



KOSELUGO, THE FIRST AND ONLY FDA-APPROVED PHARMACOTHERAPY

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)²

NF1 PN PATIENT POPULATION



NF1 with PNs is a rare and progressive genetic condition with significant morbidity.³⁻⁵

- PNs are benign tumors that can cause physical disfigurement and compromise internal organ function anywhere in the body⁶⁻⁸
- NF1 with PNs develops faster in children and adolescents and affects approximately 2000 pediatric patients in the United States⁹⁻¹¹

SPRINT TRIAL OVERVIEW^{2,12}



The efficacy and safety profile of KOSELUGO, an oral MEK 1/2 inhibitor, was evaluated in an open-label, multicenter, single-arm study of 50 pediatric patients.

- Patients eligible for the trial
 - Had NF1 with symptomatic and inoperable PNs* that caused at least 1 clinically significant PN-related morbidity at baseline
 - Were aged 2 years to 18 years, with a body surface area ≥ 0.55 m²

The primary endpoint was overall response rate (ORR).[†]

KOSELUGO EFFICACY²

66% (95% CI: 51, 79)[‡]

OF PEDIATRIC NF1 PN PATIENTS HAD AN OVERALL RESPONSE WITH KOSELUGO

33 OUT OF 50[‡]

PATIENTS HAD A CONFIRMED PARTIAL RESPONSE

7.2 MONTHS

MEDIAN TIME TO ONSET OF RESPONSE (RANGE: 3.3 MONTHS TO 1.6 YEARS)

- An independent centralized review of tumor response per REINS criteria resulted in an ORR of 44% (95% CI: 30, 59)

KOSELUGO SELECT SAFETY INFORMATION²

The most common ARs reported in $\geq 40\%$ of patients were vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

KOSELUGO (N=50)	DOSE INTERRUPTION	DOSE REDUCTION	PERMANENTLY DISCONTINUED DUE TO ARs
	80% (40/50)	24% (12/50)	12% (6/50)

- ARs requiring a dosage interruption or reduction in $\geq 5\%$ of patients were vomiting, paronychia, diarrhea, nausea, abdominal pain, rash, skin infection, influenza-like illness, pyrexia, and weight gain
- ARs resulting in permanent discontinuation included increased creatinine, increased weight, diarrhea, paronychia, MPNST, acute kidney injury, and skin ulcer

*Inoperable PNs were defined as PNs that could not be completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures; invasiveness; or high vascularity of the PN.²

[†]ORR was defined as the percentage of patients with complete response (defined as disappearance of the target PN) or confirmed partial response (defined as $\geq 20\%$ reduction in PN volume confirmed at a subsequent tumor assessment within 3 to 6 months). The target PN, defined as the PN that caused relevant clinical symptoms or complications (PN-related morbidities), was evaluated for response rate using centrally read volumetric MRI analysis per REINS criteria.²

[‡]The ORR assessment was conducted by a single NCI reviewer who was a SPRINT investigator and who evaluated all PN imaging from patients enrolled at all trial sites.²

AR=adverse reaction; FDA=US Food and Drug Administration; MEK=mitogen-activated protein kinase kinase; MPNST=malignant peripheral nerve sheath tumor; MRI=magnetic resonance imaging; NCI=National Cancer Institute; REINS=Response Evaluation in Neurofibromatosis and Schwannomatosis.

IMPORTANT SAFETY INFORMATION

Cardiomyopathy. A decrease in left ventricular ejection fraction (LVEF) $\geq 10\%$ below baseline occurred in 23% of 74 pediatric patients who received KOSELUGO in SPRINT. Four percent of patients experienced decreased LVEF below the institutional lower limit of normal (LLN). Grade 3 decreased LVEF occurred in one patient and resulted in dose reduction. All patients with decreased LVEF were asymptomatic and identified during routine echocardiography. Decreased LVEF resolved in 71% of these patients. Decreased LVEF resulting in permanent discontinuation of KOSELUGO occurred in a pediatric population with NF1 in an expanded access program. 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.

Please see additional Important Safety Information throughout and click [here](#) to access full Prescribing Information, including Patient Information.

IMPORTANT SAFETY INFORMATION (cont'd)

Ocular Toxicity. Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving KOSELUGO in SPRINT. Blurred vision resulted in dose interruption in 2.7% of patients. Ocular toxicity resolved in 82% of 11 patients. 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 RVO. Withhold KOSELUGO in patients with RPED, conduct ophthalmic assessments every 3 weeks until resolution, and resume KOSELUGO at a reduced dose. For other ocular toxicities, withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction.

Gastrointestinal Toxicity. Diarrhea occurred in 77% of 74 pediatric patients who received KOSELUGO in SPRINT, including Grade 3 in 15% of patients. Diarrhea resulting in permanent discontinuation occurred in 1.4% of patients. Diarrhea resulting in dose interruption or dose reduction occurred in 15% and 1.4% of patients, respectively. The median time to first onset of diarrhea was 17 days and the median duration was 2 days.

Advise patients to start an anti-diarrheal agent (e.g., 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 who received KOSELUGO in SPRINT. The most frequent rashes included dermatitis acneiform (54%), maculopapular rash (39%), and eczema (28%). Grade 3 rash occurred in 8% of patients. Rash resulted in dose interruption in 11% of patients and dose reduction in 4% of patients. Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction.

Increased Creatinine Phosphokinase (CPK). Increased CPK occurred in 76% of 74 pediatric patients who received KOSELUGO in SPRINT, including Grade 3 or 4 in 9% of patients. Increased CPK resulted in dose reduction in 7% of patients. Increased CPK concurrent with myalgia occurred in 8% of patients, 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 patients 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 (10 mg capsules contain 32 mg vitamin E as the excipient, D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS); while KOSELUGO 25 mg capsules contain 36 mg vitamin E as TPGS). Vitamin E can inhibit platelet aggregation and antagonize vitamin K-dependent clotting factors. Daily vitamin E intake that exceeds the recommended or safe limits may increase the risk of bleeding. 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.

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 to a pregnant woman. 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/m² twice daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with KOSELUGO and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with KOSELUGO and for 1 week after the last dose.

Breastfeeding. Due to the potential for adverse reactions in a breastfed child, advise women not to breastfeed during treatment with KOSELUGO and for 1 week after the last dose.

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 of strong or moderate CYP3A4 inhibitors or fluconazole with KOSELUGO. If coadministration with strong or moderate CYP3A4 inhibitors or fluconazole 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 of strong or moderate CYP3A4 inducers with KOSELUGO.

Most common adverse reactions (≥ 40% of patients) are: vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, musculoskeletal pain, fatigue, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

Please click [here](#) to access the full Prescribing Information, including Patient Information.

References: 1. Koselugo (selumetinib) approved in US for paediatric patients with neurofibromatosis type 1 plexiform neurofibromas [press release]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; April 13, 2020. <https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/koselugo-selumetinib-approved-in-us-for-paediatric-patients-with-neurofibromatosis-type-1-plexiform-neurofibromas.html>. Accessed April 13, 2020. 2. KOSELUGO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. 3. Kim A, Stewart DR, Reilly KM, Viskochil D, Miettinen MM, Widemann BC. Malignant peripheral nerve sheath tumors state of the science: leveraging clinical and biological insights into effective therapies. *Sarcoma*. 2017;2017:7429697. 4. Julian N, Edwards NE, DeCrane S, Hingtgen CM. Neurofibromatosis 1: diagnosis and management. *J Nurse Pract*. 2014;10(1):30-35. 5. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch Neurol*. 1988;45(5):575-578. 6. Anderson JL, Gutmann DH. Neurofibromatosis type 1. *Handb Clin Neurol*. 2015;132:75-86. 7. Batista PB, Bertollo EM, Costa Dde S, et al. Neurofibromatosis: part 2 - clinical management. *Arq Neuropsiquiatr*. 2015;73(6):531-543. 8. Miller DT, Freedberg D, Schorry E, Ullrich NJ, Viskochil D, Korf BR; Council on Genetics; American College of Medical Genetics and Genomics. Health supervision for children with neurofibromatosis type 1. *Pediatrics*. 2019;143(5):e20190660. 9. Nguyen R, Dombi E, Widemann BC, et al. Growth dynamics of plexiform neurofibromas: a retrospective cohort study of 201 patients with neurofibromatosis 1. *Orphanet J Rare Dis*. 2012;7:75. 10. Dombi E, Solomon J, Gillespie AJ, et al. NF1 plexiform neurofibroma growth rate by volumetric MRI: relationship to age and body weight. *Neurology*. 2007;68(9):643-647. 11. Data on File, REF-714111, AstraZeneca Pharmaceuticals LP. 12. Data on File, REF-70328, AstraZeneca Pharmaceuticals LP.

KOSELUGO is a trademark of the AstraZeneca group of companies.
©2020 AstraZeneca. All rights reserved. US-36191 Last Updated 4/20

