Treatment Journey of Nirogacestat: Timing Expectations of Safety and Efficacy in a Novel Drug Class

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Disclosures

I, ***Gabriel Tinoco,*** declare financial interests with the following:

- *Acting in a consulting or advisory role for SynOx, Deciphera, Servier,* SpringWorks Therapeutics *and EMD Serono, the Healthcare businesses of Merck KGaA, Darmstadt, Germany.*

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Introduction

- Nirogacestat, an oral, targeted gamma secretase inhibitor, is the only treatment approved by the US FDA, European Commission, and other major global health agencies for adults with progressing desmoid tumors who require systemic treatment[1-4]
- The safety and efficacy of nirogacestat were assessed in DeFi (NCT03785964), a global, randomized, multicenter, phase 3 clinical trial, which included a double-blind, placebo-controlled phase and an open-label extension phase[5]
- In the primary analysis of DeFi,[5] nirogacestat demonstrated a favorable safety profile and significant, clinically meaningful improvement vs placebo in:
  - Progression-free survival
  - Objective response rate
  - Patient-reported outcomes (PRO) for pain, symptom burden, physical and role functioning, and health-related quality of life
- Long-term results from DeFi indicated that treatment with nirogacestat was associated with continued tumor size reductions, durable objective responses, and sustained PRO benefits[6]

1. OGSIVEO® (nirogacestat). Full Prescribing Information. SpringWorks Therapeutics; 2024. **2.** US Food and Drug Administration. FDA approves nirogacestat for desmoid tumors. 2023. Accessed August 27, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nirogacestat-desmoid-tumors. **3.** European Commission. Union Register of medicinal products for human use - Ogsiveo. 2025. Accessed September 22, 2025. https://ec.europa.eu/health/documents/community-register/html/h1932.htm. **4.** Medicines and Healthcare Products Regulatory Agency. Nirogacestat hydrobromide approved to treat desmoid tumours. 2025. Accessed January 9, 2025. Nirogacestat hydrobromide approved to treat desmoid tumours - GOV.UK. **5.** Gounder M, et al. *N Engl J Med*. 2023;388(10):898-912. **6.** Ratan R, et al. *J Clin Oncol*. 2025;43(34):3646-3651.

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Objective

To further characterize the treatment journey with nirogacestat in patients enrolled in the DeFi clinical trial

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Methods

This analysis includes 69 patients treated with nirogacestat (150 mg BID) in the double-blind phase of the DeFi trial and includes data collected through the end of the open-label extension phase

- Incidence and timing of first onset were reported for TRAEs
- PRO measurements were assessed according to protocol[1] and included:
  - Brief Pain Inventory–Short Form (BPI-SF) for average worst pain intensity score
  - GODDESS Desmoid Tumor Symptom Scale (DTSS) pain and total symptom scores
  - GODDESS Desmoid Tumor Impact Scale (DTIS) physical function domain score
  - EORTC QLQ-C30 role and physical functioning scores
- Tumor responses were defined according to RECIST v1.1 and assessed via imaging (MRI or CT) every 3 months

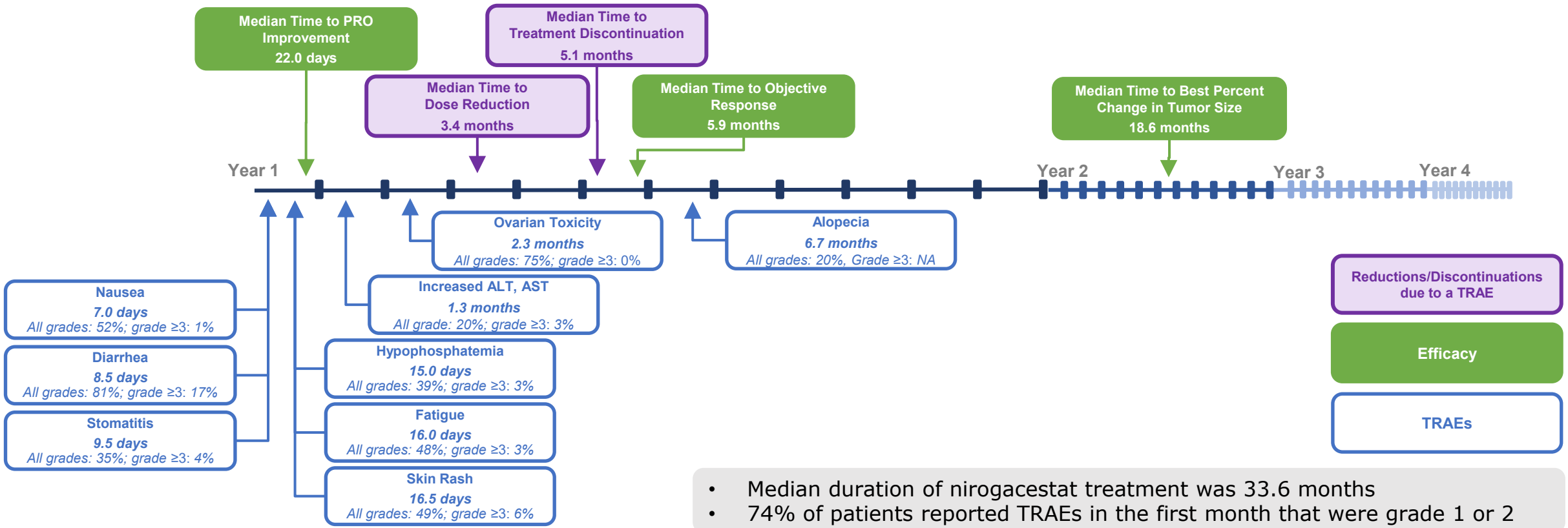
Data were reported as of the final trial data cutoff on December 19, 2024.
BID, twice daily; EORTC-QLQ0C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PRO, patient-reported outcomes; GODDESS, Gounder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale; RECIST, Response Evaluation Criteria in Solid Tumors; TRAE, treatment-related adverse events.
1. Gounder M, et al. N Engl J Med. 2023;388:898-912.

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Efficacy and Safety

Timeline of dose reductions and treatment discontinuations due to a TRAE, efficacy outcomes, and frequently reported TRAEs



- Median duration of nirogacestat treatment was 33.6 months
- 74% of patients reported TRAEs in the first month that were grade 1 or 2

TRAE data represent the incidence and median time until first onset for TRAEs reported by ≥20% of patients.
Data were collected from the start of randomization (May 2019 to August 2020) through the database lock at the end of the OLE phase on December 19, 2024.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; PRO, patient-reported outcomes; NA, not applicable; TRAE, treatment-related adverse event.

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Dose Reductions

- **Through the double-blind and open-label extension phases of DeFi, 34/69 patients receiving nirogacestat had a dose reduction due to a TEAE;** of these, 33 (97%) were deemed to be related to study treatment
  - Median duration of treatment after dose reduction due to a TEAE was 24.0 months
  - Of these 33 patients with a dose reduction due to a TRAE, only 3 (9%) went on to discontinue treatment due to the same TRAE that led to the dose reduction
  - Median time to dose reduction due to a TRAE was 3.4 months

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Treatment Discontinuations

- **In total, 20/69 patients (29%) receiving nirogacestat experienced a TEAE that led to treatment discontinuation**; of these, 18 (90%) discontinued treatment due to a TEAE determined to be related to nirogacestat treatment
  - Median time to treatment discontinuation due to a TRAE was 5.1 months

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Timing of Symptomatic Improvement in PRO

Patients experienced improvement in PRO as early as the first visit after starting treatment; this benefit was sustained throughout treatment

Assessment	Patients, n/N (%)[a]	Median time to symptomatic improvement[b]
BPI-SF Average Worst Pain Intensity[c]	43/46 (94)	22.0 days
DTSS Total Symptom Score[c]	57/66 (86)	22.0 days
DTSS Pain[c]	58/64 (91)	22.0 days
DTIS Physical Functioning	61/69 (88)	28.0 days
EORTC-QLQ-C30 Physical Functioning	44/52 (85)	29.0 days
EORTC-QLQ-C30 Role Functioning	43/49 (88)	1.8 months

[a]Denominator represents the number of patients for whom symptomatic improvement was possible (baseline score >0 for BPI-SF, DTSS TSS/Pain, and DTIS measures; baseline score <100 for EORTC QLQ measures); numerator represents the number of patients that experienced an improvement from baseline during treatment. [b]Time to symptomatic improvement was calculated as the date of the first score improvement minus the date of the first dose of nirogacestat plus 1 day. [c]Assessments were averaged over the past 7 days prior to each scheduled assessment. The actual day utilized for the time to symptomatic improvement calculation was the earliest day that contributed to the average.

BPI-SF, Brief Pain Inventory–Short Form; DTIS, Desmoid Tumor Impact Scale; DTSS, Desmoid Tumor Symptom Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PRO, patient-reported outcome.

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Conclusions

- Clinical benefit with nirogacestat is often experienced early, **but TEAEs often precede radiologic evidence of response**
- **Improvements in pain, symptom burden, physical and role functioning, and health-related quality of life with nirogacestat occurred early** and were sustained over long-term treatment
- Patients who had dose reductions were generally able to tolerate treatment over time, highlighting the **importance of dose reduction as a strategy to manage TEAEs**
- The first onset of most TRAEs was within the first month, but median time to dose reductions was not until after month 3
  - This suggests that **early monitoring and proactive management of TRAEs, including earlier dose reductions, may improve persistence or treatment continuation** with nirogacestat and, as a result, allow for early symptomatic improvement to be sustained over time and for eventual radiologic benefits to be observed in more patients

TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse events.

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*BT and **RC** were employees at the time of the analysis and is now former employees.

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Timing of Onset of the First Instance of Frequently Reported All-Grade TRAEs (≥20% of Patients)

	All grades (N=69)		Grade ≥3[a] (N=69)	
	n (%)	Median time to onset	n (%)	Median time to onset
Nausea	36 (52)	7.0 days	1 (1)	25.0 days
Diarrhea	56 (81)	8.5 days	12 (17)	15.5 days
Stomatitis[b]	24 (35)	9.5 days	3 (4)	3.0 months
Hypophosphatemia[b]	27 (39)	15.0 days	2 (3)	2.1 months
Fatigue[b]	33 (48)	16.0 days	2 (3)	1.3 months
Rash[b]	34 (49)	16.5 days	4 (6)	13.5 days
Increased ALT and/or AST[b]	14 (20)	1.3 months	2 (3)	26.5 days
Ovarian toxicity[c]	27/36 (75)	2.3 months	0	0
Alopecia	14 (20)	6.7 months	0	0

[a]Grade ≥3 results listed for those TRAEs reported by ≥20% of patients at any grade. [b]Includes multiple related composite terms. [c]Ovarian toxicity was identified by investigators (both verbatim term and grade) in females of reproductive potential (n=36) based on abnormal reproductive hormone values or perimenopausal symptoms or both. The verbatim terms for ovarian toxicity events were coded to the MedDRA preferred terms of ovarian failure, premature menopause, amenorrhea, menopause, oligomenorrhea, and ovarian disorder.

- **For most of the TRAEs reported by ≥20% of patients, the onset of first occurrence was during the first month after initiating nirogacestat treatment**

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ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; N/A, not applicable; TRAE, treatment-related adverse event.

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