CHALLENGING CASES

Desmoid Tumors

Prepared by: Cornerstone Specialty Network

Challenging Cases conducted: October 15, October 30, November 11, November 18, and December 2, 2025

Participating Practices

Challenging Cases in… Desmoid Tumors

Program conducted:

October–December 2025

Note: Aggregated results and high-level summary based on 5 practices (≤39 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of presentation.

- **Center for Cancer and Blood Disorders (n=11) October 15, 2025**
- **Advocate Health (n=9) October 30, 2025**
- **Mid-Florida Cancer Center (n=7) November 11, 2025**
- **Arizona Center for Cancer Care (n=4) November 18, 2025**
- **Atlantic Health System (n=8) December 2, 2025**

Overall Program Impact and Future Considerations

Community oncologists favor surgery for initial treatment of resectable extra-abdominal desmoid tumors, use nirogacestat for unresectable or progressing disease with proactive side-effect management through dose modification, refer cases to external sarcoma centers, and monitor progression with radiographic imaging and clinical exams; despite limited exposure nirogacestat viewed favorably and as a potential new standard of care for desmoid tumors

- **Front-line strategy:** Surgery when applicable is the standard of care for patients with an extra-abdominal tumor, often guided by multidisciplinary tumor boards; systemic therapy is used for unresectable or progressing tumors
- **Systemic therapy:** Nirogacestat recommended for unresectable disease; generally, well tolerated with dose adjustments to manage side-effects (diarrhea, nausea, stomatitis) as needed but limited use in the community setting with only 2 out of 5 practices having recently managed patients; some residual use of sorafenib due to timing of nirogacestat approval
- **Referral patterns:** Community oncologists often refer patients to specialized sarcoma centers for complex cases due to limited experience and lack of in-house surgeons
- **Monitoring:** Radiographic and clinical symptom and physical exams are the main strategies for monitoring time to response
- **Access and management:** Insurance approval can be challenging for long-term stable disease control on nirogacestat; individualized dosing and proactive side-effect management are key to staying on therapy
- ***Recommended actions:*** *Increase educational initiatives on side effect management of nirogacestat through Challenging Cases; initiate multidisciplinary meetings through CSN to support co-management of patients with desmoid tumors and increase adoption of nirogacestat for community providers with limited exposure*

Challenging Cases in… Desmoid tumor

Desmoid tumor
Patient case: progressing

- Desmoid tumors are ***rare***, low-grade, slow-growing, locally invasive, highly recurrent soft-tissue tumors
- Patients with desmoid tumors may face an ***unpredicatble*** clinical course; vital organs can be impacted
- Desmoid tumors are associated with a ***high symptom burden*** including pain, disfigurement, decreased quality of life and physical function

- ***What is the optimal treatment for progressing desmoid tumors?***

Patient History

32-year-old women

Presents with extra-abdominal 5 cm mass on the upper right neck

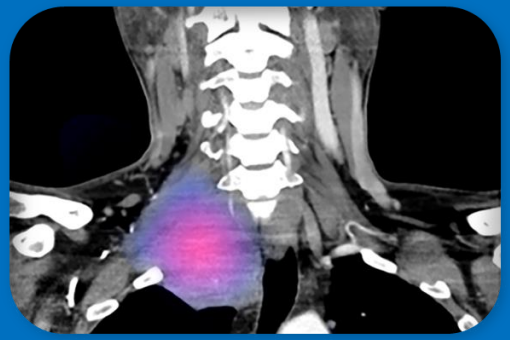
Blood work normal

Patient reported pain in the right arm and neck

Otherwise, healthy

Diagnosis

CT scan revealed tumor involving the brachial plexus



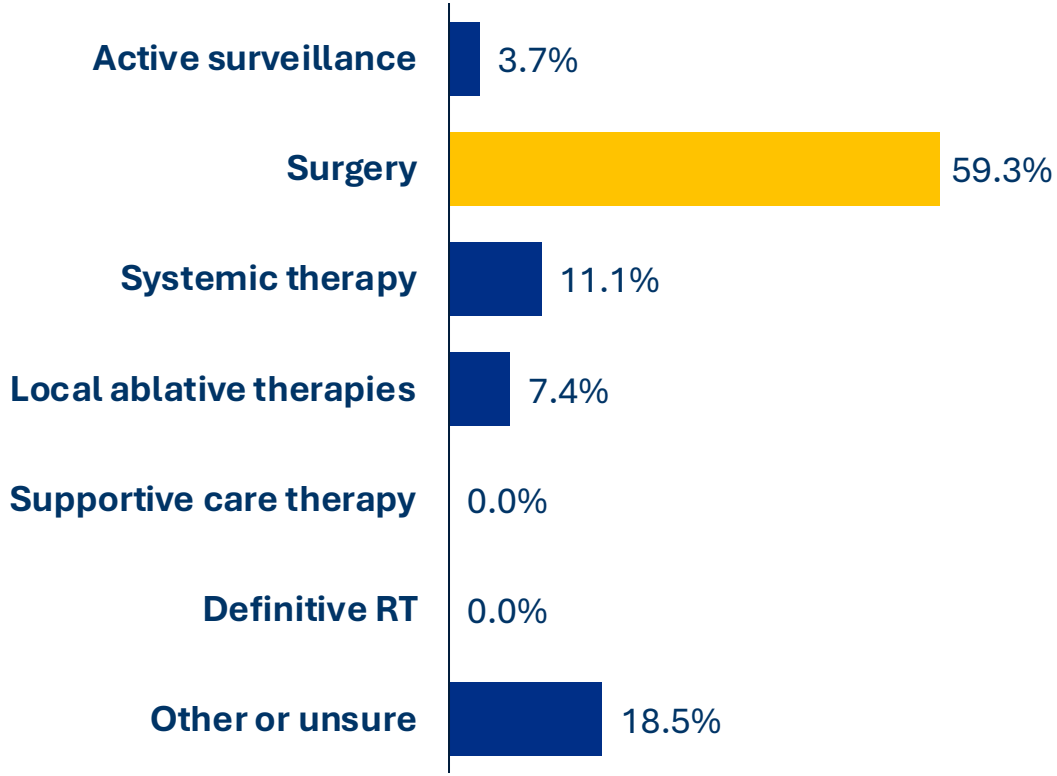
Core biopsy consistent with desmoid tumor with IHC beta catenin staining

What is your initial strategy for a patient with an extra-abdominal tumor?

Image adapted from Styring E et al. Am J Med Case Rep. 2019;7(3):36-40.

ARS Results from HCP Participants

What is your initial strategy for a patient with an extra-abdominal tumor?

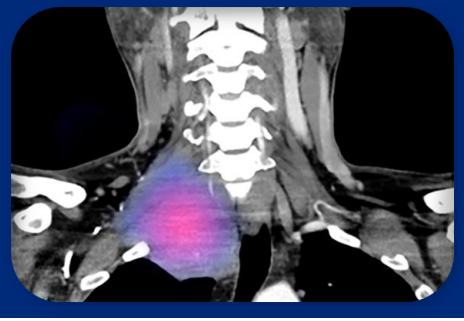


Answered: 27

Diagnosis

CT scan revealed desmoid tumor involving the brachial plexus (5 cm mass)

Patient reported manageable pain in the right arm and neck



Initial Strategy

Active surveillance

MRI at 3-6 month intervals

Mass increased in size to 10 cm within 1 year

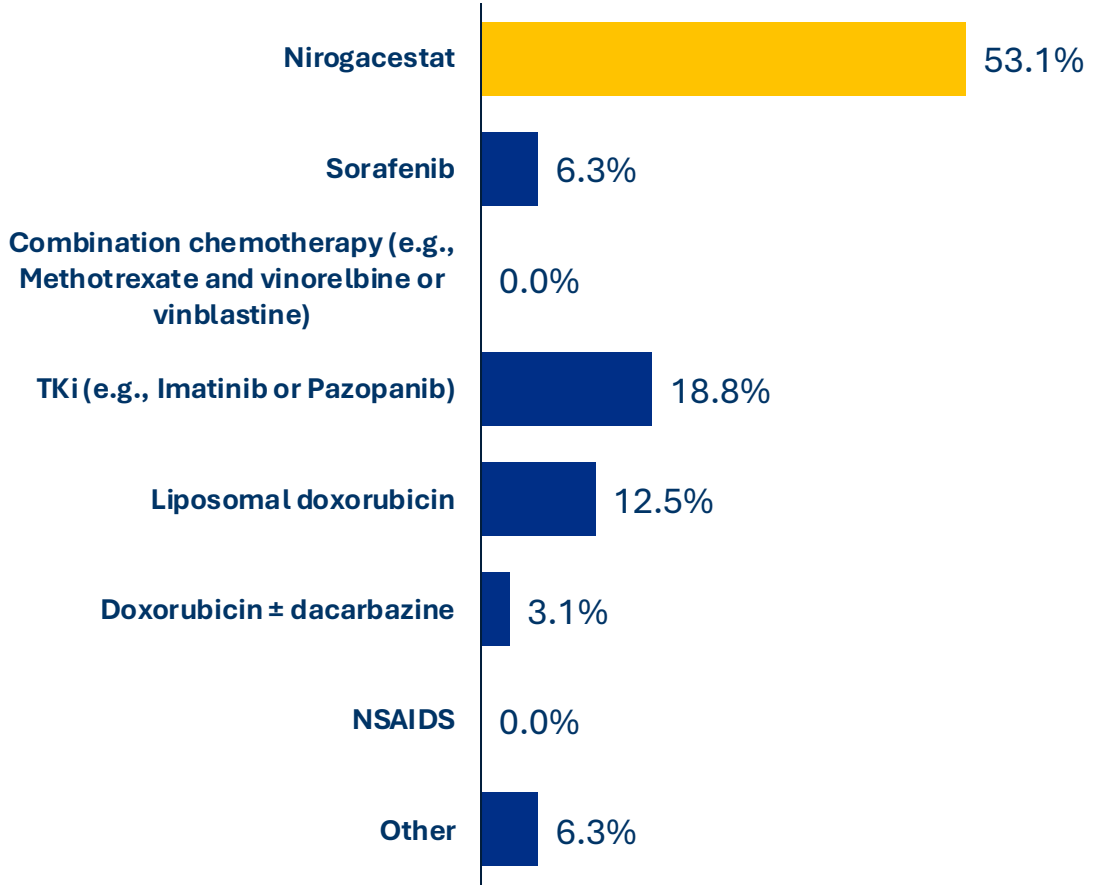
Patient experiencing increased pain, difficulty breathing, impacting use of dominant right arm

What is your initial systemic therapy recommendation with a progressing desmoid tumor not amenable to surgery?

Image adapted from Styring E et al. Am J Med Case Rep. 2019;7(3):36-40.

ARS Results from HCP Participants

What is your initial systemic therapy recommendation with a progressing desmoid tumor not amenable to surgery?



Answered: 32

How do you view the preferred category 1 regimens?

How does NCCN Guidelines impact your treatment decisions?
Practice pathways?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Soft Tissue Sarcoma

August 8, 2024

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES[d] AND AGGRESSIVE SOFT TISSUE NEOPLASMS

Desmoid Tumors (Aggressive Fibromatosis)[o]	Non-Pleomorphic Rhabdomyosarcoma
Preferred regimens • Nirogacestat (category 1)[46] • Sorafenib (category 1)[47] • Methotrexate and vinorelbine[48] • Methotrexate and vinblastine[49] • Imatinib[50,51] • Liposomal doxorubicin[52] • Doxorubicin ± dacarbazine[53-55] • Pazopanib[56] **Useful in certain circumstances** • Sulindac[57] or other nonsteroidal anti-inflammatory drugs (NSAIDs), including celecoxib (for pain)	**Preferred regimens** • Vincristine, dactinomycin, cyclophosphamide (VAC)[p,58] • Vincristine, dactinomycin, ifosfamide (VAI-Europe)[p,59] **Other recommended regimens** • Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide[60] • Vincristine, doxorubicin, cyclophosphamide[61] • Vincristine, doxorubicin, ifosfamide[62] • Cyclophosphamide and topotecan[63] • Ifosfamide and doxorubicin[64] • Ifosfamide and etoposide[65] • Irinotecan and vincristine[66,67] • Carboplatin and etoposide[68] • Vinorelbine and low-dose cyclophosphamide[j,69] • Vincristine, irinotecan, temozolomide[70] • Irinotecan[66,67,71] • Topotecan[72] • Vinorelbine[j,73] • Vinorelbine/cyclophosphamide/temsirolimus[74] **Useful in certain circumstances** • Maintenance chemotherapy (cyclophosphamide/vinorelbine) for patients with intermediate-risk RMS with complete response (CR) following treatment with VAC or VAI regimen (Please note: Children's Oncology Group [COG] has an active prospective ongoing study, but this is considered a reasonable standard of care)[69]

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FDA Approval

*On **November 27, 2023**, the FDA approved **nirogacestat** (**OGSIVEO**, SpringWorks Therapeutics, Inc.) for adult patients with **progressing desmoid tumors** who require systemic treatment based on response data from the **DeFi** trial.*

This is the first approved treatment for desmoid tumors.

How aware are you of the FDA approval of nirogacestat?

Does being the first and only FDA-approved treatment impact your treatment decision? Impact of NCCN Guidelines? Insurance?

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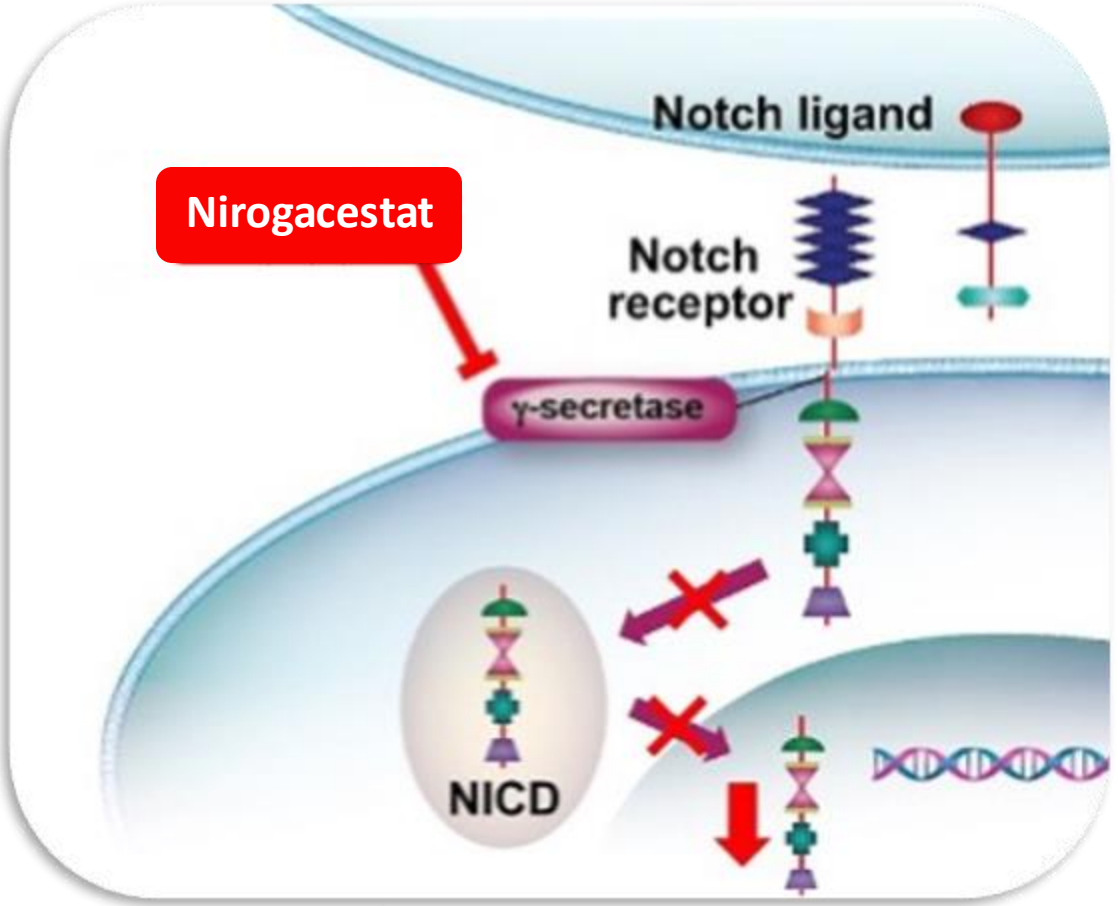
Nirogacestat (OGSIVEO) is a gamma secretase inhibitor, with a distinct mechanism of action

- **Desmoid tumors highly express Notch1**
- **γ-secretase inhibition prevents release of the Notch intracellular domain, which blocks Notch pathway signaling and cell growth**
- **Nirogacestat is thought to inhibit gamma secretase and block proteolytic activation of the Notch receptor**



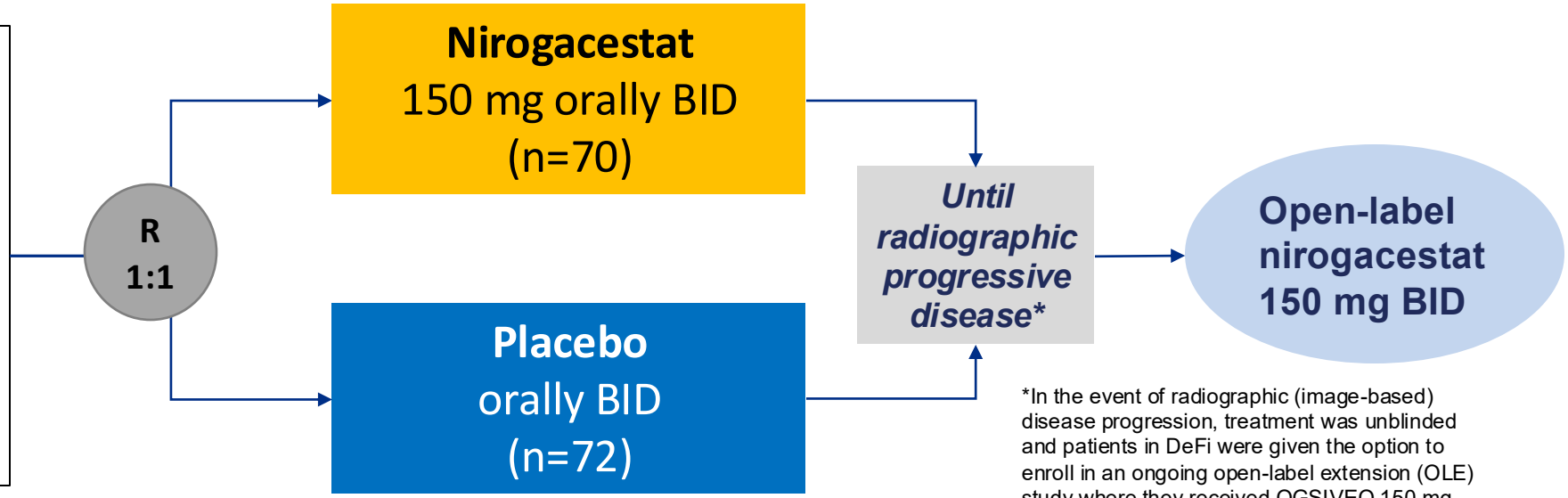
N Engl J Med 2023 388;10

KEY DATA

DeFi: International, Multicenter, randomized, double blind placebo controlled, phase 3 trial

Evaluate the efficacy of oral nirogacestat compared to placebo in patients with progressing desmoid tumors not amenable to surgery

- Histologically confirmed, progressing desmoid tumor
  - Treatment-naïve with desmoid tumor not amenable to surgery, or
  - Refractory or recurrent disease (after ≥1 line of therapy)



*In the event of radiographic (image-based) disease progression, treatment was unblinded and patients in DeFi were given the option to enroll in an ongoing open-label extension (OLE) study where they received OGSIVEO 150 mg orally twice daily

All patients had histologically confirmed desmoid tumors that had progressed ≥20% by RECIST v1.1 within 12 months before screening
If patients had multiple target tumors that were located in the intra- and extra-abdominal locations, they were classified as intra-abdominal
Patients were randomized to receive 150 mg OGSIVEO or placebo orally twice daily until disease progression or unacceptable toxicity
Tumor imaging occurred every 3 months

Primary endpoint: PFS

Key secondary endpoints: ORR, patient reported worst pain intensity (change from baseline at cycle 10)

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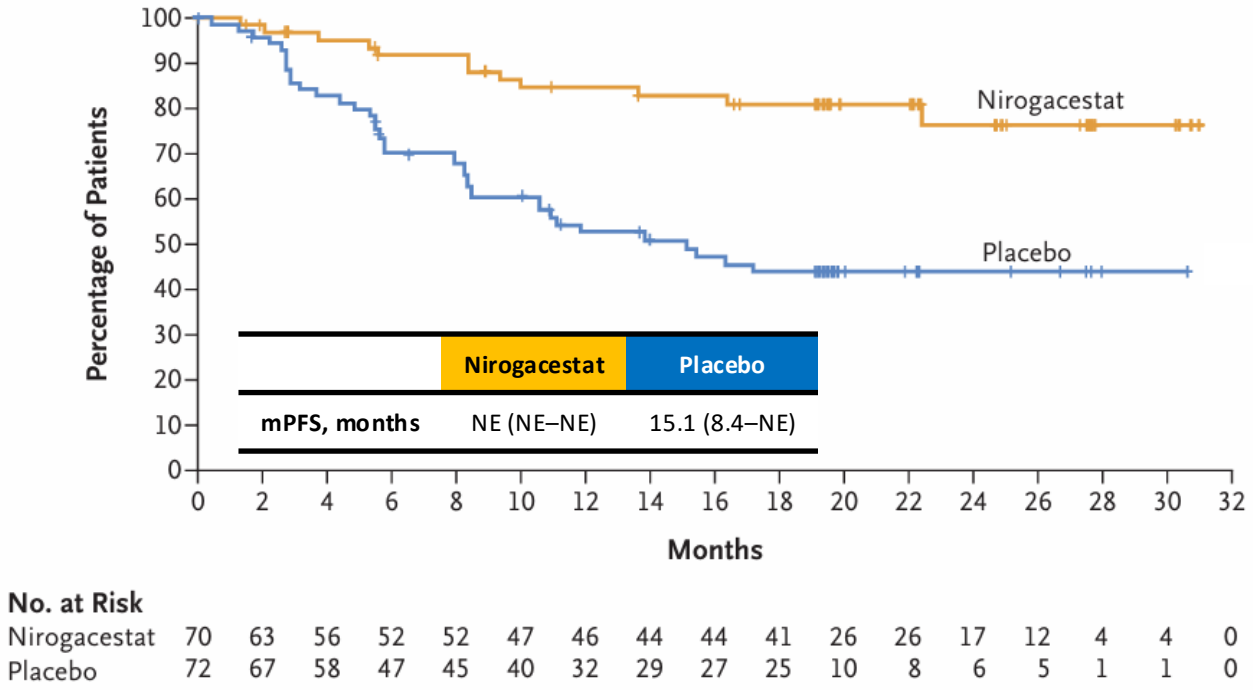
Gounder M et al. N Engl J Med. 2023;388(10):898-912

KEY DATA

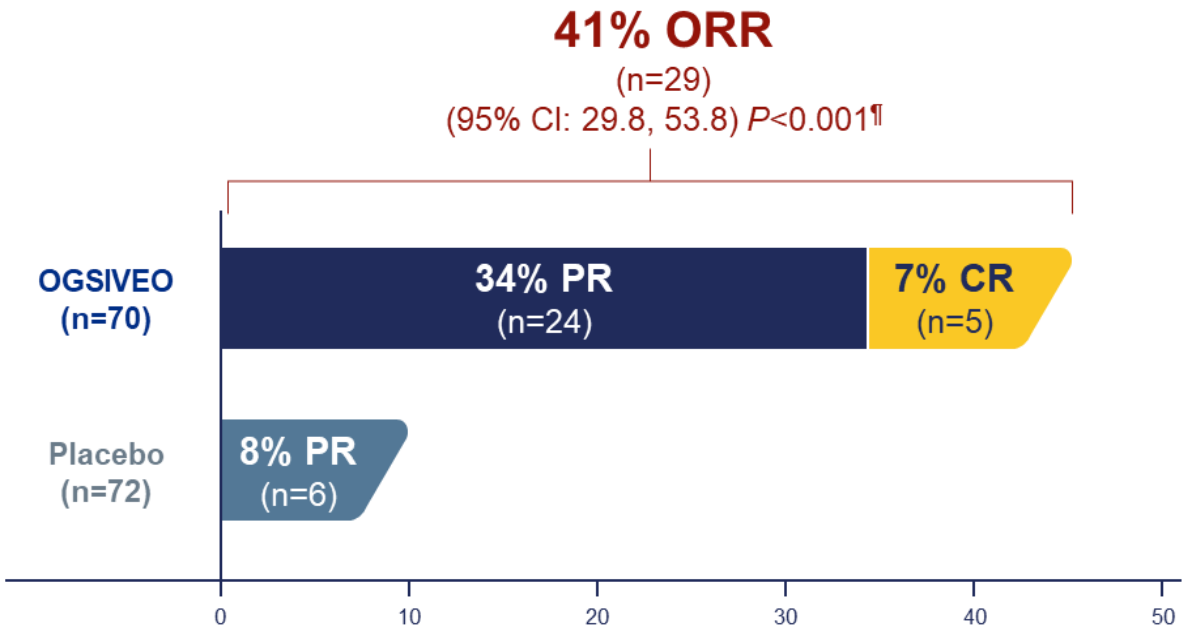
DeFi: International, Multicenter, randomized, double blind placebo controlled, phase 3 trial

Evaluate the efficacy of oral nirogacestat compared to placebo in patients with progressing desmoid tumors not amenable to surgery

Primary Endpoint: Patients receiving nirogacestat achieved a **71%** reduction in the risk of disease progression or death vs placebo (ITT) (**HR=0.29**; 95% CI: 0.15, 0.55; *P*<0.001*)



Secondary Endpoint: Patients receiving nirogacestat achieved statistically significant improvement in objective response rate vs placebo



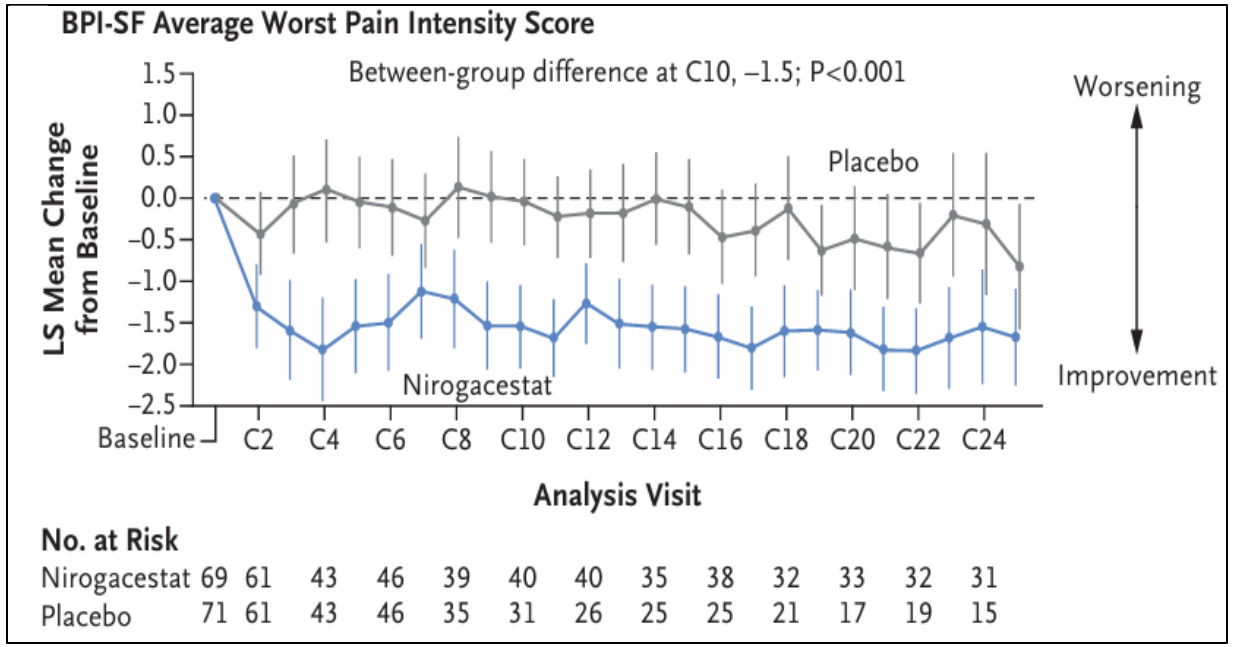
The median time to a confirmed first response was **5.6** months with nirogacestat and **11.1** months with placebo.

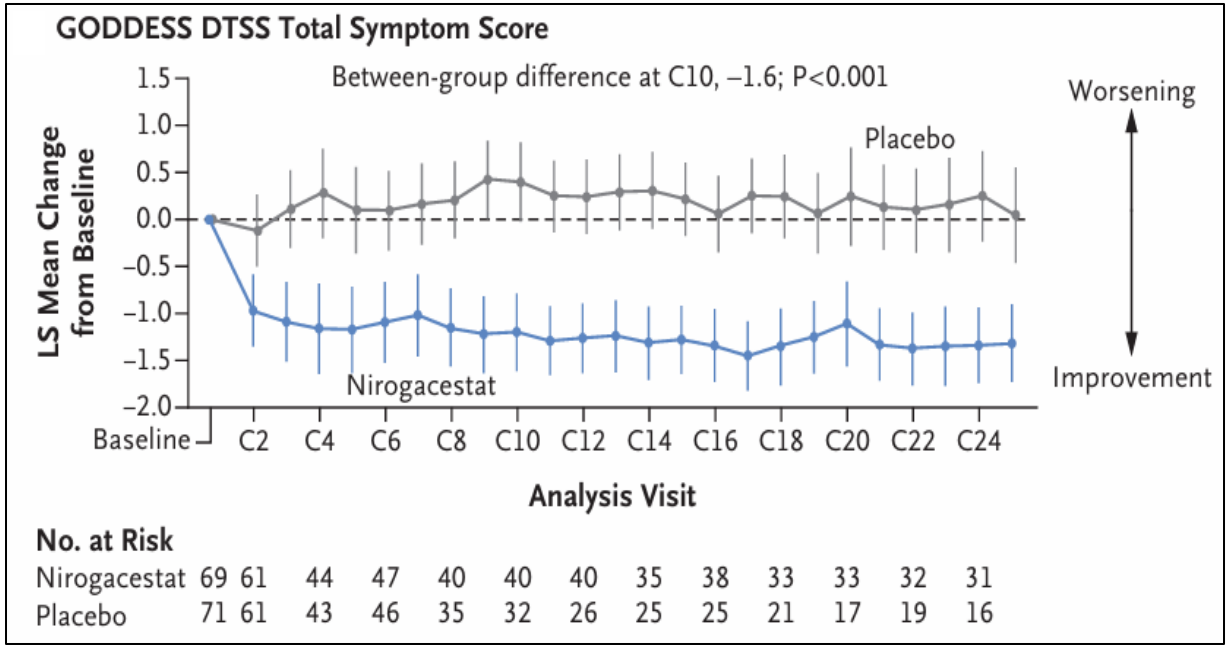
Gounder M et al. N Engl J Med. 2023;388(10):898-912

KEY DATA

DeFi: International, Multicenter, randomized, double blind placebo controlled, phase 3 trial

Improvements in PRO outcomes observed early and were sustained over time; support PFS results





Note: Desmoid tumor-specific GODDESS assessment

- *Additional PRO outcomes measured included GODDESS DTIS physical functioning Domain Score, EORTC QLQ-C30 Physical Functioning Score, EORTC QLQ-C30 Role Functioning Score, and EORTC QLQ-C30 Global Health Status-Quality of Life Score with similar early and sustained improvements with nirogacestat observed versus placebo*

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Gounder M et al. N Engl J Med. 2023;388(10):898-912

KEY DATA

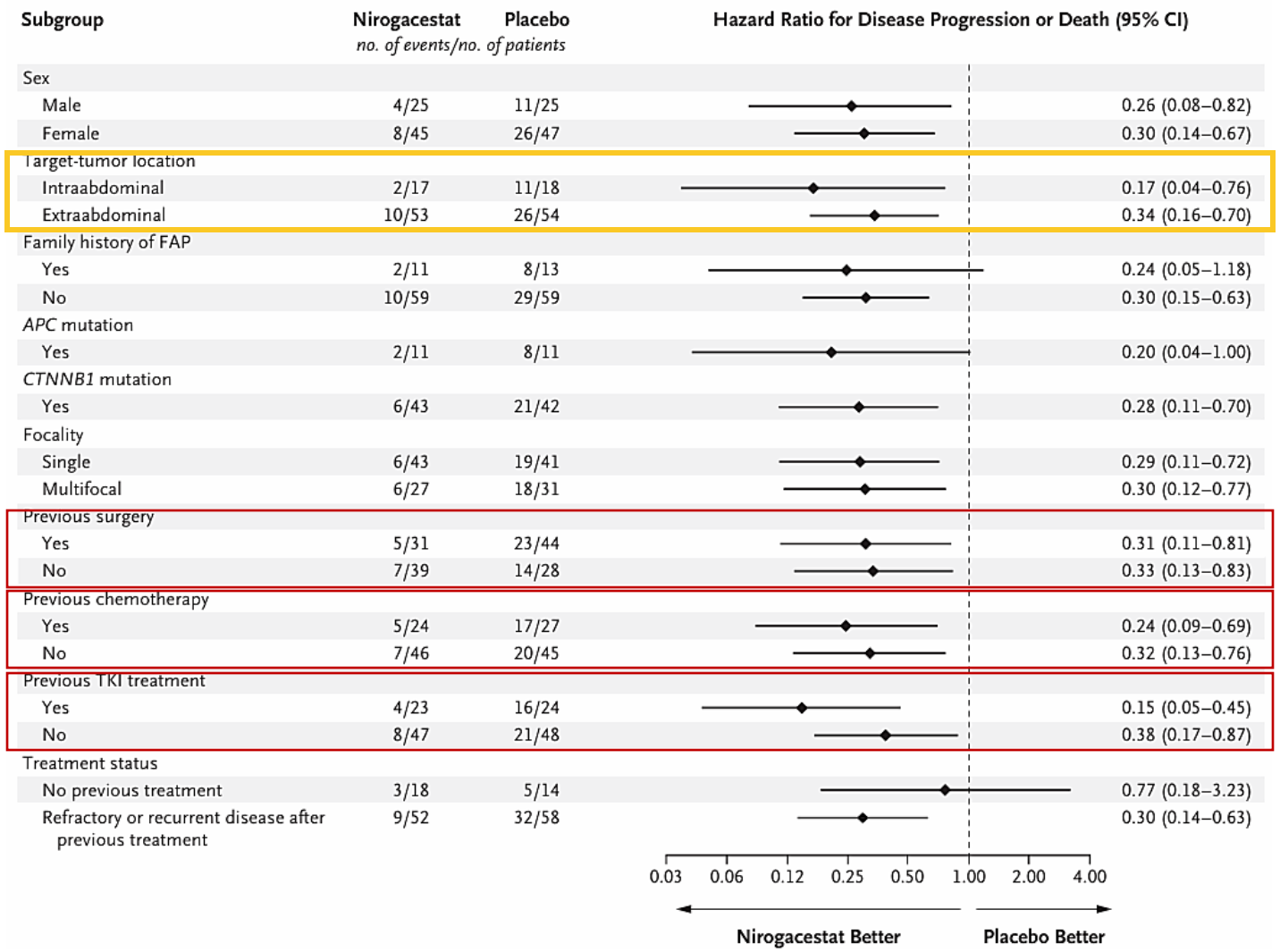
DeFi: International, Multicenter, randomized, double blind placebo controlled, phase 3 trial

Evaluate the efficacy of oral nirogacestat compared to placebo in patients with progressing desmoid tumors not amenable to surgery

Baseline Characteristics

Target-tumor location, no. (%)	Nirogacestat	Placebo
Intradominal	17 (24%)	18 (25%)
Extradominal	53 (76%)	54 (75%)

Subgroup analysis of PFS: consistent across all subgroups



Gounder M et al. N Engl J Med. 2023;388(10):898-912

KEY DATA

DeFi: International, Multicenter, randomized, double blind placebo controlled, phase 3 trial

Adverse events in the safety population

95% of AEs with nirogacestat were Grade 1 or 2

Summary No. (%)	Nirogacestat (N = 69)	Placebo (N = 72)
Adverse event, any grade	69 (100)	69 (96)
Adverse event, grade ≥3	38 (55)	12 (17)
Adverse event leading to early discontinuation of nirogacestat or placebo, any grade	14 (20)	1 (1)
Adverse event leading to death	0	1 (1)†

† The patient died from sepsis.
Shown are adverse events that emerged or worsened from the time of the first dose of nirogacestat or placebo through 30 days after the last dose. Covid-19 denotes coronavirus disease 2019

No. (%) Select Adverse Events	Nirogacestat (N = 69)	Placebo (N = 72)
Diarrhea	58 (84)	25 (35)
Nausea	37 (54)	28 (39)
Fatigue	35 (51)	26 (36)
Hypophosphatemia	29 (42)	5 (7)
Maculopapular rash	22 (32)	4 (6)
Stomatitis	20 (29)	3(4)
Headache	20 (29)	11 (15)
Dermatitis acneiform	15 (22)	0
Vomiting	14 (20)	14 (19)

Diarrhea events (of which 90% were grade 1 or 2) were most frequently managed with dose modifications, dose interruptions, and antidiarrheal agents.

What is your experience with nirogacestat? Management strategies?

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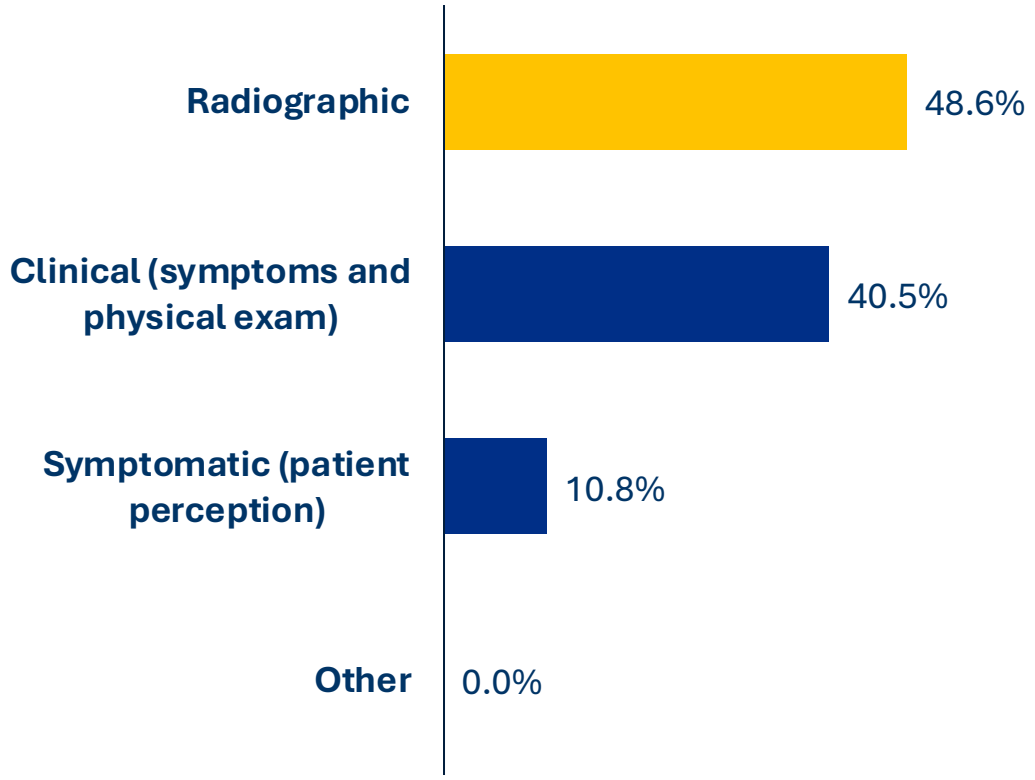
Gounder M et al. N Engl J Med. 2023;388(10):898-912

Category 1 NCCN Preferred Regimens

	Indication	Study Design	PFS	PFS rates at 2 years	ORR	Median time to response	PRO data	AEs
Nirogacestat (Ogsiveo) Gounder et al. N Engl J Med. 2023; 388(10):898-912	***Approved November 27, 2023:*** *OGSIVEO is a gamma secretase inhibitor indicated for adult patients with progressing desmoid tumors who require systemic treatment*	**Nirogacestat** 150 mg orally BID (n=70)	*Median follow-up of 15.9 months* NE (NE–NE)	76%	**41%**	**5.6 months**	At cycle 10, significant and clinically meaningful benefits over placebo across all PRO measures	**95% of AEs with nirogacestat were Grade 1 or 2:** Diarrhea (84%) Nausea (54%) Fatigue (51%) Hypophosphatemia (42%) Maculopapular rash (32%) Discontinuation rates Nirogacestat arm: 20% Placebo arm: 1%
			HR=0.29 (95% CI: 0.15 - 0.55) P<0.001			P<0.001		
		Placebo orally BID (n=72)	15.1 (8.4–NE)	44%	8%	11.1 months		
Sorafenib (Nexavar) Gounder et al., N Engl J Med 2018 379(25):2417-2428	***Not FDA approved for desmoid tumors***	**Sorafenib** 400 mg orally QD (n=50)	*Median follow-up of 27.2 months* NE (NE–NE)	81%	33%	9.6 months	*Exploratory analysis: The use of pain-palliation questionnaires was optional, and limited results were available; unable to use the Brief Pain Inventory to discern any difference between the groups*	**AEs with sorafenib were mostly Grade 1 or 2:** Rash (73%) Fatigue (67%) Hypertension (55%) Diarrhea (51%) Discontinuation rates Sorafenib arm: 20% Placebo arm: 0%
			HR=0.13 (95% CI: 0.05 - 0.31) P<0.001					
		Placebo orally QD (n=37)	11.3 (5.7–NE)	36%	20%	13.3 months		

ARS Results from HCP Participants

What is your primary strategy for monitoring time to response?



Answered: 37

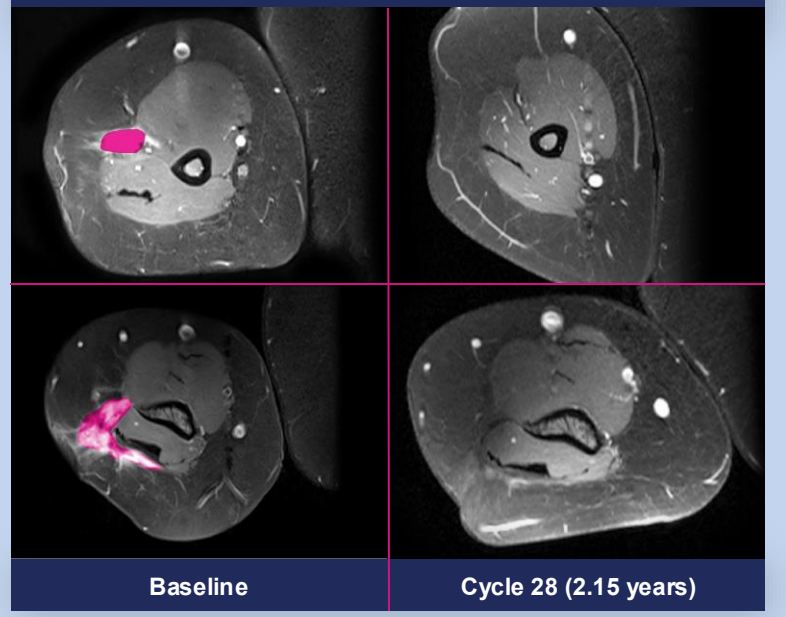
KEY DATA

DeFi: International, Multicenter, randomized, double blind placebo controlled, phase 3 trial

Evaluate the efficacy of oral nirogacestat compared to placebo in patients with progressing desmoid tumors not amenable to surgery

Desmoid tumors in the upper arm

MRI showing a **complete response** in a patient with multifocal disease in the OGSIVEO arm of the DeFi Trial



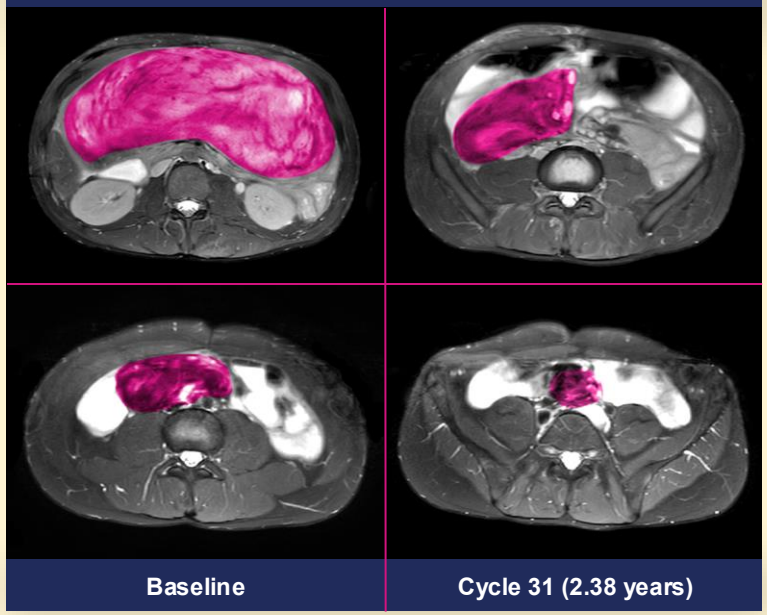
Sum of target tumor longest diameters = **72.3 mm** (23.1 mm + 49.2 mm)

Sum of target tumor longest diameters = **0 mm**

-100% change from baseline

Intra-abdominal desmoid tumors

MRI showing a **partial response** in a patient with multifocal disease in the OGSIVEO arm of the DeFi Trial



Sum of target tumor longest diameters = **369.2 mm** (251.3 mm + 117.9 mm)

Sum of target tumor longest diameters = **143.4 mm** (98.5 mm + 44.9 mm)

-61.2% change from baseline

Images adapted with permission from Alcindor T, Kasper B, Gounder M, et al. Tumor volume and T2 hyperintensity changes from DeFi: a phase 3, randomized, controlled trial of nirogacestat in patients with desmoid tumors. Poster presentation at: ASCO Annual Meeting; June 2-6, 2023; Chicago, IL. False color added.

Gounder M et al. N Engl J Med. 2023;388(10):898-912

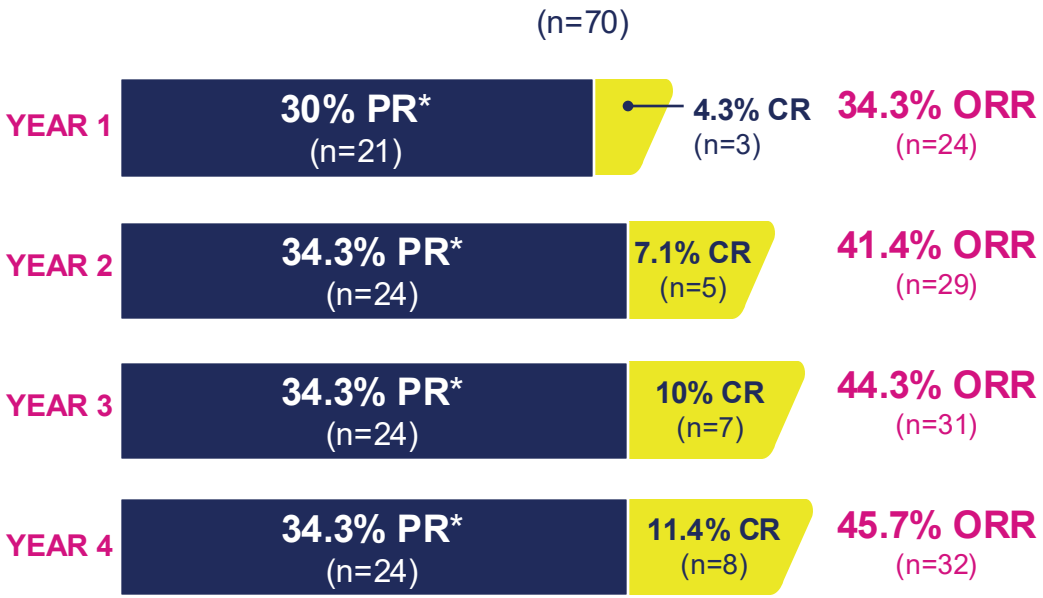
KEY DATA

DeFi: Post-Hoc analysis, Long-term Efficacy and Safety Data

Patients from both the placebo and nirogacestat (OGSIVEO) treatment arms were eligible to enroll in the open-label extension phase and receive OGSIVEO 150 mg BID

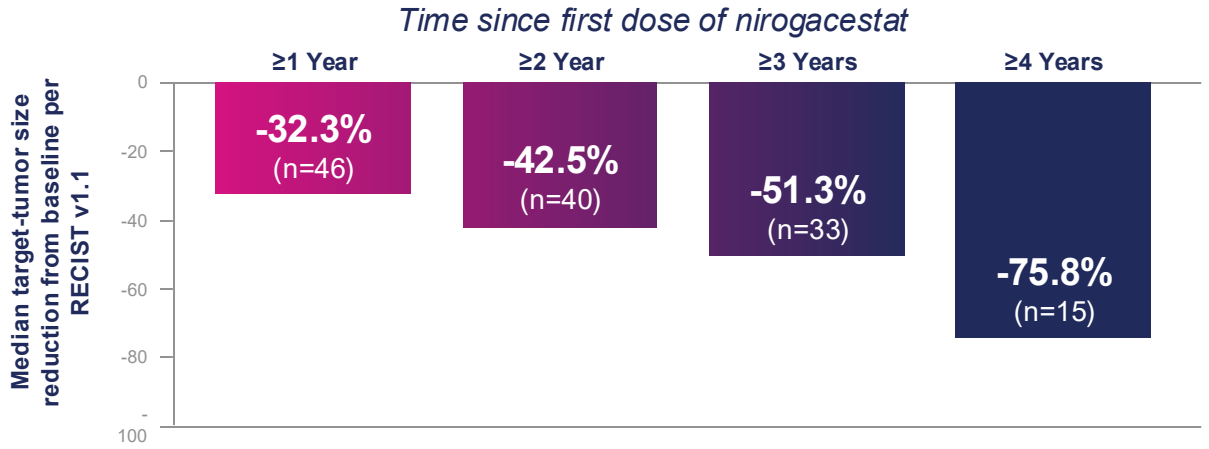
Post-hoc analysis at annual milestones of 1 year (n=46), 2 years (n=40), 3 years (n=33) and 4 years (n=15)

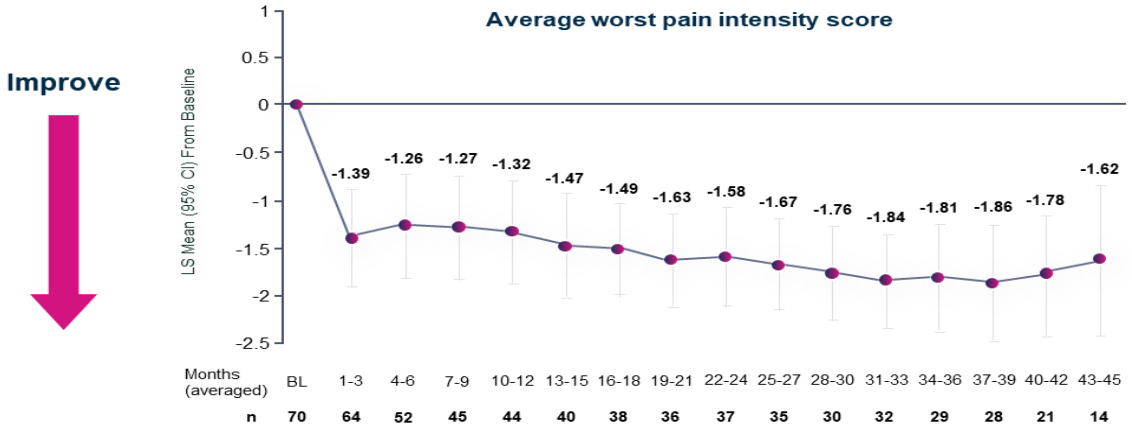
Objective Response Rate (ORR), up to 4-year exposure



Median (range) duration of nirogacestat exposure: 33.6 months (0.3-60.0 months)

Median Best Percent Change in Target-Tumor Size

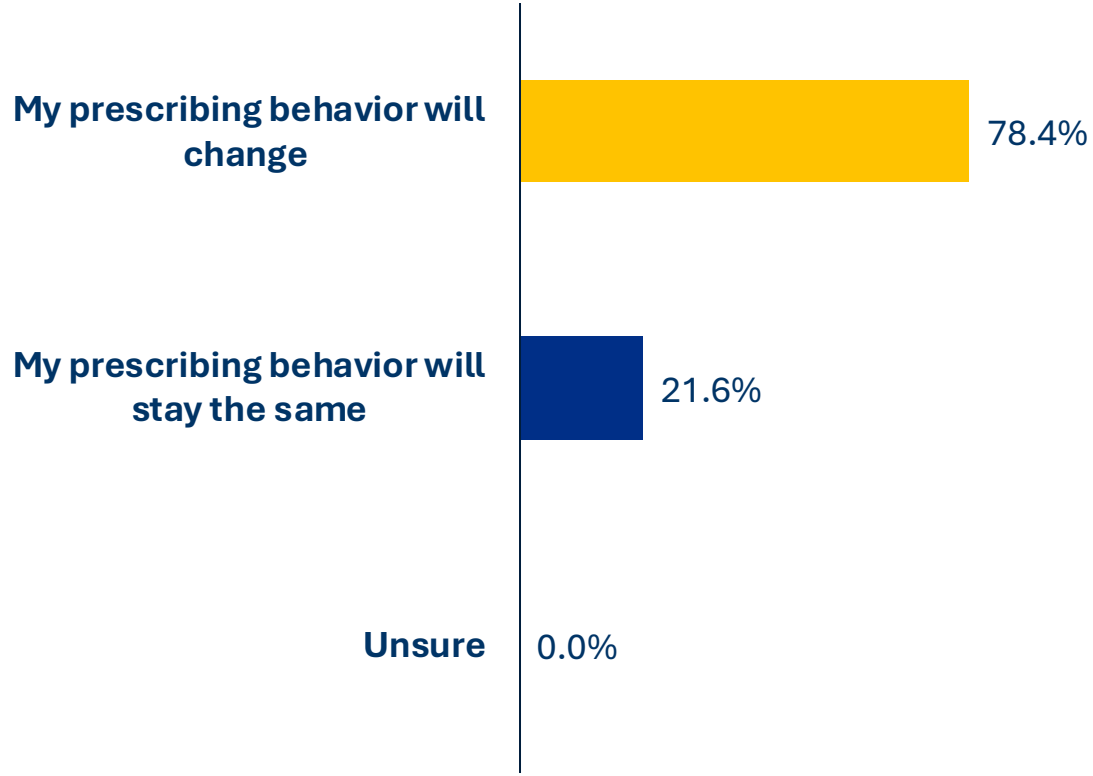




Ratan R et al. Presented at Connective Tissue Oncology Society 2024 Annual Meeting; November 13-16, 2024; San Diego, CA.

ARS Results from HCP Participants

How will the presented data impact your prescribing behavior for progressing desmoid tumors?



Answered: 37

Key Takeaways

Desmoid tumor

Patient case: progressing

- *Reduction of pain and improved QoL are key treatment goals for patients*
- *Nirogacestat (OGSIVEO) is the first and only approved gamma secretase inhibitor, with a distinct mechanism of action in the desmoid tumor treatment landscape*
- *Clinical trial data, NCCN Guidelines, and FDA approvals guide treatment decisions*