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Nirogacestat in Desmoid Tumor Management: Painful to Painless?

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Dear Editor,

Desmoid tumors are comparatively rare, locally aggressive, and nonmetastatic tumors leading to significant morbidity in the patient but rarely leading to death. Local aggressiveness of the tumor can lead to a variety of symptoms like pain, bowel obstruction, functional impairment, nerve damage, and perforation of the bowel. Management of desmoid tumors is difficult owing to variable presentation and unpredictable course of the disease, with 20 to 30% cases showing spontaneous regression. Hence, the management of desmoid tumors ranges from active surveillance to surgery, tyrosine kinase inhibitors (TKIs), and radiation therapy with no fixed modality of treatment as it varies depending on the location of tumor and the symptoms of the patient.[1]

Nirogacestat, which has been recently approved by the Food and Drug Administration (FDA) on November 27, 2023,[2] is a promising drug that holds immense potential in fighting desmoid tumors. It is the first-ever approved drug for desmoid tumors.[2] Nirogacestat was initially developed for Alzheimer's disease but later on was proved to be effective in desmoid tumors.[3]

Nirogacestat (brand name: OGSIVEO)[4] is an oral, selective, small molecule gamma secretase inhibitor that blocks prophylactic activation of Notch receptor. A Notch receptor, when dysregulated, can activate pathways that contribute to tumor growth.

This approval was based on the DeFi trial.[5] Studies demonstrated that patients with desmoid tumors have genetic mutations in Wnt–adenomatous polyposis coli–β-catenin pathway (*CTNNB1* and *APC*). In addition, desmoid tumors overexpress Notch1, which is responsible for progression of these tumors, which can thus be regulated with the help of gamma secretase inhibitors, through selective inhibition of gamma secretase–mediated cleavage of Notch receptors.

The DeFi trial is a phase 3, international, double-blind, randomized and placebo-controlled trial with an aim to determine the safety as well as efficacy of nirogacestat in adult patients of histologically proven progressive desmoid tumor. A total of 141 patients were randomized in 1:1 ratio to placebo versus nirogacestat (150 mg) twice daily continuously in 28-day cycles. The primary endpoint was progression-free survival. Imaging-based progression was determined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1. Secondary endpoints were objective response, quality of life, physical functioning, and role functioning. The median duration of exposure to nirogacestat was 20.6 versus 11.4 months for placebo. Adverse events included diarrhea, nausea, maculopapular rash, fatigue, hypophosphatemia, stomatitis, headache, dermatitis acneiform, and vomiting. Ninety-five percent of the adverse events were either grade 1 or 2. Dose reduction due to adverse events was seen in 42% patients receiving nirogacestat. Ovarian dysfunction was seen in 27 out of 36 women of childbearing age. However, 74% patients had resolution of symptoms.[5] It was observed that at cycle 10, nirogacestat showed significant benefits over placebo in terms of pain, symptom severity related to the disease, and physical functioning. Forty-one percent of patients in the nirogacestat group showed objective response, whereas only 8% in the placebo group showed the same. Complete response was seen in 7% in the nirogacestat group and was not seen in the placebo group.[5]

Gamma secretase cleaves multiple transmembrane proteins, including Notch, that are believed to play a role in activating pathways that contribute to the growth of desmoid and ovarian granulosa cell tumors. Therefore, in another phase 2 trial, the role of nirogacestat in the management of ovarian granulosa tumor is being evaluated at present. In addition, nirogacestat's usefulness in the management of multiple myeloma is being observed in preclinical models.[4]

Currently, nirogacestat is recommended for those patients who are inoperable or have been refractory to at least one line

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of therapy. The recommended dosage is 150 mg twice daily till disease progression or unacceptable toxicity. Based on the findings of animal studies, nirogacestat can cause fetal harm and hence it is not recommended in pregnancy at present. Females and males of reproductive potential are advised to use effective contraception during treatment with nirogacestat. Adverse events including ovarian dysfunction have been observed in females of reproductive age group, which was reversed on discontinuation of therapy.[6]

Another randomized trial with the drug AL102, another gamma secretase inhibitor, is enrolling patients with advanced desmoid tumors.[3]

For dose and prescription information of nirogacestat, see U.S. FDA.[6]

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Conflict of Interest
None declared.

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