

Koselugo (selumetinib) Drug Monograph

Brand Name: Koselugo

Generic Name: selumetinib

Manufacturer¹: AstraZeneca

Drug Class²: Antineoplastic Agent; MEK Inhibitor

Uses^{1,2,3}:

Labeled: Neurofibromatosis type 1 (NF1) in pediatric patients greater than 2 years of age

Unlabeled: N/A

Mechanism of Action^{1,2,3}: Selumetinib is an inhibitor of mitogen-activated extracellular protein kinases 1 and 2 (MEK 1/2), which are proteins that are upstream regulators of the extracellular signal-related kinase (ERK) pathway. MEK and ERK are both important components of the RAS-regulated RAF-MEK-ERK pathway which is often expressed in patients with cancer.

Pharmacokinetics^{1,2,3}:

Tmax	1 to 1.5 hours
Vd	78 to 171 L
Half-life	6.2 hours
Clearance	8.8 L/hour
Bioavailability	62%
Protein binding (extent to albumin)	98.4% (96%)

Metabolism^{1,2,3}: Mainly hepatic through CYP3A4. Active metabolite is N-desmethyl selumetinib (3-5 times more potent than parent) and represents ~10% of the drug levels in human plasma. It is also a substrate of BCRP/ABCG2, CYP1A2 (minor), CYP2A6 (minor), CYP2C19 (minor), CYP2C9 (minor), CYP2E1 (minor), P-glycoprotein/ABCB1 (minor), and undergoes glucuronidation by UGT1A1, UGT1A3.

Elimination^{1,2}: Feces (59%, 19% as unchanged drug); urine: 33% (<1% as parent drug)

Efficacy^{4,5,6}:

Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas. N Engl J Med. 2020 Apr 9;382(15):1430-1442.

Study design: Open-label, phase II, multisite, one arm trial

Description of study: Fifty patients between 2 and 18 years of age with neurofibromatosis type 1 (NF1) and symptomatic inoperable plexiform neurofibromas (PN) who were able to swallow whole capsules were included. This trial's purpose was to evaluate the objective response rate, to assess clinical benefit (pain, quality of life, disfigurement, and function), and toxic effects. Selumetinib was administered as 25 mg/m² by mouth every 12 hours in continuous 28-day cycles. Doses could be reduced up to two times if patients were experiencing toxic effects, and patients were required to discontinue treatment if they had disease progression while taking selumetinib. Thirty-seven patients (74%) had a partial response (defined as a 20% or greater reduction), 34 (68%) had a confirmed partial response, and 28 (56%) had a durable response. The median progression-free survival after 3 years of treatment was 84%. Medication adherence had a mean of >95% according to pill counts. A mean decrease of 2 points was seen in tumor pain-intensity scores after 1 year of treatment. Interference of pain in daily life and overall quality of life also showed improvement from baseline. The most common toxic effects seen were nausea, vomiting, diarrhea, increase in creatine phosphokinase levels, acneiform rash, and paronychia.

Limitations: The company that provided the drug had access to the review and manuscript which could have introduced bias. This study had small patient numbers and was an open-label, one arm trial and results of selumetinib could not be compared to any other treatment or placebo. This trial also only included children so there is no efficacy or safety data in adults.

Conclusion: This study showed that selumetinib is a clinically beneficial treatment for patients between the ages of 2 to 18 with progressive NF1 and inoperable PN. Although toxic effects were common, none of them were irreversible showing that the benefits likely outweigh the risk of side effects. However, longer studies with more patients should be performed to evaluate the long-term safety and efficacy of selumetinib especially compared to other treatments.

Fangusaro J, Onar-Thomas A, Young Poussaint T, Wu S, Ligon AH, Lindeman N, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. Lancet Oncol. 2019 Jul;20(7):1011-1022.

Study design: Multicenter, open label, one arm, prospective phase II trial

Description of study: Patients aged 3 to 21 years with a Lansky or Karnofsky score greater than 60 who had a recurrent, refractory or progressive pediatric low-grade glioma (pLGG) after at least one standard therapy were eligible for this trial. This study categorized patients by strata 1 through 6. Although the study is still ongoing for some

strata, the results for strata 1 and 3 are discussed in this study. Stratum 1 included patients with grade I pilocytic astrocytoma with either *KIAA1549-BRAF* fusion or the *BRAF^{V600E}* mutation, whereas stratum 3 included patients with any neurofibromatosis type 1 (NF1)-associated pLGG grades I and II. Patients received 25 mg/m² twice daily by mouth for 26 cycles (28 days per cycle). Doses could be reduced up to 2 times due to toxic effects, but the dose could not be re-escalated. Twenty-five children were evaluated in both strata 1 and 3. MRIs were completed every 2 months throughout the first year then every 3 months to assess tumor size. Laboratory tests were completed every 4 weeks, prior to the next cycle, along with an echocardiogram every 3 months. Adherence to selumetinib was assessed through patient diaries and pill counts. Stratum 1 achieved a partial response (defined as a 50% or greater reduction) in 9 patients (36%) and 10 patients (40%) achieved a partial response in stratum 3. Eleven patients in stratum 1 and 9 patients in stratum 3 discontinued treatment before the conclusion of the trial. The most common toxic effects seen were creatine phosphokinase elevation, hypoalbuminemia, dyspnea, rash, duodenal ulcer, anemia, dry skin, fatigue and diarrhea. Ten of the patients in stratum 1 required one dose reduction and 1 patient required 2 dose reductions. Eight of the patients in stratum 3 required a dose reduction due to toxic effects.

Limitations: This trial only evaluated selumetinib in patients between the ages of 3 and 21 which limits the extrapolation of the data. The majority of the patients were white which limits extrapolation. Patient/parent-reported outcomes were not assessed. This was a one arm trial in which all patients received selumetinib, thus comparison of results to other treatments or placebo could not be performed.

Conclusion: Overall, this trial showed response rates in patients with grade I pilocytic astrocytoma with two common *BRAF* aberrations and NF1-associated pLGG grades I and II. Although toxic effects were common, the benefits outweighed the side effects in most patients. Further studies should be completed to assess patient-reported outcomes for quality-of-life improvement as well as comparisons to other treatments.

Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas. N Engl J Med. 2016 Dec 29;375(26):2550-2560.

Study design: Open-label, phase I trial

Description of study: Twenty-four patients between the ages of 3 and 18 years with NF1 and inoperable, measurable PN that had the possibility of causing significant complications were included in this study. Selumetinib was administered every 12 hours by mouth at a dose of 20 mg/m² with potential dose increases up to 50 mg/m² in continuous 28-day cycles. MRI evaluation was completed after cycles 5 and 10 then every 6 cycles thereafter. Patients without documented disease progression at the start of the trial could continue taking selumetinib for 2 years. However, if patients had a partial response while taking selumetinib they could continue it for longer than 2 years. Doses could be reduced up to 2 times due to toxic effects. Twelve patients were receiving 20 mg/m², 6 patients at 25 mg/m², and 6 patients at 30 mg/m². Confirmed partial response (defined as 20% or greater decrease in tumor size for at least 4 weeks) was seen in 17 patients (71%). None of the patients have had disease progression to date, with a median

treatment length of 30 cycles. Five patients were reported to have discontinued treatment. The most common toxic effects included creatine kinase elevation, gastrointestinal disturbances, acneiform rash, and maculopapular rash. In later cycles, the most common toxic effects were mucositis, aminotransferase elevation, decreased neutrophil count, and paronychia. Adherence to the medication was assessed through patient diaries and pill counts. Overall, the optimal dose was found to be 25 mg/m² in order to limit toxic effects while still maintaining response rates.

Limitations: The only evaluation for patient/parent-reported outcomes was completed retrospectively. Potential conflicts of interest existed due to the manufacturer having access to the final review and manuscript. This trial was only completed in patients aged 3 to 18 years so extrapolation of the data is limited. There was no comparator group so results cannot be compared to other treatments.

Conclusion: Overall, this study showed improvement in tumor size in patients with inoperable, measurable plexiform neurofibromas. The optimal dose was found to be 25 mg/m² twice daily in order to still see benefit without significant toxic effects.

Contraindications^{1,2,3}: None listed.

Precautions^{1,2}: Cardiomyopathy, ocular toxicity, gastrointestinal toxicity, skin toxicity, increased creatine phosphokinase, increased levels of Vitamin E and risk of bleeding, embryo-fetal toxicity, hepatic impairment

Adverse effects^{1,2,3,4,5,6}:

Cardiovascular: Cardiomyopathy (23%), edema (20%), facial edema (<20%), hypertension (<20%), reduced ejection fraction (22%), sinus tachycardia (20%)

Dermatologic: Acneiform eruption (50% to 54%), changes of hair (32%), dermatitis (36%), eczema (28%), maculopapular rash (39%), paronychia (48%), pruritus (46%), skin infection (20%), skin rash (80% to 91%), xeroderma (60%)

Endocrine & metabolic: Decreased serum albumin (51%), decreased serum potassium (18%), decreased serum sodium (16%), increased amylase (18%), increased serum potassium (27%), increased serum sodium (18%), weight gain (<20%)

Gastrointestinal: Abdominal pain (76%), constipation (34%), decreased appetite (22%), diarrhea (70% to 77%; severe diarrhea: 24%), increased serum lipase (32%), nausea (66%), stomatitis (50%), vomiting (82%), xerostomia (<20%)

Genitourinary: Hematuria (22%), proteinuria (22%)

Hematologic & oncologic: Anemia (24%), decreased neutrophils (33%, grades ≥3: 4%), lymphocytopenia (20%, grades ≥3: 2%)

Hepatic: Increased serum alanine aminotransferase (35%), increased serum alkaline phosphatase (18%), increased serum aspartate aminotransferase (41%)

Nervous system: Fatigue (56%), headache (48%), Malignant peripheral nerve sheath tumor (no percentage reported)

Neuromuscular & skeletal: Increased creatine phosphokinase (76% to 79%), musculoskeletal pain (58%)

Ophthalmic: Blurred vision ($\leq 15\%$), cataract ($\leq 15\%$), ocular hypertension ($\leq 15\%$), periorbital edema ($< 20\%$), photophobia ($\leq 15\%$), visual impairment ($< 20\%$)

Renal: Acute renal failure ($< 20\%$)

Respiratory: Dyspnea ($< 20\%$), epistaxis (28%), hypoxia (24%)

Miscellaneous: Fever (56%)

Drug Interactions^{1,2,3}:

May decrease the serum concentration of Selumetinib:

CYP3A4 Inducers (Moderate)

CYP3A4 Inducers (Strong)

May increase the serum concentration of Selumetinib:

CYP3A4 Inhibitors (Moderate)

CYP3A4 Inhibitors (Strong)

Vitamin K Antagonists (ex: warfarin): Selumetinib may enhance the anticoagulant effect of Vitamin K Antagonists.

Vitamin E (Systemic): Selumetinib may enhance the adverse/toxic effect of Vitamin E.

Agents with Antiplatelet Properties (e.g., P2Y₁₂ inhibitors, NSAIDs, SSRIs, etc.):

Selumetinib may enhance the antiplatelet effect of Agents with Antiplatelet Properties.

Dosing/Administration^{1,2,3}:

Usual dose: 25 mg/m²/dose by mouth twice daily for ages 2 to 18 years with a max of 50 mg by mouth twice daily

Body Surface Area	Recommended Dosage
0.55 – 0.69 m ²	20 mg in the morning and 10 mg in the evening
0.7 – 0.89 m ²	20 mg twice daily
0.9 – 1.09 m ²	25 mg twice daily
1.1 – 1.29 m ²	30 mg twice daily
1.3 – 1.49 m ²	35 mg twice daily
1.5 – 1.69 m ²	40 mg twice daily

1.7 – 1.89 m ²	45 mg twice daily
≥1.9m ²	50 mg twice daily

Geriatric dose: Not studied.

Renal impairment dose: No adjustment necessary.

Hepatic impairment dose: Moderate hepatic impairment (Child-Pugh B): Reduce dose to 20 mg/m² twice daily

Recommended dosage modifications for adverse reactions based on severity of adverse reaction¹:

Cardiomyopathy → Asymptomatic decrease in left ventricular ejection (LVEF) of 10% or greater from baseline and less than lower level of normal = withhold until resolution and resume at reduced dose.

Symptomatic decreased LVEF Grade 3 or 4 decreased LVEF = permanently discontinue.

Ocular Toxicity → Retinal Pigment Epithelial Detachment (RPED) = withhold until resolution and resume at reduced dose.

Retinal vein occlusion (RVO) = permanently discontinue.

Gastrointestinal Toxicity → Grade 3 Diarrhea = withhold until improved to Grade 0 or 1 and resume at same dose. Permanently discontinue if no improvement within 3 days.

Grade 4 Diarrhea = permanently discontinue.

Grade 3 or 4 Colitis = permanently discontinue.

Skin Toxicity → Grade 3 or 4 = withhold until improvement and resume at reduced dose.

Use in special circumstances^{1,2}: Avoid use during pregnancy and lactation, as fetal harm was seen in animal studies and infant harm while breastfeeding cannot be ruled out. It is recommended that patients be on effective contraception while taking, and for 1 week after stopping this medication.

Conclusion: Selumetinib is a promising novel treatment for children with neurofibromatosis type 1 based on efficacy and safety data currently available. There are limited effective treatments for neurofibromatosis type 1 so selumetinib has an important role in clinical practice, but toxic effects need to be taken into account. Dose reductions due to toxic effects should be followed based off the recommendations in the package insert. Larger studies with longer term treatment and safety effects need to be evaluated as well as evaluations with other treatment options. Additional studies are currently being performed to assess the role of selumetinib in adults and other forms of cancer that involve the RAS-regulated RAF-MEK-ERK pathway.

References:

1. Koselugo [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, LP; 2020.

2. Selumetinib. Lexi-Drugs [database online]. Lexi-Comp, Inc; April 7, 2021.
3. Selumetinib. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed April 7, 2021.
4. Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas. *N Engl J Med*. 2020 Apr 9;382(15):1430-1442.
5. Fangusaro J, Onar-Thomas A, Young Poussaint T, Wu S, Ligon AH, Lindeman N, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. *Lancet Oncol*. 2019 Jul;20(7):1011-1022.
6. Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas. *N Engl J Med*. 2016 Dec 29;375(26):2550-2560.

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