Selumetinib in the Treatment of Neurofibromatosis Type 1 (NF1)

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Abstract: Neurofibromatosis type 1 (NF1) is a prevalent genetic neurocutaneous disease globally and may result in various complications. Among these complications, cancer is the leading cause of death. Patients with NF1 have a high possibility of plexiform neurofibroma (PN), which may later transform into malignant peripheral nerve sheath. Treatment of NF1 is case-to-case based considering the variety of complications. For NF1 patients with PN, surgery is the standard solution. However, due to the complexity of nerves and the difficulty of performing surgeries, resorting to surgery is not merely effective. The preclinical trials on mice with plexiform neurofibroma indicated that selumetinib (commercial name, Koselugo) has a positive effect in NF1 disease in case of shrinkage in the size of the tumor. Similar results were obtained when conducting the first-in-human trials. Safety and side effects of selumetinib were also evaluated by a phase I trial of the drug in pediatric patients with recurrent or refractory low-grade glioma. In addition, Selumetinib is an inhibitor of mitogen-activated protein kinase 1 or 2 (MEK) essential for the MAPK signaling pathway of tumorigenesis. The inhibition caused by selumetinib precludes the activation of MEK1/2 and transcription factors, which stops the cellular proliferation of cancer cells. This comprehensive review introduces Selumetinib and its mechanism of inhibiting the proliferation of Neurofibromatosis cells, focusing on the completed and ongoing clinical trials to provide a reference for clinicians to make better clinical decisions.

1. Introduction

Neurofibromatosis type 1(NF1) is one of the most prevalent Mendelian neurocutaneous diseases. The prevalence of NF1 in the United States is estimated to be 1 out of every 2,500 to 3,000 births based on different studies [1, 2]. The average life expectancy of NF1 patients is possibly reduced by 10 to 15 years. Additionally, NF1 leads to various complications, including plexiform neurofibroma (PN), cognitive and behavioral problems, bone abnormalities, and malignancy, contributing to the most significant proportion of death. PN, a benign tumor type that locates on peripheral nerve sheath, is a complication of NF1, which is most common and enfeebling [1]. PN, with the possibility of transforming into malignant peripheral nerve sheath tumors (MPNSTs), also leads to pain, disfigurement, cosmetic problems, difficulties with swallowing and breathing [3,4]. Due to the variability of complications of NF1, the treatments are not standardized and are mostly based on individual symptoms. For NF1 patients with PN, treatment options are limited since the major solution is surgery which can often be challenging since the association with the nervous system.

Selumetinib, commercially known as Koselugo, is a mitogen-activated protein kinase 1 / 2 (MAPK) inhibitor, has been approved by FDA as the first drug for NF1 patients with inoperable PNs

[4]. FDA granted this drug priority review and Breakthrough Therapy designation, which expedited the process of approval. This orally taken drug inhibits the hyper-activated RAS MAPK pathway in NF1 due to its essential role on the MAPK signaling pathway relevant to tumor growth [5]. Animal and clinical trials are conducted to test the efficacy and efficiency of this new drug.

This review introduces Selumetinib, the mitogen-activated protein kinase 1 / 2 inhibitor, as the drug of NF1 patients with inoperable PNs from the perspective of composition, mechanism, and finished and ongoing clinical trials.

2. Overview of Selumetinib

Selumetinib is a mitogen-activated protein kinase 1 and 2 (MEK1/2) inhibitor developed by Astrazeneca for the treatment of neurofibromatosis and various cancers. The drug received FDA approval for the treatment of tumors associated with neurofibromatosis and various cancers last year [6].

In 50 children with inoperable plexiform neurofibromas at least one year of follow-up, the overall response rate assessed by each NCI investigator was 66% (95% confidence interval). Over 80% of responding patients experienced a response duration of ≥one year. The clinical evaluation results provide supporting data for the efficacy of selumetinib [7]. The risk of selumetinib is consistent with the effects of MAPK (MEK) inhibitors, including ocular, cardiac, musculoskeletal, gastrointestinal, and cutaneous toxicity. Safety was evaluated in a pooled database of over 70 pediatric patients with plexiform neurofibromas and supported clinical trial data for adult and pediatric selumetinib cancer indications.

2.1 The Mechanism of Selumetinib inhibiting the proliferation of Neurofibromatosis cell

The main signal pathways studied for NF1 are Ras and MAPK. The main reason for inheriting NF1 is the loss mutation of constitutional heterozygous tumor suppressor gene NF1. The NF1 gene encoding RAS GTPase activates neurofibromin. It is one of several genes that affect RAS-MAPK signaling in multiple downstream pathways involved in RA signal transduction (RALGDS, PI3K, RASSF, TIAM1, BRAP2, RIN, GRB7). Only a few have been evaluated, of which RAS-MAPK is the best researched [8].

One research group compared the transcriptome of NF1 tumors, with the normally differentiated peripheral nerves indifferent species, to clarify the molecular mechanisms of tum genesis and potential targets. Their results suggested that overactive Ras induces gene expression and inhibits the classical downstream pathway Raf/MEK/ERK in benign neurofibroma and MPNST.ERK remains active in these tumors, although transcriptional results suggest that a negative feedback loop has been induced. Preclinical trials of the inhibitor PD0325901 in a mouse model of NF1-associated peripheral nerve tumors have shown significant efficacy [9]. Likewise, the significant response to PD0325901 in a mouse model of juvenile monocytic leukemia (JMML) by Nf1 inactivation was reported [10]. Together, these data provide a strong case for MEK targeting NF1-associated tumors.

Currently, three main sublines of the MAPK pathway are recognized: JNK/SAPK, p38 MAPK, and MEK/ERK (extracellular signal-related kinases. Two common kinase groups of MEK are involved in the phosphorylation of serine/threonine and tyrosine residues. At the same time, MEK1 and MEK2 have only one known substrate. It involves many cell functions, including transcription, cell cycle progression, and cell movement [11] (Figure 1).

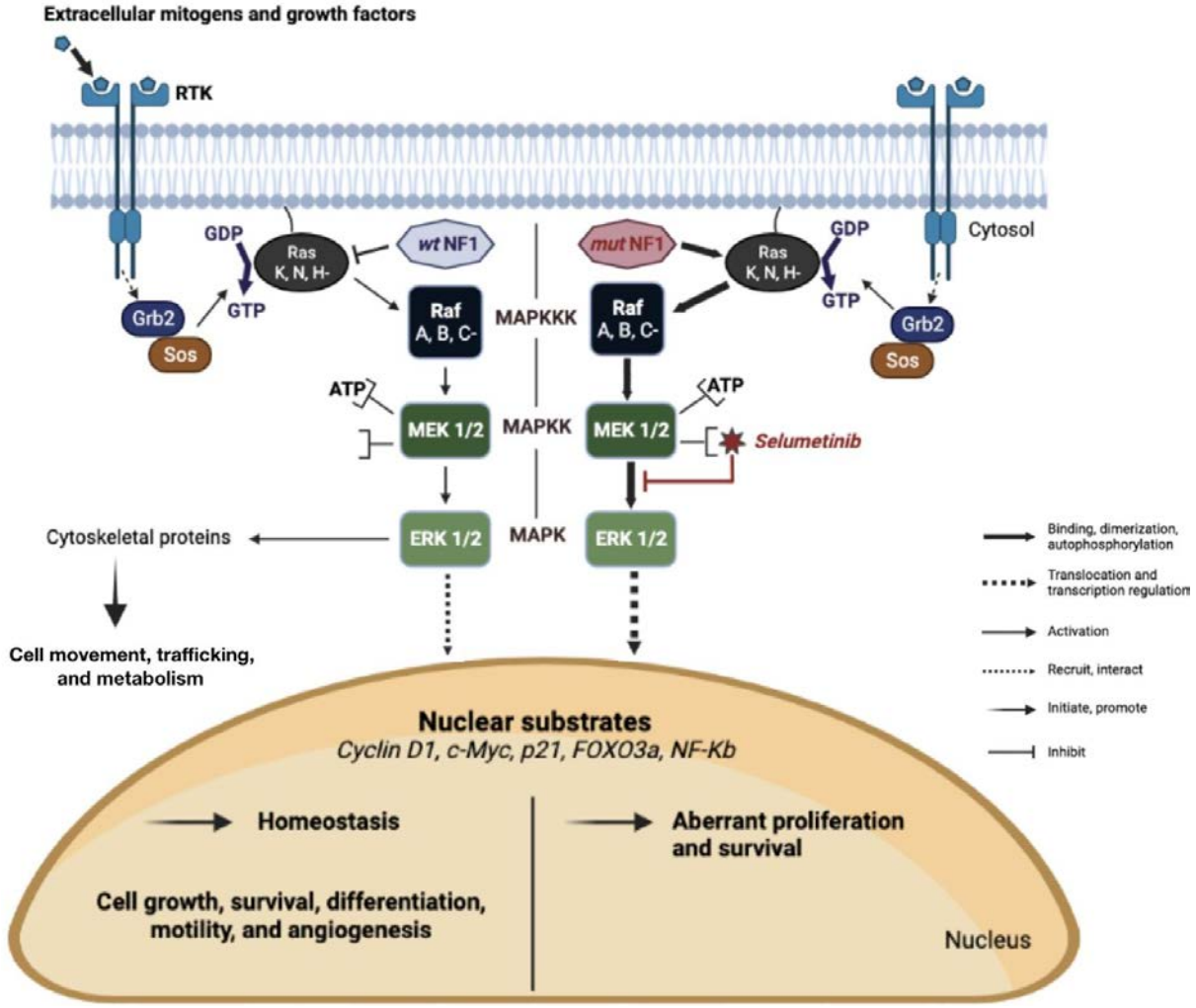

Figure 1. Inhibition path of Mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK 1/2) [12].

2.2 The activation of MAPK-ERK1/2

The activation of MAPK-ERK1/2 begins with extracellular growth and the binding of mitogens to cell membrane receptor tyrosine kinases (RTKs). The activated RTK recruits modified proteins to activate Ras-GDP by inducing a molecular change from GDP to GTP. Ras-GTP activates Raf, which catalyzes MEK1/2 and ERK1/2 through phosphorylation. ERK1/2 translocate to regulate cell differentiation through activation of function protein and gene expression to achieve connection and survival. ERK1/2 protein also targets cytoplasmic substrates to regulate cell metabolism. The MAPK-ERK pathway relies on scaffold proteins and is strictly regulated by negative regulators and feedback systems [12]. While NF1 ismututed, itmaybrokeneurofibromin function, leading to excessive activation of the MAPK-ERK pathway [13].

3. Clinical Trials of Selumetinib (Alice and Jingzi)

3.1 Preclinical Trials

To test for the efficacy of Selumetinib, considerable preclinical trials are conducted mainly using genetically engineered mouse (GEM) models. The purpose of these preclinical trials is designated to determine the safety of this therapy and if it is effective in enhancing the conditions of patients [5].

Selumetinib was tested and was found to decrease the size of the plexiform neurofibroma in response to treatment. The mice were housed in temperature and humidity-controlled facilities on a 0.5day darklight cycle, with easy access to food and water. They received 10mg/kg selumetinib (from

AstraZeneca, UK) or vehicle twice daily via oral gavage, five days per week for a total of 56 days. Then the volumetric analysis was used to evaluate the effect of selumetinib [14, 15]. The blood samples and tumor samples were obtained for pharmacokinetic analysis and pharmacodynamics studies, respectively.

The pharmacokinetic result showed that phosphorylated extracellular signal-regulated kinase (ERK) was found to be reduced in mouse tumor samples. In the mouse model of neurofibromatosis type 1–related neurofibroma, selumetinib was associated with decreases in neurofibroma volume from baseline in around65%; however, neurofibroma volume increased from baseline in 90% vehicle-treated control animals [16]. Figure 2 shows percentage changes in tumor volume.

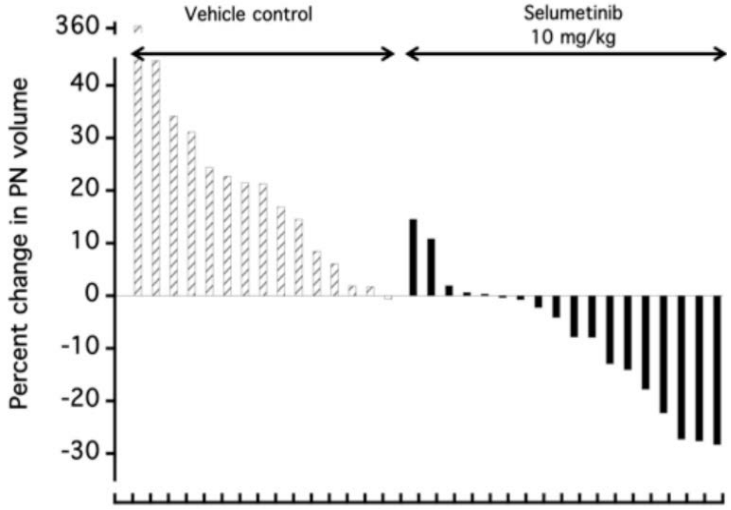

Figure 2. Percent change in tumor size with respect to Phase I trials [17].

3.2 Phase I trials

Children with neurofibromatosis type 1 and inoperable plexiform neurofibromas were found to benefit from long-term dose-adjusted treatment with selumetinib without having excess toxic effects. To determine the maximum tolerated dose and evaluate plasma pharmacokinetics, Scientists conducted a phase I trial of selumetinib in children with NF1 and inoperable plexiform neurofibromas. On a continuous dosing schedule, selumetinib was given twice daily at a dose of 20 to 30 mg per square meter of body surface area (in 28-day cycles). The result of this experiment was similar to the animal experiment: all patients had a decrease in plexiform neurofibroma volume compared to baseline. For patients who received 20mg treatment, there was a 31% decrease in tumor volume, and for the 25mg treatment group, selumetinib showed the most dramatic effect on NF1 tumor, which decreased its volume by 34%. The slightest volume change (19%) compared to baseline was obtained from the 30mg treatment group. Overall, the median change is -31%, with a range of -5.8 to -47. Also, it is worth noting that the highest tolerable dose was 25 mg per square meter (approximately 60 percent of the recommended adult dose) [16].

3.3 Phase II, phase III, and phase IV trials for selumetinib in treatment of NF type 1 disease.

According to NIH, there are few completed phase II to phase IV studies for selumetinib in the specific treatment of NF type 1 disease. Many studies are under the recruiting status; for example, the study titled “Phase I Study to Assess the Effect of Food on the PK and Gastrointestinal Toxicity of Selumetinib in Adolescent Children with Neurofibromatosis Type 1 Related Plexiform Neurofibromas” [17] is the latest phase I study that is designed for selumetinib, sponsored by *AstraZeneca*. The goal of the study is to evaluate how effective low-fat meals are concerning stabilizing the exposure of selumetinib. This study is designed to have selumetinib as the only drug intervention. The participants will be adolescents who have been diagnosed with NF1 but with inoperable PN. The researchers of the study aim to obtain information about whether the GI toxicity will be affected by having selumetinib under fed and fasted conditions. Also, the results from the

study might potentially be able to give a recommended selumetinib dosage with low-fat meals. This study was posted on November 1st, and is currently under recruiting.

The complete study sponsored by *AstraZeneca* [18] involves 24 healthy and five different treatments (Table 1), of which each has different doses of selumetinib. The goal of this study-- to evaluate the efficacy of selumetinib in healthy male participants-- is not necessarily for the testing of whether selumetinib works for the NF type 1 disease. However, it does help investigate the pharmacokinetics of the drug in general. Moreover, that could be useful as a reference when studying the efficacy of selumetinib in the specific treatment of NF 1.

Table 1. Experimental data for the study to evaluate bioavailability and food effect of Selumetinib (AZD6244) in healthy male participants [18].

Drug	Dosage
Treatment A	25 mg granule, fasted state
Treatment B	50 mg capsule, fasted state
Treatment C	25 mg granule, fed state
Treatment D	50 mg capsule, fed state
Acetaminophen	a single 500mg dose of Acetaminophen

Another Study Sponsored by *Astrazeneca* [19] Is an Expanded Access Study [20], And the Treatment Within the Study Was Approved for Marketing. This Study Involved Approximately One Hundred Participants Who Had Been Diagnosed with Nf1 as Well As Having Inoperable and Progressive/Symptomatic Plexiform Neurofibromas (Pn). In Addition, Those Participants Did Not Have Any Other Available Treatments for Their Nf Type 1 Disease at The Time. Therefore, They Have Prescribed Selumetinib and Were Under Observation for The Evaluation of Whether the Treatments Worked. The Time of Treatment Was Not Specified and Varied on A One-To-One Basis as Each Individual Had a Different Level of Response to The Treatment. The Length and Dosage of Treatment Were Determined by Participants' Corresponding Physicians, And Whether They Shall Pause the Treatment Was Also Under Physician Supervision. The Ages of Participants Span From 2 To 130, And All Gender Was Included.

3.4 Ongoing trials

Currently, there are three phase-3 clinical trials of selumetinib, and detailed information on those is shown in Table 2.

The first one is a randomized, double-blind, placebo-controlled, 2-arm multicenter, global phase III study, which aims to evaluate the participation of selumetinib in adult NF1 with symptomatic, inoperable PN compared with placebo. Efficacy and safety among patients [21].

The second trial investigated whether selumetinib is the same as carboplatin/vincristine (CV) standard treatment for NF1-related low-grade glioma (LGG) subjects and observed that selumetinib could improve the Whether the visual acuity of subjects with NF1 is better than that of CV visual pathway (optical nerve) LGG [22].

The last one compared selumetinib with carboplatin and vincristine (CV) standard care treatment in the treatment of newly diagnosed or previously untreated patients with LGG. TheseLGG do not

have a genetic abnormality called BRAF V600E mutation and are not related to systemic neurofibromatosis type 1 [23]. Since these experiments are still in progress, we are still tracking their latest development results.

Table 2. Ongoing trials of selumetinib.

Condition or Disease	Intervention or Treatment	Status	Stage	Time	Sponsor	Identification Number
Neurofibromatosis 1 Plexiform neurofibroma (PN)	Drug: Smeltinib Other: placebo	Recruiting	III	2021.9-2023.11	AstraZeneca	NCT04924608
Low-grade glioma Neurofibromatosis type 1 visual pathway glioma	Drug: Carboplatin Other: Quality of Life Assessment Other: Questionnaire management Drug: Selumetinib Sulfate Drug: Vincristine Sulfate	Recruiting	III	2019.10-2027.5	National Cancer Institute (NCI)	NCT03871257
Low-grade astrocytoma low-grade glioma metastatic low-grade astrocytoma metastatic low-grade glioma	Drug: Carboplatin Other: Quality of Life Assessment Other: Questionnaire Management Drug: Selumetinib Sulfate Drug: Vincristine Sulfate	Recruiting	III	2020.1-2026.12	National Cancer Institute (NCI)	NCT04166409

4. Side effects and drug interactions

The safety of koselugo was evaluated in SPRINT phase II Stratum 1 for patients with inoperable partial nephrectomy (PN). The subjects were excluded from the study due to various factors, including uncontrolled hypertension and abnormal LVEF. Among the patients, 38% were exposed to the drug for more than two years. They experienced various severe adverse reactions, including diarrhea, abdominal pain, and hypoxia. Adverse reactions included nausea, diarrhea, and weight gain.

Permanent discontinuation of selumetinib was also associated with higher creatinine, increased blood pressure, and skin ulcers. 5% of patients experienced a dosage interruption or reduction due to an adverse reaction. The most common reactions included vomiting, abdominal pain, nausea, and skin infection.

In children with LGG, selumetinib has shown promising antitumor activity. The mitogen-activated protein kinase pathway is required for the growth of pediatric low-grade gliomas (LGGs). The goal of this study was to find out what the recommended phase II dose (RP2D) and dose-limiting toxicities (DLTs) of the MEK inhibitor selumetinib were in kids with progressive LGG.

Selumetinib is provided by AstraZeneca in 10 mg and 25 mg capsules taken orally twice over four weeks in a four weeks cycle.The protocol enrolled over ten years old subjects with a starting dose and a planned dose escalation with toxicity reduced to class zero. The protocol was modified to include level 1 and level 2 to further increase the toxic dose and to include children aged over three and below twelve in the RP2D.

There were 38 subjects who were eligible to participate. Doses 1 and 2 were highly toxic. DLTs included elevated amylase/lipase at grade 3, headache, mucositis, and rash at grades 2–3. Only 3 of the 24 experienced DLTs at dose level zero. The median area under the curve and apparent oral clearance of selumetinib at the R2PD were 3855 ng*h/mL (1780 to 7250 ng h/mL) and 6.5 L h1 m2 (3.4 to 14.0 L h1 m2, respectively). BRAF mutations were found in 13 of 19 tumors. 4 of the 5 subjects with sustained partial responses, all at the RP2D, had BRAF mutations, and one had insufficient tissue. The subjects were given a total of 13 cycles. 14 (37%) completed all protocol treatment, 13 cycles with at least stable disease; 2-year progression-free survival at the RP2D was 69% [24].

There are some drug interactions that patients should take care of. For example, concurrent use of selumetinib with a strong or moderate CYP3A4 inhibitor or fluconazole will result in higher selumetinib plasma concentrations, increasing the risk of side effects. Co-administration of selumetinib with strong or moderate CYP3A4 inhibitors or fluconazole should be avoided. Since selumetinib contains vitamin E, exceeding the recommended or safe daily vitamin E intake may increase the risk of bleeding. Patients taking a vitamin-K antagonist or an antiplatelet agent with Koselugo may experience a higher risk of bleeding. The above test data show that different ages have different responses to Selumetinib. Therefore, when making a clinical treatment plan for NF1 patients, clinicians need to fully consider the patient's medication status and age. Whether gender, race, and tumor classification will affect the efficacy of the drug requires further research. Selumetinib is a new type of tumor drug, and future research needs more time to explore its mechanism, effect and safety

5. Conclusion

As a relatively common neurological disease, NF1 can cause many complications and disabilities. The incidence of NF1 is high, and the average life expectancy of patients is reduced, which is a heavy burden on society and families. However, the treatment method is mainly based on individual symptoms, and does not improve the patient's survival and prognosis much. Due to the size of the tumor, internal involvement, etc., surgery is not always feasible. Moreover, as the main solution, surgical treatment is usually challenging. At present, there are still a lot of blanks in the drug treatment of NF1. MEK1/2 protein is the upstream regulator of the ERK pathway. MEK and ERK are also critical components of the Ras-regulated RAF-MEK-ERK pathway, which is usually activated in different types of cancer. In animal models, oral selumetinib can inhibit ERK phosphorylation and reduce the number, volume, and proliferation of neurofibromas [25].

By confirming the reasonable safety of the efficacy results, selumetinib became the first drug approved by the FDA for the treatment of NF1. Since no drugs have been approved for this major disease before, its approval process has also been accelerated. Studies have shown that children with neurofibromatosis type 1 and inoperable plexiform neurofibromas benefit from smetatinib treatment, and long-term treatment options do not produce excessive toxic effects.

However, in phase II to phase IV clinical studies, the efficacy and safety of Selumetinib in the specific treatment of NF type 1 diseases are very small, and most of the trials are still in progress. Follow-up results and feedback need to be further tracked. Moreover, the long-term safety, effectiveness, cost-effectiveness, and usefulness of the drug in different age groups still need further research. In the future, smetinib may become the first-line treatment for NF1 diseases.

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