treatment, every 3 months during the first year of treatment, every 6 months thereafter, and as clinically indicated. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction. In patients who interrupt Koselugo for decreased LVEF, obtain an echocardiogram or a cardiac MRI every 3 to 6 weeks. Upon resolution of decreased LVEF, obtain an echocardiogram or a cardiac MRI every 2 to 3 months.

**Ocular Toxicity.** Blurred vision, photophobia, cataracts, and ocular hypertension occurred. Retinal pigment epithelial detachment (RPED) occurred in the pediatric population during treatment with single agent Koselugo and resulted in permanent discontinuation. Conduct ophthalmic assessments prior to initiating Koselugo, at regular intervals during treatment, and for new or worsening visual changes. Permanently discontinue Koselugo in patients with retinal vein occlusion (RVO). Withhold Koselugo in patients with RPED, conduct ophthalmic assessments every 3 weeks until resolution, and resume Koselugo at a reduced dose.

**Gastrointestinal Toxicity.** Diarrhea occurred, including Grade 3. Diarrhea resulting in permanent discontinuation, dose interruption or dose reduction occurred. Advise patients to start an anti-diarrheal agent (eg, loperamide) and to increase fluid intake immediately after the first episode of diarrhea. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

**Skin Toxicity.** Rash occurred in 91% of 74 pediatric patients. The most frequent rashes included dermatitis acneiform (54%), maculopapular rash (39%), and eczema (28%). Grade 3 rash occurred, in addition to rash resulting in dose interruption or dose reduction. Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse

reaction.

**Increased Creatine Phosphokinase (CPK).** Increased CPK occurred, including Grade 3 or 4 resulting in dose reduction. Increased CPK concurrent with myalgia occurred, including one patient who permanently discontinued Koselugo for myalgia. Obtain serum CPK prior to initiating Koselugo, periodically during treatment, and as clinically indicated. If increased CPK occurs, evaluate for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

**Increased Levels of Vitamin E and Risk of Bleeding.** Koselugo capsules contain vitamin E which can inhibit platelet aggregation and antagonize vitamin K-dependent clotting factors. Supplemental vitamin E is not recommended if daily vitamin E intake (including the amount of vitamin E in Koselugo and supplement) will exceed the recommended or safe limits due to increased risk of bleeding. An increased risk of bleeding may occur in patients who are coadministered vitamin-K antagonists or anti-platelet antagonists with Koselugo. Monitor for bleeding in these patients and increase international normalized ratio (INR) in patients taking a vitamin-K antagonist. Perform anticoagulant assessments more frequently and adjust the dose of vitamin K antagonists or anti-platelet agents as appropriate.

**Embryo-Fetal Toxicity.** Based on findings from animal studies, Koselugo can cause fetal harm when administered during pregnancy. In animal studies, administration of selumetinib to mice during organogenesis caused reduced fetal weight, adverse structural defects, and effects on embryo-fetal survival at approximate exposures >5 times the human exposure at the clinical dose of 25 mg/m<sup>2</sup> twice daily. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with Koselugo and for 1 week after the last dose.

### ADVERSE REACTIONS

**Common adverse reactions ≥40% include** vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, musculoskeletal pain, fatigue, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

### DRUG INTERACTIONS

**Effect of Other Drugs on Koselugo** Concomitant use of Koselugo with a strong or moderate CYP3A4 inhibitor or fluconazole increased selumetinib plasma concentrations, which may increase the risk of adverse reactions. Avoid coadministration with Koselugo. If coadministration cannot be avoided, reduce Koselugo dosage.

**Concomitant use of Koselugo with a strong or moderate CYP3A4 inducer** decreased selumetinib plasma concentrations, which may reduce Koselugo efficacy. Avoid concomitant use with Koselugo.

### SPECIAL POPULATIONS

**Pregnancy & Lactation.** Verify the pregnancy status of patients of reproductive potential prior to initiating Koselugo. Due to the potential for adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with Koselugo and for 1 week after the last dose.

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or at <https://us-aereporting.astrazeneca.com> or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please see full Prescribing Information for Koselugo (selumetinib) at [https://alexion.com/Documents/koselugo\\_uspi.pdf](https://alexion.com/Documents/koselugo_uspi.pdf).

US/KOS-NF1/0614 V1 06/2024

### References:

1. KOSELUGO. Prescribing Information. AstraZeneca Pharmaceuticals LP.
2. Gross AM, Dombi E, Wolters PL, et al. Long-term safety and efficacy of selumetinib in children with neurofibromatosis type 1 on a phase 1/2 trial for inoperable plexiform neurofibromas. *Neuro Oncol*. 2023;25(10):1883-1894. doi: 10.1093/neyes/noad086.