FDA Approval Summary: Selumetinib for Plexiform Neurofibroma

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ABSTRACT

On April 10, 2020, the FDA approved selumetinib (KOSELUGO, AstraZeneca) for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibromas. Approval was based on demonstration of a durable overall response rate per Response Evaluation in Neurofibromatosis and Schwannomatosis criteria and supported by observed clinical improvements in plexiform neurofibroma–related symptoms and functional impairments in 50 pediatric patients with inoperable plexiform neurofibromas in a single-arm, multicenter trial. The overall reponse rate per NCI investigator assessment was 66% (95% confidence interval, 51–79) with at least 12 months of follow-up. The median duration of response was not reached, and 82% of responding patients experienced duration of response ≥12 months. Clinical outcome assessment endpoints provided supportive efficacy data. Risks of selumetinib are consistent with MAPK (MEK) inhibitor class effects, including ocular, cardiac, musculoskeletal, gastrointestinal, and dermatologic toxicities. Safety was assessed across a pooled database of 74 pediatric patients with plexiform neurofibromas and supported by adult and pediatric selumetinib clinical trial data in cancer indications. The benefit–risk assessment for selumetinib in patients with inoperable plexiform neurofibromas was considered favorable.

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant, tumor predisposition disorder arising from inherited or spontaneous mutations of the *NF1* gene, which encodes neurofibromin. The incidence is approximately 1:3,500 (>80,000 persons affected in the United States; refs. 1, 2). Neurofibromatosis type 1 is characterized by cutaneous, neurologic, skeletal, and neoplastic manifestations. Patients risk developing tumors of the central and peripheral nervous system, including plexiform neurofibromas and benign nerve sheath tumors composed of neoplastic Schwann cells that proliferate and infiltrate nerve fascicles (3, 4). Plexiform neurofibromas are typically diagnosed early in life, grow at a faster rate during the first decade, and rarely show spontaneous regression (5–7). Plexiform neurofibroma–associated morbidity depends on tumor location and compressive effects on nearby structures. Orbital plexiform neurofibromas can displace the globe and compromise vision, paraspinal tumors may compress the spinal cord causing paralysis, plexiform neurofibromas arising in the mediastinum may cause airway compromise, and tumors arising in extremities can result in progressive weakness and pain (3, 6). Plexiform neurofibromas can negatively impact growth and cause substantial disfigurement, and there is risk for malignant transformation to malignant peripheral never sheath tumor (MPNST) in approximately 10% of patients (3, 8, 9). Surgical resection is rarely curative and subsequent regrowth is common. Prior to the approval of selumetinib, there were no FDA-approved products for patients with inoperable plexiform neurofibroma.

Chemistry, Manufacturing, and Control

Selumetinib formulation development focused on maximizing solubility of the selumetinib active moiety. The commercial formulation is an HPMC capsule (10 and 25 mg strengths) composed of selumetinib hydrogen-sulfate salt, which exhibits improved solubility and bioavailability relative to selumetinib free base. The drug product is a mixture of selumetinib hydrogen-sulfate drug substance with vitamin E polyethylene glycol succinate (TPGS) in a hypromellose capsule. TPGS is a synthetic water-soluble derivative of vitamin E formed by esterification of vitamin E succinate with polyethylene glycol 1000. The TPGS excipient and manufacturing process maintains the hydrogen-sulfate form of the drug substance. The package insert does not allow for extemporaneous solutions or dosage form modifications to accommodate patients with trouble swallowing capsules. The commercial presentation is a 75-mL white, high-density polyethylene bottle with a child-resistant screw closure.

Nonclinical Pharmacology and Toxicology

Neurofibromatosis type 1 is a genetic disorder caused by germline mutations in the *NF1* gene that codes for neurofibromin, a widely expressed Ras GTPase-activating protein (GAP; refs. 10–12). Ras GAPs catalyze conversion of Ras from GTP-bound active conformation to GDP inactive conformation, thereby limiting

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downstream Ras signaling through the ubiquitously expressed Ras–Raf–MEK–ERK signaling cascade (13). Selumetinib is a kinase inhibitor targeting MAPK kinases 1 and 2 (MEK1/2). As *NF1* mutations commonly lead to increased Ras pathway signaling and dysregulated growth, blocking downstream Ras signaling by targeting MEK1/2 may help circumvent effects of losing neurofibromin GAP activity and clinical consequences of this loss in patients with neurofibromatosis type 1 (14).

Major target organs in adult animal studies conducted to support clinical development included the gastrointestinal tract and skin; growth plate dysplasia was an additional finding at high exposures. In animal developmental and reproductive toxicity studies ending after organogenesis, selumetinib showed increases in postimplantation loss, developmental delays, and malformations at exposures ≥ approximately five times the human exposure; studies that continued dosing through postnatal day 21 showed dose-dependent increases in prematurely open eyes and cleft palate at maternal exposures ≥0.6 times human exposure. Selumetinib was negative in carcinogenicity studies in mice and rats.

Clinical Pharmacology

The pharmacokinetics of selumetinib in pediatric patients were characterized following single and multiple dosing based on body surface area. Selumetinib plasma exposure (AUC and C_{max}) increases proportionally over the dose range of 20 to 30 mg/m^2. The maximum plasma concentration was reached at 1 to 1.5 hours postdose. The mean elimination half-life was approximately 6.2 hours following the recommended dosage of 25 mg/m^2 twice daily. The pharmacokinetics of selumetinib appeared to be within the range of values in adults and pediatric patients.

Selumetinib should be administered on an empty stomach. Selumetinib AUC and C_{max} decreased following a low-fat meal, but exposures did not substantially change following a high-fat meal in healthy adults. Postmarketing requirements (PMRs) to confirm food effect on the marketed capsule, evaluate whether administration with food may alleviate gastrointestinal toxicity, and confirm dosing recommendations with a low-fat meal were part of the approval (15, 16). **Table 1** provides recommended pediatric dose modifications for hepatic impairment and drug interactions. No dose adjustment is recommended for renal impairment (15).

Clinical Efficacy and Safety

FDA approval of this original new drug application (NDA) was based on safety and efficacy results from SPRINT (NCT01362803), an open-label, single-arm, multicenter, two-part trial of selumetinib in pediatric patients with neurofibromatosis type 1 plexiform neurofibroma conducted by the NCI Pediatric Oncology Branch (POB). SPRINT phase I was a dose-finding study ($N = 24$) that established the recommended phase II dose of 25 mg/m^2 twice daily in 28-day cycles. SPRINT phase II stratum 1 ($N = 50$) enrolled patients with inoperable neurofibromatosis type 1 plexiform neurofibroma and tumor-related morbidity who formed the primary efficacy population. The major efficacy outcome measure was overall response rate (ORR) using 3D-volumetric MRI assessment according to Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. Partial response (PR) was defined as ≥20% reduction in tumor volume confirmed at a subsequent assessment within 3 to 6 months (17). Secondary endpoints included duration of response (DOR), time to progression, progression-free survival, safety, and change from baseline in pain, physical functioning (e.g., vision, airway, motor, and bowel/bladder), and disfigurement as measured by clinical outcome assessments (COAs). Specific COAs and relevant measurement tools were determined at enrollment on the basis of individual patients' plexiform neurofibroma–related morbidities. Radiographic response was evaluated every four cycles for 2 years. Photographic assessments and COAs occurred every four cycles for 1 year and then every 12 cycles thereafter.

Patient characteristics

A total of 50 patients were enrolled and received at least one dose of selumetinib in SPRINT phase II stratum 1. The median age was 10 years (range, 3–17), 60% of patients were male, 84% were White, 8% were Black, and 2% were Asian. A total of 78% of patients had received prior therapy [surgical resection (48%) and systemic therapies (62%)]. The median target plexiform neurofibroma volume was 488 mL (range, 6–3820 mL), 42% of tumors were progressive, and patients had a median of three plexiform neurofibroma–related morbidities at enrollment. Morbidities that occurred in at least 20% of patients included disfigurement (88%), pain (52%), motor dysfunction (66%), airway compromise (32%), bowel/bladder dysfunction (20%), and vision compromise (20%). Baseline tumor-related symptoms grade ≥2 were present in 68% of patients, including 24% with grade 3 to 4 symptoms. The most common symptoms were weakness, limb asymmetry, tumor pain, decreased range of motion, and scoliosis.

Efficacy results

The confirmed ORR per REiNS criteria from SPRINT phase II stratum 1 was 66% [95% confidence interval (CI), 51–79] according to NCI review and 44% (95% CI, 30–59) according to an independent central review (ICR). All responses were confirmed PRs. The difference

Table 1. Recommended dosage of selumetinib for pediatric patients.

Setting	Selumetinib dosage
Recommended dosage	25 mg/m^2 twice daily
Dosage modifications for hepatic impairment	
Moderate hepatic impairment (Child-Pugh B)	20 mg/m^2 twice daily
Severe hepatic impairment (Child-Pugh C)	Avoid
Dosage modifications for drug interactions	
Concomitant strong or moderate CYP3A4 inhibitors or fluconazole[a]	20 mg/m^2 twice daily if current dosage is 25 mg/m^2 twice daily; 15 mg/m^2 twice daily if current dose is 20 mg/m^2 twice daily
Concomitant strong or moderate CYP3A4 inducers	Avoid

Note: Adapted from the U.S. Prescribing Information dated April 2020 (15).
[a]Dosage recommendation is for when coadministration with concomitant strong or moderate CYP3A4 inhibitors or fluconazole is unavoidable.

Table 2. Common AEs (≥30%) in SPRINT.

	SPRINT phase II $N = 50$		SPRINT phase I and II $N = 74$	
Preferred term	**Any grade (%)**	**Grade ≥3[a] (%)**	**Any grade (%)**	**Grade ≥3[a] (%)**
Any AE	49 (98)	31 (62)	73 (99)	50 (68)
Vomiting	41 (82)	3 (6)	61 (82)	6 (8)
Rash[1]	46 (80)	3 (6)	67 (91)	6 (8)
Abdominal pain[2]	38 (76)	0	58 (78)	1 (1)
Diarrhea	35 (70)	8 (16)	57 (77)	11 (15)
Nausea	33 (66)	1 (2)	54 (73)	1 (1)
Dry skin	30 (60)	0	43 (58)	0
Musculoskeletal pain[3]	29 (58)	0	47 (64)	0
Fatigue[4]	28 (56)	0	45 (61)	0
Pyrexia	28 (56)	4 (8)	42 (57)	6 (8)
Dermatitis acneiform	25 (50)	2 (4)	40 (54)	2 (3)
Stomatitis[5]	25 (50)	0	38 (51)	1 (1)
Headache	24 (48)	1 (2)	40 (54)	2 (3)
Oropharyngeal pain	24 (48)	0	30 (41)	0
Paronychia[6]	24 (48)	3 (6)	35 (47)	7 (10)
Pruritus	23 (46)	0	31 (42)	0
Cough	20 (40)	0	37 (50)	0
Dermatitis[7]	18 (36)	2 (4)	25 (34)	2 (3)
Constipation	17 (34)	0	25 (34)	0
Nasal congestion	17 (34)	0	32 (43)	0
Hair disorder[8]	16 (32)	0	29 (39)	0
Influenza-like illness[9]	15 (30)	2 (4)	21 (28)	2 (3)
Rhinitis allergic	15 (30)	0	16 (22)	0

Note: Source, FDA multidisciplinary review (21).
[a]No grade 5 AEs occurred.
[1]Includes dermatitis acneiform, rash maculo-papular, erythema, rash pustular, rash, urticaria, exfoliative rash, rash pruritic, and rash erythematous.
[2]Includes abdominal pain, abdominal pain upper, abdominal discomfort, gastrointestinal pain.
[3]Includes pain in extremity, back pain, neck pain, musculoskeletal pain.
[4]Includes fatigue and malaise.
[5]Includes stomatitis and mouth ulceration.
[6]Includes paronychia and nail infection.
[7]Includes dermatitis, dermatitis atopic, dermatitis diaper, eczema, seborrheic dermatitis, skin irritation dermatitis bullous, and dermatitis contact.
[8]Includes alopecia, hair color change, and hair disorder.
[9]Includes influenza and influenza-like illness.

in ORR observed between NCI review and ICR was partly due to tumor volume measurements for six patients who had plexiform neurofibroma shrinkage between −19.2% and −19.9% as best objective response thereby not meeting the 20% threshold for PR per REiNS criteria. Among the 33 responders in the NCI assessment, the median DOR was not reached, 82% had DOR of at least 12 months, and 88% remained on selumetinib at the data cut-off date. A natural history study of neurofibromatosis type 1 conducted by the NCI POB submitted to the NDA confirmed the uncommon occurrence of spontaneous regression such that observed responses in SPRINT were reasonably deemed the effect of selumetinib treatment.

The applicant additionally submitted an individual patient review (IPR) document for each patient in the efficacy population. The applicant and FDA agreed upon the content of the IPRs at presubmission meetings for the application. Review of IPRs allowed for characterization of functional impairments and symptoms patients were experiencing, potential selumetinib effects on clinical outcomes, and patient safety in the context of radiographic response results. FDA review of these descriptive analyses generated the following conclusions: patients in SPRINT had substantial baseline morbidity due to large and disfiguring plexiform neurofibromas, as well as relatively small tumors located in critical areas, such as near the airway or orbit; further reduction in tumor volume after initial objective response was common; a trend existed for tumor volume reduction that correlated with at least one improved clinical outcome in most patients with an objective response; objective measures of function (e.g., range of motion and pulmonary function tests) were not always consistent with patient/parent reporting of improvements or MRI tumor volume reduction; and photographic data revealed modest changes in disfigurement from baseline for most patients despite patient/parent-reported improvements in tumor appearance and texture.

Safety results

The safety population included 74 patients with neurofibromatosis type 1 plexiform neurofibroma treated with selumetinib administered at doses ranging from 20 to 30 mg/m^2 twice daily during SPRINT phase I ($N = 24$) and phase II stratum 1 ($N = 50$). FDA also reviewed data from a pooled population of 347 adults who received selumetinib monotherapy across seven oncology trials, the selumetinib plexiform neurofibroma expanded access program, and analyses of the applicant's global database to further characterize selumetinib's safety profile.

The median selumetinib exposure for the 74 SPRINT patients was 28 months (range, 1–71). **Table 2** lists common adverse reactions observed during SPRINT. There were no fatal adverse events (AEs).

Serious AEs (SAEs) occurred in 23% of patients, including diarrhea, creatine kinase (CK) elevation, anemia, pyrexia, and hypoxia SAEs in at least two patients each. AEs leading to permanent discontinuation occurred in 12% of patients (diarrhea, paronychia, nausea, stomatitis, fatigue, acute kidney injury, skin ulcer, MPNST, increased weight, myalgia, and gastroesophageal reflux), and 32% had AEs requiring dose reduction (four patients were reduced from a starting dose of 30 mg/m^2). AEs prompting dose reduction in at least two patients were CK elevation, increased weight, paronychia, stomatitis, and rash. Grade 3 to 4 AEs occurred in 68% of patients.

MEK inhibitor class effects include cardiac, ocular, musculoskeletal, gastrointestinal, dermatologic, and embryofetal toxicities (18–20). Decreased left ventricular ejection fraction (LVEF) ≥10% below baseline occurred in 23% of SPRINT patients, including one grade 3 decrease requiring dose reduction. A total of 4% of patients experienced decreased LVEF below institutional lower limits of normal. All LVEF decreases were asymptomatic and detected on routine echocardiograms. Nonserious ocular AEs, including blurred vision, photophobia, cataracts, and ocular hypertension, occurred in 15% of SPRINT patients; retinal pigment epithelial detachment requiring selumetinib discontinuation occurred in one pediatric patient on a separate trial. Retinal vein occlusion events occurred in the adult database. While CK elevation was common, there was no rhabdomyolysis in SPRINT; however, two cases of rhabdomyolysis were identified in adult data. Diarrhea occurred in 77% of SPRINT patients, including 15% with grade 3 diarrhea. Serious gastrointestinal toxicities, including perforation, colitis, ileus, and intestinal obstruction, were not reported during SPRINT, but occurred in adults. Skin and nail toxicities, including dermatitis acneiform (54%), nonacneiform rashes (65%), pruritis (42%), dry skin (58%), and paronychia (47%), were common during SPRINT. Most skin AEs were mild/moderate in severity and did not require dose modifications, however, did require skin care regimens consisting of emollients, topical antibiotics, or steroids, and in some cases, systemic antibiotics. Palmar-plantar erythrodysesthesia syndrome occurred in adult patients.

Regulatory Insights

Selumetinib was granted regular approval for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibroma. The ORR of 66% with 82% of responses durable for ≥12 months, supported by the observed trend of improved function or symptomatology correlating with tumor volume reduction was considered evidence of direct clinical benefit. Knowledge of selumetinib's mechanism of action (interruption of signaling pathways downstream from RAS) and the natural history of plexiform neurofibroma characterized by lack of spontaneous regression provided biologic rationale and confidence that observed responses were treatment related.

Key issues arising during FDA's review of the application included use of ORR as a regulatory endpoint in a histologically benign tumor indication, assessment of supportive efficacy from patient-level clinical outcomes data, and evaluation of the safety of chronic MEK inhibitor use in pediatric patients.

Neurofibromatosis type 1 plexiform neurofibroma is a benign tumor and as such, tumor shrinkage, even when treatment related and durable, is not predictive of improved survival. FDA advised the applicant that for ORR results to be clinically relevant, SPRINT should be designed to show that reduction in tumor volume is reliably accompanied by a detectable effect on plexiform neurofibroma–related functional impairment or symptoms, or improvement in disfigurement. Because of the heterogeneity among patients for age, tumor location, and morbidities, multiple COA tools were employed to measure changes from baseline in symptoms and function. IPRs were submitted as supportive efficacy data and included COA results in the context of radiographic response and safety data. Acknowledging the challenges of interpreting COA results from an open-label trial in a small sample size lacking an internal control, and potential instrument limitations, FDA considered the descriptive COA data and IPRs as part of the totality of evidence intended to characterize the benefit of selumetinib.

Table 3. FDA benefit–risk summary.

Parameter	Benefit–risk analysis
Analysis of condition	NF1 PN is a rare, progressive, and highly morbid condition. Depending on the location of the tumor, patients may experience substantial disfigurement and pain, as well as motor dysfunction (weakness and restricted mobility), vision impairment, bladder/bowel dysfunction, neurologic dysfunction, and airway compromise, and there is risk for malignant transformation. Surgical management is challenging due to tumor encasement of nerves and vessels and surgical morbidities, and regrowth following surgery is common.
Current treatment options	There are currently no FDA-approved therapies for patients with NF1 PN. Safe and effective treatments are needed.
Benefit	A single-arm, multicenter study of selumetinib in 50 pediatric patients demonstrated a confirmed ORR of 66% (95% CI, 51–79) and more than 80% of responders had durable responses of least 12 months. The trial evaluated selumetinib effects on PN-related functional impairment, symptoms, and disfigurement via secondary COA endpoints. Descriptive patient-level data showed a trend of reduction in tumor volume correlating with durable improvement in clinical outcomes.
Risk and risk management	The safety risks of selumetinib in pediatric patients with NF1 PN are consistent with the profiles of other approved MEK inhibitors. Adverse drug reactions in pediatric patients receiving selumetinib were frequent; however, most were low-grade and manageable with dose modifications and supportive care. Selumetinib appears tolerable given that the majority of patients in the SPRINT safety population continued treatment for more than 2 years. Risk management based on labeling, as well as routine and enhanced pharmacovigilance will be employed to ensure safe and effective use of selumetinib in the indicated population.
Conclusion	Selumetinib demonstrated clinically meaningful efficacy, including confirmed ORR that is durable and improvements in PN-related clinical morbidities. These results represent direct clinical benefit for pediatric patients with NF1 PN. The safety profile of selumetinib is consistent with other MEK inhibitors and is acceptable in view of the serious nature of inoperable PN.

Abbreviations: NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

As part of risk assessment, FDA considered the benign indication and intended chronic dosing of selumetinib in pediatric patients with neurofibromatosis type 1. Multiple selumetinib safety databases were reviewed to generate an informed risk profile, including SPRINT, adult trial data, the plexiform neurofibroma expanded access program database, and data from externally sponsored pediatric trials. There is no evidence that pediatric patients are at less risk for uncommon, but serious, MEK class effects not identified in SPRINT; therefore, specific safety precautions, dose modifications, and management guidelines for these risks are included in product labeling (15, 21). The relatively long treatment exposure with low discontinuation rates observed in SPRINT suggests that selumetinib at the recommended dose was reasonably safe and tolerable. The longer term safety profile will be further assessed through PMRs to collect data from pediatric patients enrolled on SPRINT and other selumetinib studies for a minimum of 7 years, to evaluate the potential for adverse risks on growth and development and for occurrence of specific ocular, muscle, gastrointestinal, and dermatologic toxicities. In addition, an enhanced pharmacovigilance program was implemented for monitoring and expedited reporting of serious ocular, cardiac, muscle, and gastrointestinal AEs that occur in pediatric patients receiving selumetinib (16).

Additional studies are required to investigate the potential effects of MEK inhibition in other neurofibromatosis type 1–related diseases. There was no evidence that malignant transformation to MPNST was prevented or altered by selumetinib in SPRINT as two patients developed MPNST during treatment. Combined targeting of MEK and other signaling pathways has been evaluated in MPNST preclinical models (22, 23), and there is an ongoing trial of selumetinib in combination with sirolimus in advanced MPNST (NCT03433183). Clinical studies of selumetinib in neurofibromatosis type 1–related cutaneous neurofibroma, low-grade glioma, and gastrointestinal stromal tumors are also ongoing (24).

Conclusions

The approval of selumetinib for the treatment of inoperable and symptomatic neurofibromatosis type 1 plexiform neurofibroma offers the first systemic treatment for pediatric patients with a serious disease who are subject to significant and progressive morbidity. The confirmed ORR and associated effects on plexiform neurofibroma–related morbidities were of sufficient magnitude and durability to be deemed direct evidence of clinical benefit. The overall benefit–risk assessment (**Table 3**) was considered favorable in a nonmalignant disease associated with debilitating functional impairments and progressive disfigurement with no approved therapeutic options.

Authors' Disclosures

No disclosures were reported.

Disclaimer

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