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Positive Quality Intervention: Nirogacestat (OGSIVEO®) use in Management of Adults with Progressing Desmoid Tumors (or fibromatosis or aggressive fibromatosis)

Description: This PQI will discuss the initiation and management of adult patients with desmoid tumors (DT) with nirogacestat (OGSIVEO®).

Background: Nirogacestat (OGSIVEO®) is an oral targeted gamma secretase inhibitor indicated for adult patients with progressing desmoid tumors who require systemic treatment.[1] Desmoid tumors are rare, non-cancerous, locally aggressive tumors. They may occur in any anatomical location, and, while affecting all ages, often occur in people 20-30 years old. [2,3] Inhibition of gamma secretase prevents activation of the notch receptor and downstream effects that may contribute to desmoid tumor growth. Nirogacestat is recommended by the National Comprehensive Cancer Network® (NCCN®) as a category 1, preferred systemic therapy option for patients with desmoid tumors (aggressive fibromatosis).[2]
The efficacy and safety of nirogacestat were demonstrated through enrollment in the DeFi study. DeFi was a phase 3 international, multicenter, double-blind, randomized (1:1), placebo-controlled trial of nirogacestat in 142 adults with progressing (≥20%) desmoid tumors (DT) per RECIST version 1.1 criteria within 12 months prior to treatment initiation. Patients were randomized to oral nirogacestat (150 mg) or placebo twice daily, taken continuously in 28-day cycles until disease progression or unacceptable toxicity. Nirogacestat demonstrated a statistically significant improvement in the primary endpoint, progression-free survival (PFS), with 71% reduction in the risk of disease progression compared to placebo (hazard ratio = 0.29 [95% CI: 0.15, 0.55]; P<0.001). The PFS benefit was shown across patients who received prior therapy with tyrosine kinase inhibitors or chemotherapy. In addition, nirogacestat resulted in a statistically significant improvement in the secondary endpoint of objective response rate (ORR; 41%, n=29 [95% CI, 29.8, 53.8] vs 8%, n=6, [95% CI, 3.1, 17.3], respectively; P<0.001). At Cycle 10, nirogacestat demonstrated statistically significant and clinically meaningful improvement in all prespecified assessments of patient-reported outcomes of pain, DT-specific symptom burden, physical functioning, role functioning (P<0.001), and overall quality of life (P≤0.01).[4]
The most common (≥ 15%) adverse reactions experienced by patients who received nirogacestat were diarrhea, ovarian toxicity, rash, nausea, fatigue, stomatitis, headache, abdominal pain, cough, alopecia, upper respiratory tract infection, and dyspnea. Most (95%) adverse events were Grade 1 or 2 in patients treated with nirogacestat. Laboratory abnormalities (≥15%) that worsened from baseline in patients who received nirogacestat in DeFi were decreased phosphate, increased urine glucose, increased urine protein, increased AST, increased ALT, and decreased potassium. Overall, investigators identified ovarian toxicity events in 27 of 36 (75%) females of reproductive potential on nirogacestat, based on abnormal reproductive hormone levels and/or presence of peri-menopausal symptoms (e.g., changes in menstrual cycle regularity). However, investigators reported that ovarian toxicity resolved in 71% (10/14) while receiving nirogacestat and in 100% (11/11) after stopping nirogacestat for any reason (excluding 2 patients for whom follow-up data were not available).[5]

PQI Process: Upon receiving prescription for nirogacestat (OGSIVEO®)[1]

- Confirm diagnosis of a patient with progressing DT who requires systemic treatment
- Verify dose – the recommended dosage is 150 mg by mouth BID administered orally until disease progression or unacceptable toxicity
    - Available tablet strengths:
        - 50 mg (180-count bottle)
        - 100 mg (14-count blister pack)
        - 150 mg (14-count blister pack)
- Dose modifications for adverse reactions
    - The recommended dose modifications for nirogacestat for selected severe adverse reactions are

summarized in Table 1[1]
    - Dose reductions occurred in 42% with 20% of patients discontinuing therapy[4]
    - For other severe adverse reactions, life-threatening adverse reactions, or persistent intolerable Grade 2 adverse events, withhold drug until resolved to Grade ≤ 1 or baseline[1]
    - Only restart at a dose of 100 mg twice daily after considering the potential benefit and likelihood of recurrence of the adverse reaction[1]
    - Permanently discontinue nirogacestat for recurrence of severe or life-threatening adverse reaction upon rechallenge at the reduced dose[1]
    - Dermatologic adverse events, such as maculopapular rashes, may commonly develop. One study on the use of a gamma secretase inhibitor reported resolution of rash within 3 to 4 weeks of discontinuation.[6] Consult a provider to discuss dose modifications in the event of rash development.

Table 1. Recommended Dose Modifications for Adverse Reactions[1]

Adverse Reaction	Severity	Nirogacestat Dosage Modifications
Diarrhea persisting for ≥ 3 days despite maximal medical therapy	Grades 3 or 4	Withhold nirogacestat until resolved to Grade ≤ 1 or baseline, then restart at a dose of 100 mg twice daily
ALT or AST increased	Grade 2 (≥ 3 to 5 × ULN)	Withhold nirogacestat until ALT, AST, or both are resolved to < 3 × ULN or baseline, then restart at a dose of 100 mg twice daily
	Grades 3 or 4 (> 5 × ULN)	Permanently discontinue
Hypophosphatemia persisting for ≥ 3 days despite maximal replacement therapy	Grades 3 or 4	Withhold nirogacestat until resolved to Grade ≤ 1 or baseline, then restart at a dose of 100 mg twice daily
Hypokalemia despite maximal replacement therapy	Grades 3 or 4	Withhold nirogacestat until resolved to Grade ≤ 1 or baseline, then restart at a dose of 100 mg twice daily

- Monitoring[1]
    - Diarrhea: Monitor patients and manage symptoms with antidiarrheal medications, loperamide or diphenoxylate/atropine; modify dose as recommended. Check serum phosphorus and replace if low. Median time to onset of first event was 9 days (range 2 to 434 days)
    - Ovarian Toxicity: Discuss fertility preservation in women of childbearing potential. Check baseline reproductive hormone levels (anti-Mullerian hormone, FSH, LH, estradiol), and monitor periodically during treatment. Monitor females who can become pregnant for changes in menstrual cycle regularity or the development of symptoms of estrogen deficiency, including hot flashes, night sweats, and vaginal dryness
    - Hepatotoxicity: Monitor liver function tests regularly before and routinely during treatment and modify dose as recommended
    - Non-melanoma Skin Cancers: Perform dermatologic evaluations prior to initiation of nirogacestat and routinely during treatment
    - Electrolyte Abnormalities: Monitor phosphate and potassium levels regularly, and for symptoms of muscle pain or weakness; supplement as necessary; modify dose as recommended
    - Embryo-fetal Toxicity: Advise females and males of reproductive potential to use effective contraception during treatment with nirogacestat and for 1 week after the last dose
    - Lactation: Advise women not to breastfeed during treatment with nirogacestat and for 1 week after the last dose
    - Nasal congestion or allergic rhinitis symptoms such as postnasal drip and cough: No known treatment but nasal steroids anti-allergy/inflammatory or nasal rinses may relieve symptoms. Dose holds or decrease based on toxicity grade
- Screen for drug interactions

- Strong or moderate CYP3A inhibitors: Avoid concomitant use of nirogacestat with medications such as azoles and macrolides that are strong or moderate CYP3A inhibitors, as well as dietary considerations in avoiding grapefruit products, Seville oranges, and starfruit
- Strong or moderate CYP3A inducers: Avoid concomitant use of nirogacestat with strong or moderate CYP3A inducers such as rifampin or efavirenz
- In vitro studies indicate pharmacokinetic interactions without clinical significance with nirogacestat and other CYP enzymes and p-glycoprotein pathways. Confirm complete patient medication list and ensure comprehensive drug interaction checks
- Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors, H2 blockers, and antacids; if concomitant use cannot be avoided, stagger antacids 2 hours before or 2 hours after nirogacestat dose
- *For additional information about potential drug interactions with nirogacestat, see Table 4 (Section 7.1) and Table 5 (Section 7.2) of the Prescribing Information*

Patient-Centered Activities:[1]

- Patient Education
  - Provide Oral Chemotherapy Education (OCE) Sheet
  - Provide Treatment Support Kit (TSK)
  - Counsel patient should take their dose twice daily without regard to food and instructed to swallow tablets whole and not to break, crush, or chew prior to swallowing
  - If a patient vomits or misses a dose of nirogacestat, instruct the patient to take the next dose at its scheduled time
  - Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products
    - Patients should take nirogacestat 2 hours before or 2 hours after taking gastric reducing agents (e.g., omeprazole, famotidine, Tums, Mylanta, Rolaids, etc.)
    - Patients should avoid eating or drinking grapefruit products, Seville oranges, and starfruit during treatment with nirogacestat
  - Store nirogacestat tablets at room temperature
  - Advise females of reproductive potential to inform their healthcare provider
    - of a known or suspected pregnancy, and to stop taking nirogacestat if they become pregnant
    - use effective contraception during treatment with nirogacestat and for 1 week after the last dose
    - tell their healthcare provider if they experience hot flashes or menstrual irregularities
  - Advise males with female partners of reproductive potential to use effective contraception during treatment with nirogacestat and for 1 week after the last dose
  - Advise women not to breastfeed during treatment with nirogacestat and for 1 week after the last dose
- Monitor patient for diarrhea, ovarian toxicity, hepatoxicity, non-melanoma skin cancers, maculopapular rash, electrolyte abnormalities, embryo-fetal toxicity
- Patient Assistance - NCODA Financial Assistance Tool

References:

1. OGSIVEO®. Prescribing Information. SpringWorks Therapeutics, Inc.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.3.2023. ©National Comprehensive Cancer Network, Inc. 2023. Accessed December 12, 2023.
3. Alman B, Attia S, Baumgarten C, et al. The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients. European Journal of Cancer. 2020. 127: 96-107. Access April 5, 2023. https://www.sciencedirect.com/science/article/pii/S0959804919308329.
4. Gounder M, et al. Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors. *N Engl J Med*. 2023 Mar 9;388(10):898-912.
5. Loggers ET, Chugh R, Federman N, et al. Onset and resolution of ovarian toxicity with nirogacestat treatment in females with desmoid tumors: Updated safety analyses from the DeFi phase 3 study. *Cancer*. Published online May 4, 2024. doi:10.1002/cncr.35324.
6. Coric V, van Dyck CH, Salloway S, et al. Safety and tolerability of the γ-secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease. *Arch Neurol*. 2012;69(11):1430–1440. doi:10.1001/archneurol.2012.2194.