RNS Number : 7968L
AstraZeneca PLC
12 November 2024

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Koselugo showed statistically significant and clinically meaningful objective response rate vs. placebo in adults with neurofibromatosis type 1 in global KOMET Phase III trial

Results demonstrated reduction in tumour volume, building on established safety and efficacy profile of Koselugo in children and supporting expanded use in adults

Positive high-level results of KOMET, the largest, global randomised double-blind placebo-controlled multicentre Phase III trial in adults with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN), showed that *Koselugo* (selumetinib), an oral, selective MEK inhibitor, met its primary endpoint, demonstrating a statistically significant and clinically meaningful objective response rate (ORR) versus placebo in these adult patients.

NF1 is a rare, progressive genetic condition affecting an estimated 1.7 million individuals worldwide, approximately 70% of whom are adults.[1,2] In 30-50% of patients, tumours develop on the nerve sheaths and may cause debilitating symptoms.[3-8] NF1 is usually diagnosed in early childhood, however, NF1 often progresses into adulthood.[9,10] There are no approved treatments for adults, leaving many to experience disfigurement, dysfunction, persistent pain or endure multiple surgeries.[11]

Prof. Ignacio Blanco Guillermo, MD, PhD, Chairman of the Genetic Counselling and Clinical Genetics Programme at the Germans Trias i Pujol University Hospital, Chairman of the Spanish National Reference Centre for Adult Patients with Neurofibromatosis and Principal Investigator of the KOMET trial, said: "With limited options to manage NF1 PN in adults, many patients experience functional impairment and symptoms, which can substantially impact their lives. These clinically meaningful data show *Koselugo* has the potential to make a positive impact in patient care by reducing the size of plexiform neurofibromas."

Marc Dunoyer, Chief Executive Officer, Alexion, AstraZeneca Rare Disease, said: "These promising results demonstrate that *Koselugo*, the first and only approved targeted therapy for certain children with NF1 PN, now has the potential to benefit adult patients for whom there are no approved targeted therapies. As the largest and only global placebo-controlled Phase III trial in adults with NF1 PN, KOMET reinforces our leadership in advancing potential treatment options for people living with this debilitating disease. We look forward to sharing these findings with regulatory authorities."

Scot Ebbinghaus, MD, Vice President, Global Clinical Development, MSD Research Laboratories, said: "Adults with NF1 are in critical need of treatment options to help manage symptomatic, inoperable plexiform neurofibromas. These positive results from the Phase III KOMET trial demonstrate the potential to expand the use of *Koselugo* beyond paediatric patients to also treat adult patients living with this rare and challenging genetic condition."

In the trial, ORR was defined as the percentage of patients with confirmed complete response (disappearance of PNs) or partial response (at least 20% reduction in tumour volume) by cycle 16 (28 days per cycle) as determined by independent central review (ICR) per response evaluation in neurofibromatosis and schwannomatosis (REiNS) criteria.

The safety profile of *Koselugo* in this study was consistent with that observed in clinical trials among children and adolescents. No new safety signals were identified.

Alexion, AstraZeneca Rare Disease will share these data with regulatory authorities and present at a forthcoming medical meeting. AstraZeneca and MSD are jointly developing and commercialising *Koselugo* globally.

Notes

NF1
NF1 is a rare, progressive, genetic condition that is caused by a spontaneous or inherited mutation in the NF1 gene.[3,11] NF1 is associated with a variety of symptoms, including soft lumps on and under the skin (cutaneous neurofibromas) and, in 30-50% of patients, tumours develop on the nerve sheaths (PNs).[4,11] These PNs can cause clinical issues such as disfigurement, motor dysfunction, pain, airway dysfunction, visual impairment and bladder or bowel dysfunction.[4-8] PNs begin during early childhood, with varying degrees of severity, and can reduce life expectancy by up to 15 years.[5,8,11,12]

KOMET
KOMET is a global Phase III randomised, double-blind, placebo-controlled, multicentre trial designed to evaluate the efficacy and safety of *Koselugo* in adults with NF1 who have symptomatic, inoperable PNs. The trial enrolled 145 adults from 13 countries across North America, South America, Europe, Asia and Australia, with participants' baseline characteristics, including gender and distribution of PNs, reflective of the global adult NF1 patient population. Patients were enrolled and randomised to receive *Koselugo* or placebo (1:1) for 12 28-day cycles. Participants were required to have diagnosis of NF1, at least one symptomatic, inoperable PN measurable by volumetric MRI analysis, chronic PN pain score documented during screening, adequate organ and marrow function and stable chronic PN pain medication use at enrolment.[13]

The primary endpoint is confirmed ORR by cycle 16 as assessed by ICR. ORR is defined as the percentage of patients with confirmed complete response (disappearance of PNs) or partial response (at least 20% reduction in tumour volume).[13]

After 12 cycles, patients on placebo were switched to *Koselugo* and patients on *Koselugo* remained on treatment for an additional 12 cycles. Patients who had the opportunity to complete 24 cycles of treatment have the option to participate in a long-term extension period and continue to receive *Koselugo*.[13]

Koselugo
Koselugo (selumetinib) is a kinase inhibitor that blocks specific enzymes (MEK1 and MEK2), which are involved in stimulating cells to grow. In NF1, these enzymes are overactive, causing tumour cells to grow in an unregulated way creating so-called plexiform neurofibromas (PN). By blocking these enzymes, *Koselugo* slows down the growth of tumour cells and, therefore, the PN growth.

Koselugo is approved in the US, EU, Japan, China and other countries and has been granted Orphan Drug Designation in the US, EU, Japan and other countries for the treatment of certain paediatric patients with NF1 who have symptomatic, inoperable PN.

AstraZeneca and MSD Strategic Collaboration
In July 2017, AstraZeneca and Merck & Co., Inc., Rahway, NJ, US, known as MSD outside the US and Canada, announced a global strategic collaboration to co-develop and co-commercialise *Lynparza* (olaparib), a first-in-class PARP inhibitor, and *Koselugo*. Working together, the companies will develop *Lynparza* and *Koselugo* in combination with other potential new medicines and as monotherapies.

Alexion
Alexion, AstraZeneca Rare Disease, is focused on serving patients and families affected by rare diseases and devastating conditions through the discovery, development and delivery of life-changing medicines. A pioneering leader in rare disease for more than three decades, Alexion was the first to translate the complex biology of the complement system into transformative medicines, and today it continues to build a diversified pipeline across disease areas with significant unmet need, using an array of innovative modalities. As part of AstraZeneca, Alexion is continually expanding its global geographic footprint to serve more rare disease patients around the world. It is headquartered in Boston, US.

AstraZeneca
AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca's innovative medicines are sold in more than 125 countries and used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on social media @AstraZeneca

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References

1. Evans DG, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. *Am J Med Genet A.* 2010;152A(2):327-332.
2. Ejerskov C, et al. Clinical characteristics and management of children and adults with neurofibromatosis type 1 and plexiform neurofibromas in Denmark: a nationwide study. *Oncol Ther.* 2023;11(1):97-110.
3. Tamura R. Current understanding of neurofibromatosis type 1, 2, and schwannomatosis. *Int J Mol Sci*. 2021;22(11):5850.
4. Gross AM, et al. Selumetinib in children with inoperable plexiform neurofibromas. *N Engl J Med.* 2020;382(15):1430-1442.
5. Hirbe AC, et al. Neurofibromatosis type 1: a multidisciplinary approach to care. *Lancet Neurol*. 2014;13:834-843.
6. Dombi E, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. *N Engl J Med.* 2016;375:2550-2560.
7. Mayo Clinic. Neurofibromatosis. Available here. Accessed November 2024.
8. National Health Service. Neurofibromatosis type 1, symptoms. Available here. Accessed November 2024.
9. Cancer.Net. Neurofibromatosis type 1. Available here. Accessed November 2024.
10. National Human Genome Research Institute. About neurofibromatosis. Available here. Accessed November 2024.
11. National Institute of Neurological Disorders and Stroke. Neurofibromatosis. Available here. Accessed November 2024.
12. Evans DGR, et al. Reduced life expectancy seen in hereditary diseases which predispose to early-onset tumors. *Appl Clin Genet.* 2013;6:53-61.
13. ClinicalTrials.gov. Efficacy and safety of selumetinib in adults with NF1 who have symptomatic, inoperable plexiform neurofibromas (KOMET). NCT Identifier: NCT04924608. Available here. Accessed November 2024.

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