Letter

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Vimseltinib: A novel colony stimulating factor 1 receptor (CSF1R) inhibitor approved for treatment of tenosynovial giant cell tumors (TGCTs)

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SUMMARY: A tenosynovial giant cell tumor (TGCT) is a rare benign neoplasm arising from the tendon sheaths, bursae, or synovial lining of joints and is characterized by locally aggressive growth and the potential for recurrent disease. Surgery is still the main form of treatment for a TGCT, but these neoplasms, and most notably the diffuse type, exhibit a high proclivity for recurrence, thus highlighting the unmet clinical need for novel therapeutic modalities. At the same time, a subgroup of patients deemed ineligible for surgery are confronted with limited therapeutic alternatives, further underscoring the urgent need for innovative treatment paradigms. On February 14, 2025, the US Food and Drug Administration approved a new colony-stimulating factor 1 receptor (CSF1R) inhibitor, vimseltinib, for the treatment of symptomatic TGCTs in adult patients for whom surgical resection would likely result in severe functional limitations or serious complications. As the second-in-class CSF1R inhibitor approved for TGCTs, vimseltinib exhibits enhanced selectivity for CSF1R over pexidartinib, the first-in-class agent, suggesting potential translational benefits in safety profiles. The clinical utility of vimseltinib is anticipated to be further elucidated by real-world evidence and expanded clinical evaluations.

Keywords: CSF1R, TGCT, pexidartinib, vimseltinib, hepatotoxicity

A tenosynovial giant cell tumor (TGCT) is a non-malignant neoplasm originating from the tendon sheath of joints, bursae, or joint synovia (*1*). TGCT is a rare disease, with the highest incidence occurring in individuals ages 25 to 50, at a rate of approximately 43 per 1 million people (*2,3*). TGCT is classified into two types: localized and diffuse. The growth of the tumor can damage surrounding tissues and structures, causing pain, swelling, and restricted joint movement. Surgery is the primary treatment for TGCT, but recurrence is common, and especially in patients with the diffuse type (*3*). Persistent recurrence can lead to joint and surrounding tissue damage and degeneration, potentially resulting in severe disability. For a small subset of TGCT patients who are not eligible for surgery, therapeutic options are very limited, highlighting an urgent need for new treatment strategies.

On February 14, 2025, the US Food and Drug Administration approved a new colony stimulating factor 1 receptor (CSF1R) inhibitor, vimseltinib, for the treatment of symptomatic TGCTs in adult patients for whom surgical resection would likely result in severe functional limitations or serious complications (*4*). Due to chromosomal translocation, TGCT cells overexpress the *CSF1* gene, leading to excessive production of CSF1 (*5*). This protein recruits CSF1R-expressing cells, such as macrophages and other inflammatory cells, that make up the bulk of a TGCT (*1*). CSF1R inhibitors suppress CSF1R kinase activity, reducing the recruitment and activation of macrophages (*1*). By blocking downstream signaling pathways, these inhibitors suppress tumor cell proliferation, survival, and migration while inducing tumor cell apoptosis. The first CSF1R inhibitor, pexidartinib, was approved in 2019 for the treatment of TGCT and it exhibited significant antitumor activity with an overall response rate (ORR) of 38%, including a complete response rate of 15% and a partial response rate of 23% (*6*). However, its potential hepatotoxicity has limited its clinical use (*7*). In terms of specificity, pexidartinib inhibits not only CSF1R but also other tyrosine kinase receptors, such as FLT3, KIT, and PDGFR (*7*). In contrast, vimseltinib is a more selective CSF1R inhibitor, possibly leading to a better safety profile with fewer adverse reactions (*7*).

The results of a multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial (MOTION, NCT05059262) showed that the drug vimseltinib demonstrated significant efficacy in

patients with TGCTs for whom surgical resection may have caused worsening functional limitation or severe morbidity (*8*). After patients received oral administration of vimseltinib at a dose of 30 mg twice a week during a 24-week treatment cycle, the ORR reached 40% (*8*). Of the patients, 85% of responders had a duration of response (DOR) of ≥ 6 months, and 58% of responders had a DOR of ≥ 9 months (*8*). At the 25-week assessment, the vimseltinib group had statistically significant improvements in functional outcomes compared to the placebo group (*8*). The most common adverse reactions are increased aspartate aminotransferase, periorbital edema, fatigue, rash, increased cholesterol, peripheral edema, facial edema, decreased neutrophils, decreased leukocytes, pruritus, and increased alanine aminotransferase (*4,8*).

Currently, multiple small molecule inhibitors targeting the CSF1R are in the clinical development stage, and some of them have entered phase III clinical trials, where they have demonstrated encouraging efficacy. For example, pimicotinib resulted in an overall response rate of 68% in patients with TGCTs in initial clinical trials (*9*). Meanwhile, antibody drugs targeting CSF1R (such as emactuzumab and cabiralizumab) are also undergoing clinical trials (*1*). A point worth noting is that the clinical value of these drugs has gone beyond the field of oncology, and exploratory studies in fields such as inflammatory diseases and bone-related diseases are underway. With the in-depth development of translational medicine research, these drugs are expected to achieve breakthroughs in precision treatment in multiple fields and provide innovative solutions for more refractory diseases.

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References

1. Benner B, Good L, Quiroga D, Schultz TE, Kassem M, Carson WE, Cherian MA, Sardesai S, Wesolowski R. Pexidartinib, a novel small molecule CSF-1R inhibitor in use for tenosynovial giant cell tumor: A systematic review of pre-clinical and clinical development. Drug Des Devel Ther. 2020; 14:1693-1704.
2. Ehrenstein V, Andersen SL, Qazi I, Sankar N, Pedersen AB, Sikorski R, Acquavella JF. Tenosynovial giant cell tumor: Incidence, prevalence, patient characteristics, and recurrence. A registry-based cohort study in Denmark. J Rheumatol. 2017; 44:1476-1483.
3. National Organization for Rare Disorders. Tenosynovial giant cell tumor. *https://rarediseases.org/rare-diseases/tenosynovial-giant-cell-tumor/#affected* (accessed February 21, 2025).
4. US Food and Drug Administration. FDA approves vimseltinib for symptomatic tenosynovial giant cell tumor. *https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-vimseltinib-symptomatic-tenosynovial-giant-cell-tumor* (accessed February 23, 2025).
5. van IDGP, Matusiak M, Charville GW, *et al*. Interactions in CSF1-driven tenosynovial giant cell tumors. Clin Cancer Res. 2022; 28:4934-4946.
6. US Food and Drug Administration. FDA approves pexidartinib for tenosynovial giant cell tumor. *https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pexidartinib-tenosynovial-giant-cell-tumor* (accessed February 28, 2025).
7. Caldwell TM, Ahn YM, Bulfer SL, Leary CB, Hood MM, Lu WP, Vogeti L, Vogeti S, Kaufman MD, Wise SC, Le Bourdonnec B, Smith BD, Flynn DL. Discovery of vimseltinib (DCC-3014), a highly selective CSF1R switch-control kinase inhibitor, in clinical development for the treatment of Tenosynovial Giant Cell Tumor (TGCT). Bioorg Med Chem Lett. 2022; 74:128928.
8. Gelderblom H, Bhadri V, Stacchiotti S, *et al*. Vimseltinib versus placebo for tenosynovial giant cell tumour (MOTION): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024; 403:2709-2719.
9. Abbisko News. Abbisko therapeutics obtained approval from U.S. FDA for pivotal global multi-center phase III clinical trial of CSF-1R inhibitor pimicotinib (ABSK021). *https://www.abbisko.com/newsDetail/135.html* (accessed February 28, 2025).

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