DOI: 10.1002/msp2.70020

Malignancy Spectrum

LETTER TO THE EDITOR

Mirdametinib (Gomekli) wins FDA approval, bringing relief to NF-1 patients with surgically inoperable plexiform neurofibromatosis worldwide

Dear Editor,

Neurofibromatosis type 1 (NF-1) is an autosomal dominant, complex multi-system disorder that primarily affects the skin and nervous system. It is characterized by mutations in the *NF1* gene on chromosome 17, leading to abnormal production of neurofibromin protein. Common symptoms include café au lait spots, Lisch nodules, neurofibromas, plexiform neurofibromas, scoliosis, vision disorders, and learning and mental disabilities [1]. Managing NF-1 can be challenging because it is a lifelong disorder in which chronic pain is a prominent feature; consequently, opioids are prescribed and somnolence is frequently reported. Surgical interventions to remove tumors can also result in long-term physical impairments [2]. In recent years, new treatments like Selumetinib (Koselugo) have been approved. However, its effectiveness is mainly limited to children, and it can cause adverse effects like vomiting, raised creatinine phosphokinase, dry skin, and diarrhea [3]. A new development is the U.S. Food and Drug Administration's (FDA) approval on February 11, 2025 of mirdametinib (Gomekli), a mitogen-activated protein kinase kinase (MEK) inhibitor, for the treatment of adults and pediatric patients aged 2 years and older with NF-1-associated surgically inoperable plexiform neurofibromas. [4].

Loss of neurofibromin protein in NF-1 patients causes Ras signaling dysregulation. This results in MEK hyperactivation, driving uncontrolled cell growth and tumor formation. Mirdametinib, a specific non-competitive MEK inhibitor (MEKi), blocks MEK activity, reducing hyperactivation of Ras and shrinkage of surgically inoperable plexiform neurofibromatosis. A Phase II trial assessed the safety and efficacy of mirdametinib in adolescents and adults of age ≥ 16 years with *NF1*-related plexiform neurofibromas. The results showed that mirdametinib is well-tolerated and effective, with a 42% partial response rate and at least 20% tumor shrinkage by volume [5].

The ReNeu trial, a pivotal Phase IIb study, evaluated the efficacy of mirdametinib in 114 patients. The results demonstrated a substantial confirmed objective response rate, durable reductions in plexiform neurofibromas volume, and clinically meaningful improvements in pain and health-related quality of life [6]. Crucially, mirdametinib stands out as a treatment distinct from traditional approaches like selumetinib, as it has been proved to be effective in the treatment for both children and adults.

Although mirdametinib represents a breakthrough for plexiform neurofibromas in NF-1, it carries a broad side-effect profile. Most commonly, cutaneous toxicities, including acneiform rash, eczema, seborrheic dermatitis, paronychia, and xerosis, have been reported [7], along with fatigue, profound changes in bile acid metabolism leading to nausea, vomiting, diarrhea [8], as well as MEKi-associated retinopathy [9].

Mirdametinib is specifically designed for the treatment of NF-1 pediatric and adult patients, aged 2 years and above, who are affected by surgically inoperable plexiform neurofibromas. In a study, mirdametinib has been shown to amplify the effectiveness of radiotherapy in treating tumors associated with *NF1* deficiency, particularly in low-grade gliomas and, to lesser extent, high-grade gliomas [10]. Furthermore, a groundbreaking study reveals that mirdametinib can disrupt and weaken fear memories when combined with memory destabilization techniques. This breakthrough suggests that mirdametinib holds potential as a novel treatment for posttraumatic stress disorders [11]. Another study revealed that mirdametinib shows promise in developing new treatments for acute kidney injury in patients undergoing chemotherapy with cisplatin [12].

AUTHOR CONTRIBUTIONS

Memuna J. Zeb: Protocol development, manuscript writing, and final editing.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
© 2025 The Author(s). *Malignancy Spectrum* published by John Wiley & Sons Australia, Ltd on behalf of Higher Education Press.

ACKNOWLEDGMENTS
The author has nothing to report.

CONFLICT OF INTEREST STATEMENT
The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT
The author has nothing to report.

ETHICS STATEMENT
The author has nothing to report.

Memuna J. Zeb

Department of Medicine,
Ayub Medical College, Abbottabad, Pakistan

Correspondence
Memuna J. Zeb, Department of Medicine, Ayub Medical College, Main Mansehra Rd., Abbottabad, Khyber Pakhtunkhwa 22040, Pakistan.
Email: memunajehanzeb@gmail.com

REFERENCES
1. Miller DT, Freedenberg D, Schorry E, et al. Health supervision for children with neurofibromatosis type 1. *Pediatrics*. 2019; 143(5):e20190660.
2. Buono FD, Grau LE, Sprong ME, Morford KL, Johnson KJ, Gutmann DH. Pain symptomology, functional impact, and treatment of people with neurofibromatosis type 1. *J Pain Res*. 2019;12:2555-2561.
3. *Canadian Agency for Drugs and Technologies in Health*. CADTH Reimbursement Recommendation. 2023.
4. U.S. Food and Drug Administration. FDA Approves Mirdametinib for Adult and Pediatric Patients With Neurofibromatosis Type 1 who have symptomatic plexiform neurofibromas not amenable to complete resection. Accessed February 21 2025.
5. Weiss BD, Wolters PL, Plotkin SR, et al. NF106: a neurofibromatosis clinical trials consortium phase II trial of the MEK inhibitor mirdametinib (PD-0325901) in adolescents and adults with NF1-related plexiform neurofibromas. *J Clin Oncol*. 2021; 39(7):797-806.
6. Moertel CL, Hirbe AC, Shuhaiber HH, et al. ReNeu: a pivotal, phase IIb trial of mirdametinib in adults and children with symptomatic neurofibromatosis type 1-associated plexiform neurofibroma. *J Clin Oncol*. 2025;43(6):716-729.
7. Peacock BC, Tripathy S, Hanania HL, Wang HY, Sadighi Z, Patel AB. Cutaneous toxicities of mitogen-activated protein kinase inhibitors in children and young adults with neurofibromatosis-1. *JNO*. 2024;167(3):515-522.
8. Verzijl CRC, van de Peppel IP, Eilers RE, et al. Pharmacological inhibition of MEK1/2 signaling disrupts bile acid metabolism through loss of *Shp* and enhanced *Cyp7a1* expression. *Biomed Pharmacother*. 2023;159:114270.
9. Hummel L, Ameri M, Alqahtani S, Sadighi Z, Al-Zubidi N. Incidence of ophthalmological complications in NF-1 patients treated with MEK inhibitors. *Curr Oncol*. 2024;31(5):2644-2649.
10. Ioannou M, Lalwani K, Ayanlaja AA, Chinnasamy V, Pratilas CA, Schreck KC. MEK inhibition enhances the antitumor effect of radiotherapy in *NF1*-deficient glioblastoma. *Mol Cancer Ther*. 2024;23(9):1261-1272.
11. Raut SB, Joly F, Haass NK, et al. The clinically relevant MEK inhibitor mirdametinib combined with D-cycloserine and prediction error disrupts fear memory in PTSD models. *Transl Psychiatry*. 2024;14(1):492.
12. Suman I, Šimić L, Čanadi Jurešić G, Buljević S, Klepac D, Domitrović R. The interplay of mitophagy, autophagy, and apoptosis in cisplatin-induced kidney injury: involvement of ERK signaling pathway. *Cell Death Discov*. 2024; 10(1):98.