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Positive Quality Intervention (PQI): 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] Nirogacestat (OGSIVEO) is recommended by the National Comprehensive Cancer Network® (NCCN®) as an NCCN 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 (Nirogacestat for Adults with Desmoid Tumor/Aggressive Fibromatosis) is a phase 3 international, multicenter, double-blind, randomized (1:1), placebo-controlled trial of nirogacestat, in 142 adults with progressing desmoid tumors (DT) per RECIST version 1.1 criteria. Patients were randomized to oral nirogacestat (150 mg) or placebo twice daily, taken continuously in 28-day cycles until disease progression or unacceptable toxicity. The study statistically and clinically met all primary and key secondary efficacy endpoints. Nirogacestat demonstrated a statistically significant improvement in the primary endpoint, progression-free survival, 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). 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 (QoL) (P≤0.01). 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. Clinically relevant adverse reactions occurring in < 15% of patients receiving nirogacestat in DeFi included non-melanoma skin cancers, epistaxis, hidradenitis suppurativa, folliculitis, and influenza-like illness. 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 64% (9/14) 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).[3]

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 BID administered orally until disease progression or unacceptable toxicity (each 150 mg dose of nirogacestat consists of three 50 mg tablets)
    - Available tablet strength: 50 mg tablet: nirogacestat is supplied as orange, film-coated 50 mg tablets debossed with a “50” on one side
    - Dose modifications for adverse reactions
        - The recommended dose modifications for nirogacestat for selected severe adverse reactions are summarized in Table 1
        - 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
    - Only restart at a dose of 100 mg twice daily after considering the potential benefit and likelihood of recurrence of the adverse reaction
    - Permanently discontinue nirogacestat for recurrence of severe or life-threatening adverse reaction upon rechallenge at the reduced dose

Table 1. Recommended Dose Modifications for Adverse Reactions

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 using antidiarrheal medications; modify dose as recommended
        - Median time to first event 9 days (range 2 to 434 days)
    - Ovarian Toxicity: 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
- Screen for drug interactions
    - Strong or moderate CYP3A inhibitors: Avoid concomitant use of nirogacestat with strong or moderate CYP3A inhibitors, including grapefruit products, Seville oranges, and starfruit
    - Strong or moderate CYP3A inducers: Avoid concomitant use of nirogacestat with strong or moderate CYP3A inducers
    - Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors and H2 blockers; 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 OGSIVEO™ Prescribing Information*

Patient-Centered Activities:[1]

- Patient Education
  - Provide Oral Chemotherapy Education (OCE) Sheet – *Coming Soon*
  - 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 antacids (e.g., 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; also, advise females of reproductive potential to use effective contraception during treatment with nirogacestat and for 1 week after the last dose
  - 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, 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. Gounder M, et al. Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors. *N Engl J Med*. 2023 Mar 9;388(10):898-912.