Nirogacestat (OGSIVEO) in Desmoid Tumors
National Drug Mini-monograph
January 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Gamma secretase inhibitor
Indication Under Review[1]	Adult patients with progressing desmoid tumors who require systemic treatment
Dosage Regimen	150mg orally twice daily until disease progression or unacceptable toxicity
Dosage Forms Under Review	Oral tablets

EFFICACY CONSIDERATIONS

Trial	**DeFi (NCT03785964)**
Design	Phase 3, international, double-blind, randomized, placebo-controlled
Population	N=142; adult patients with progressing desmoid tumors not amenable to surgery and had not received previous treatment or had refractory or recurrent disease after ≥1 line of therapy (defined as ≥ 20% progression according to RECIST within 12 months before screening); Stratification by location of target tumor: intraabdominal vs. extraabdominal
Demographic (nirogacestat vs. placebo)	mAge 34 yrs (18-76); female 65% (childbearing potential 52%); no previous treatment 26 vs. 19%; Refractory or recurrent disease 74 vs. 82%; median LOT 2; systemic therapy 61%; sorafenib 24 vs. 25%; uncontrolled pain 39 vs. 43%
Intervention	150 mg nirogacestat or placebo orally twice daily in continuous 28-day cycles until disease progression or unacceptable toxicity

Results

Median follow-up for PFS at 15.9 months

	Nirogacestat (n=70)	**Placebo (n=72)**
# events	12	37
Median PFS (95% CI)	NR (NR, NR)	15.1 (8.4, NR)
HR (95% CI)	0.29 (95% CI, 0.15-0.55); p < 0.001	
ORR (%)	41	8
CR (%); PR (%)	7; 34	0; 8
P value	P < 0.001	
Patient reported outcomes (PRO)	At cycle #10 improvement with nirogacestat was noted: BPI-SF average worst pain intensity score (P<0.001) GODDESS DTSS total symptom score (P<0.001) GODDESS DTIS physical function score (P< 0.001) EORTC QLQ-C30 physical function score (P<0.001) EORTC QLQ-C30 role function score (P<0.001) EORTC QLQ-C30 quality of life score (P≤ 0.01)	

A forest plot of prespecified subgroups indicates that the point estimates favor nirogacetat in all groups; the confidence interval for those (1) with a family history of familial adenomatous polyposis (FAP) and those (2) with no previous treatment crossed the value of 1, which may indicate no difference exists.

SAFETY CONSIDERATIONS	
Boxed Warnings	None
Contraindications	None
Other Warnings	Diarrhea, ovarian toxicity, hepatotoxicity, electrolyte abnormalities, embryo-fetal toxicity
Top 5 AEs (all grade/ gr 3-4)	Diarrhea (84%; 16%), Ovarian toxicity (female reproductive function and fertility impaired; reversible upon dc) Hepatotoxicity (AST incr 30%; ALT incr 33%) Rash (68% 6%) Nausea (54%; 1.4%) Fatigue (54%; 2.9%)
Drug Interactions	Avoid strong or moderate CYP3A4 inducers and inhibitors, PPIs and H2 antagonists

PLACE IN THERAPY

DRUG	VANF	CFU	FDA	GUIDELINES, Etc.
Nirogacestat	NF	No	Approved	P2, nirogacestat vs. placebo in 142 patients with progressive desmoid tumors, mPFS NR vs. 15 months; ORR 41 vs. 8% UTD: nirogacestat preferred, TKIs are reasonable alternative, esp if ovarian dysfunction is to be avoided NCCN: preferred category 1 along with sorafenib VA STS pathway - Desmoid tumors, anatomic location with morbid progression: systemic therapy either sorafenib or nirogacestat dependent on symptoms and comorbidities
Sorafenib	PA-F	Yes, in HCC	No	P2, Sorafenib vs. placebo in 87 patients with progressive desmoid tumors, ORR 33 vs. 20%; 2-yr PFS 81 vs. 36%; no PRO data provided as disease specific tools were developed after this trial; AEs: rash 73%; fatigue 67%; htn 55%, diarrhea 51% NCCN: preferred category 1 along with nirogacestat VA STS pathway - Desmoid tumors, anatomic location with morbid progression: systemic therapy either sorafenib or nirogacestat dependent on symptoms and comorbidities
Pazopanib	NF	No	No	P2, pazopanib vs. MTX/vinblastine, @ median 23 months, PFS 84 vs. 45%; AEs: gr ¾ toxicities: htn 21%, diarrhea 15% vs. neutropenia 45%, liver transaminitis 18% NCCN: Preferred category 2A VA: not on pathway

VHA PLACE IN THERAPY		
	Potential Use in VHA	• Desmoid tumors are rare, slow growing, mesenchymal tumors that have no potential to metastasize. These tumors are locally invasive and can cause significant morbidity with great impact to physical/ psychosocial functioning and quality of life. • The clinical course of desmoid tumors is unpredictable; 20-30% of patients may spontaneously regress. • There are no approved therapies. Management depends on tumor location, symptoms, and progression; may involve surveillance, surgery, radiation, local ablation, cytotoxic chemotherapy, and tyrosine kinase inhibitor (TKI) therapy. If a rapid response is needed or oral absorption is compromised, cytotoxic chemotherapy may be preferred. 1. In this rare disease state, nirogacestat is the only FDA-approved therapy for progressive desmoid tumors, which was compared to placebo in a phase 2 trial. Evidence with TKIs similarly indicate that this class is also effective. Sorafenib was compared to placebo while pazopanib was compared to combination chemotherapy with MTX/vinblastine. 2. Compared to placebo, patients receiving nirogacestat experienced more adverse events, the majority being grade 1-2 toxicities. Ovarian toxicity, in terms of female reproductive function and fertility, may be impaired. Long-term impact has not been established. 3. Nirogacestat evidence includes patient-reported outcomes suggesting benefit in pain reduction, physical functioning, and quality of life. Of note, PROs were not provided by the sorafenib investigators. 4. Guidelines and VA pathway includes both nirogacestat and sorafenib as preferred therapies to be directed by patient symptoms, comorbidities, and toxicity profile. 5. Nirogacestat has not been compared to another effective drug that has longer track record (i.e. sorafenib) to demonstrate superiority.

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References

1. Nirogacestat (OGSIVEO) [prescribing information] SpringWorks Therapeutics, Inc. Stamford, CT; 2024
2. Gounder M, Ratan R, Alcindor T et al. Nirogacestat, a gamma-Secretase inhibitor for desmoid tumors. N Engl J Med. 2023; 388:898-912.
3. Gounder MM, et al. Sorafenib for advanced and refractory desmoid tumors. N Engl J Med 2018; 379: 2417.
4. Toulmonde M, et al. Pazopanib or methotrexate-vinblastine combination chemotherapy in adult patients with progressive desmoid tumours (DESMOPAZ): a non-comparative, randomised, open-label, multicentre, phase 2 study. Lancet Oncol. 2019;20(9):1263. Epub 2019 Jul 19.