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Nirogacestat Treatment in Adult Patients with Desmoid Tumors: Long-Term Efficacy and Safety From the Phase 3 DeFi Trial

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Disclosures

- Dr. Ravin Ratan reports the following:
  - Consulting/Advisory role for Inhibrx, Ipsen, and SpringWorks Therapeutics, Inc
  - Honoraria from PeerView and touchIME; and travel, accommodations, and expenses from SpringWorks Therapeutics, Inc
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  - Stock and other ownership interests in Johnson & Johnson/Janssen and Medtronic
- The DeFi trial was sponsored by SpringWorks Therapeutics, Inc

Nirogacestat and the Phase 3 DeFi Trial

- **Nirogacestat**: oral, targeted gamma secretase inhibitor[1]
  - Only FDA-approved therapy for adults with progressing DT who require systemic treatment[2]
- **DeFi (NCT03785964)**: global, randomized, multicenter, placebo-controlled, phase 3 trial for nirogacestat[3]
  - **Double-blind (DB) Phase**: Adults with progressing DT (≥20% by RECIST v1.1) were randomized to nirogacestat 150 mg (n=70) or placebo (n=72), twice daily in 28-day cycles until progression or unacceptable toxicities
  - **Open-label Extension (OLE) Phase**: If eligible, patients were given the option to enroll in an OLE phase
- **DeFi primary analysis**[3,a]:
  - **Nirogacestat demonstrated statistically significant and clinically meaningful improvement** versus placebo in the primary endpoint of PFS [HR 0.29; 95% CI: 0.15–0.55; (*P*<.001)] and key secondary endpoints of ORR [41% vs 8%; (*P*<.001)] and PROs (all *P*≤.01)
  - **Nirogacestat exhibited a favorable safety profile**: 95% of all treatment-emergent adverse events were Grade 1 or 2
  - **Median (range) duration of exposure** was 20.6 (0.3–33.6) months in patients receiving nirogacestat[a]

[a]Datacut: 07Apr2022.

1. OGSIVEO® (nirogacestat) [package insert]. Stamford, CT: SpringWorks Therapeutics, Inc: 2023. 2. SpringWorks Therapeutics, Inc. SpringWorks Therapeutics Announces FDA Approval of OGSIVEO (nirogacestat) as the First and Only Treatment for Adults with Desmoid Tumors. November 27, 2023. https://ir.springworkstx.com/news-releases/news-release-details/springworks-therapeutics-announces-fda-approval-ogsiveotm. Accessed Sept 27, 2024. 3. Gounder MM, et al. *N Engl J Med*. 2023;388(10):898-912.

CI, confidence interval; DT, desmoid tumor; FDA, Food and Drug Administration; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; PROs, patient-reported outcomes; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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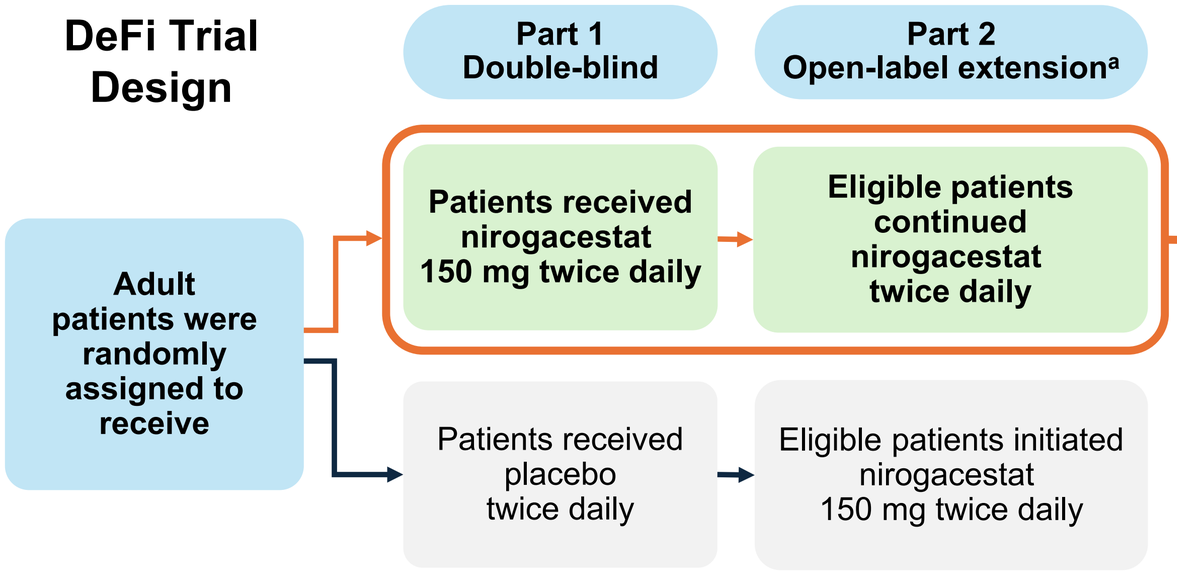
DeFi: Continuous Nirogacestat Treatment

Objective: Evaluate the efficacy and safety of continuous nirogacestat at annual landmark milestones of 1, 2, 3, and 4 years

DeFi Trial Design



Tumor response and durability

- Evaluated per RECIST v1.1
- Patients were assessed for responses up to the specified milestone timepoints

PROs: Least squares (LS) mean (95% CI) change from baseline

- BPI-SF Average worst pain intensity score
- GODDESS DTSS Total symptom score and DTIS Physical functioning domain score

Safety

- Reported as TEAEs

Datacut: 13Aug2024.

[a]Following imaging-based progression or primary analysis completion, patients were unblinded and given the option to enroll in an open-label extension phase if eligible.

BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; DTIS, Desmoid Tumor Impact Scale; DTSS, Desmoid Tumor Symptom Scale; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; LS, least squares; PROs, patient-reported outcomes; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TEAEs, treatment-emergent adverse events.

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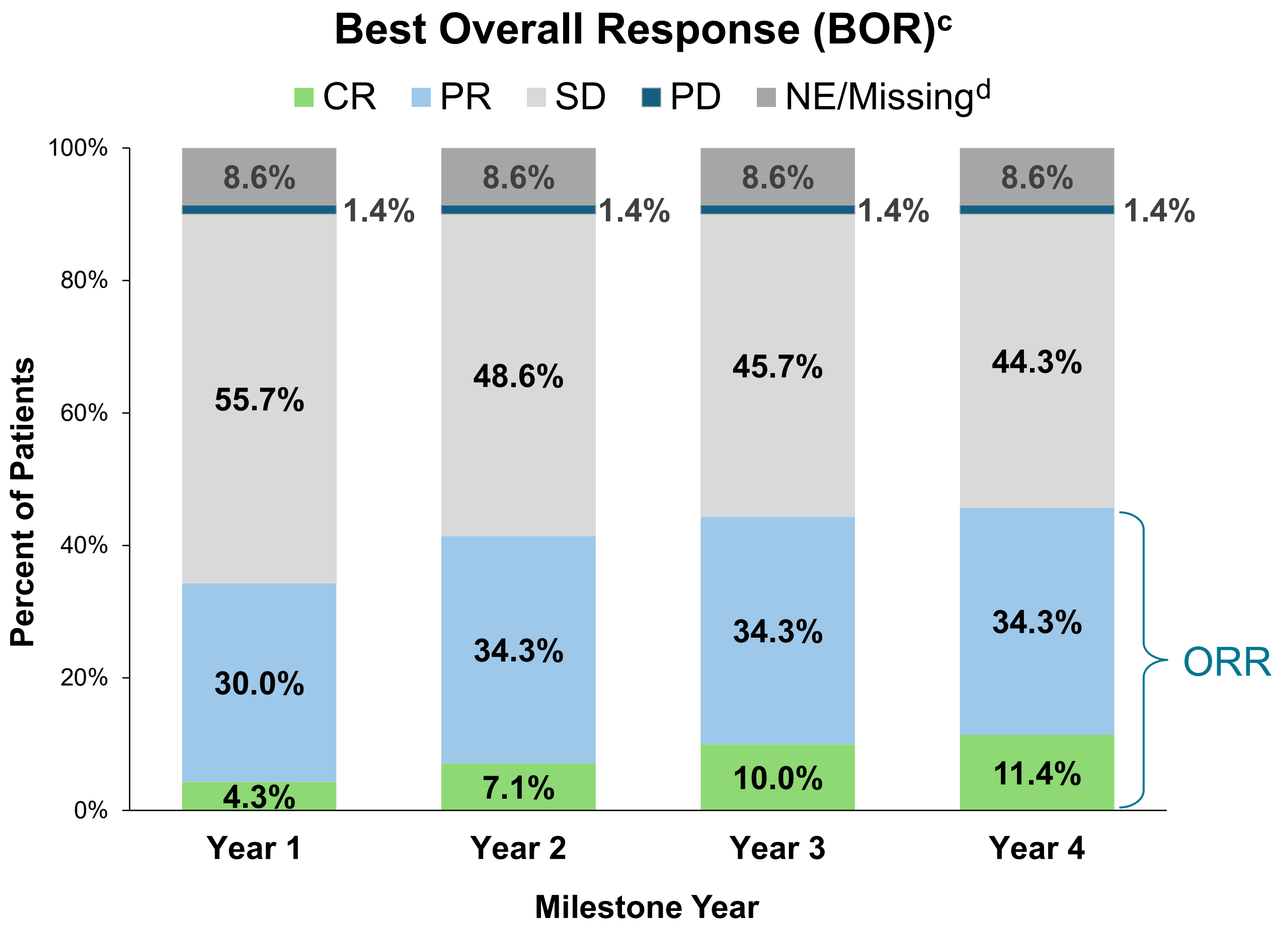
Landmark Analysis of Best Overall Responses

ORR in ITT Population of N=70

- **Nirogacestat exposure**, median (range): 33.6 (0.3–60.0) months[a]
- **ORR[b] increased from 34.3% for patients staying on nirogacestat for up to 1 year to 45.7% for those on nirogacestat for up to 4 years**
  - 3 new PRs and 3 new CRs were reported across years 3 and 4
  - Total of 8 (11.4%) CRs were reported



[a]Datacut: 13Aug2024. [b]ORR was defined as the proportion of patients having a BOR of CR or PR by RECIST v1.1. [c]BOR was defined as the best response obtained across all assessments per independent central review. PR and CR required confirmation by subsequent scans. [d]At each year, NE was 7.1% and Missing was 1.4%.
BOR, best overall response; CR, complete response; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

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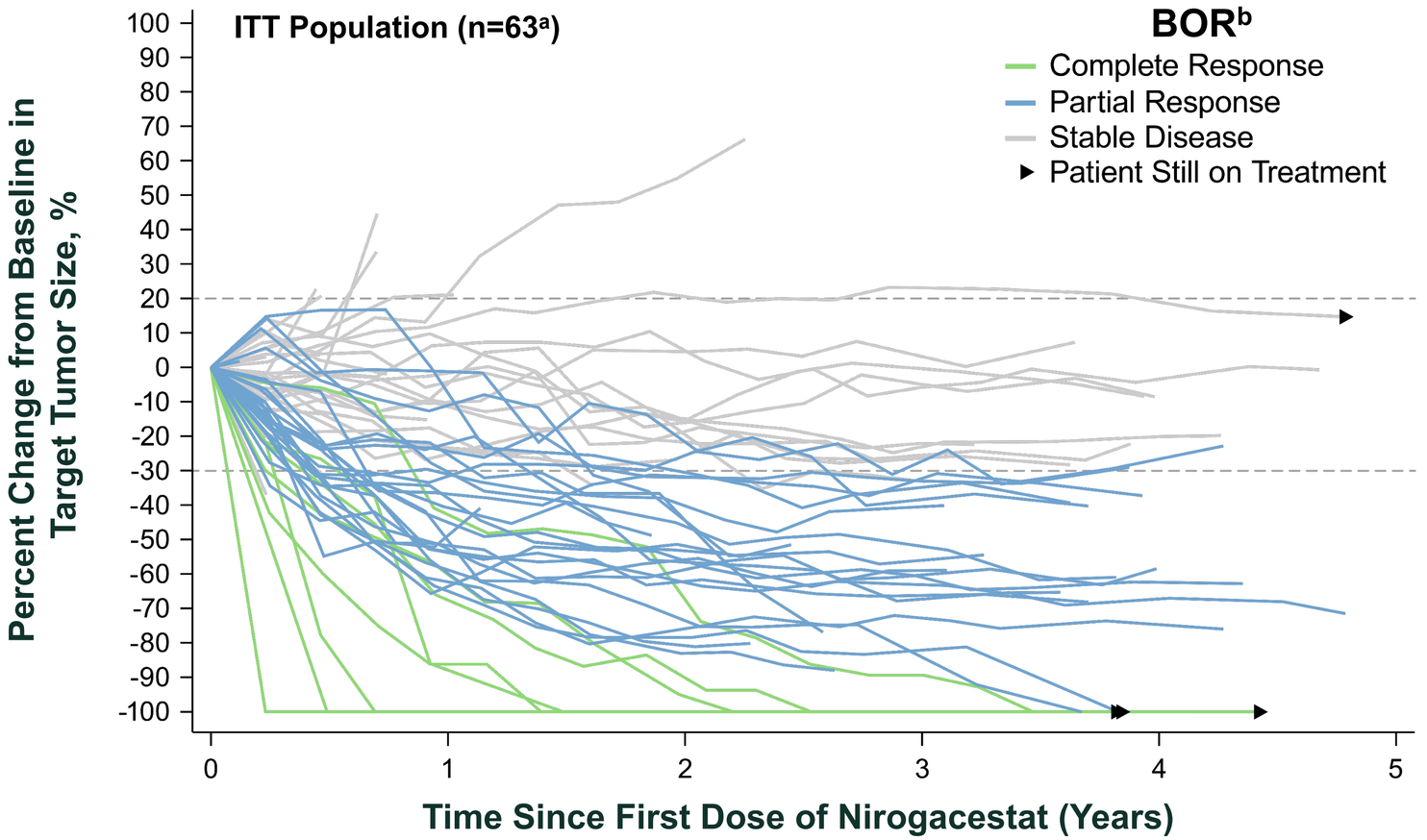
Longer-term Nirogacestat Treatment Was Associated with Durable Tumor Size Reductions and Evidence of Deepening Responses



- **Median best percent change** from baseline target tumor size per RECIST v1.1 improved at each annual milestone

median % (min, max)

- at least 1 year of treatment (n=46): **−32.3 (−100, 6)**
- at least 2 years of treatment (n=40): **−42.5 (−100, 2)**
- at least 3 years of treatment (n=33): **−51.3 (−100, 2)**
- at least 4 years of treatment (n=15): **−75.8 (−100, 2)**

[a]Eligible patients (n=63) who received at least one dose of nirogacestat and had both baseline and post-baseline target tumor size measurements. The analysis included scheduled visits only; the 1 patient with PD is not shown as there were only unscheduled visits for post-baseline tumor size evaluation. [b]BOR was defined as the best response obtained across all assessments per independent central review. Partial response and complete response required confirmation by subsequent scans.

BOR, best overall response; ITT, intent-to-treat; PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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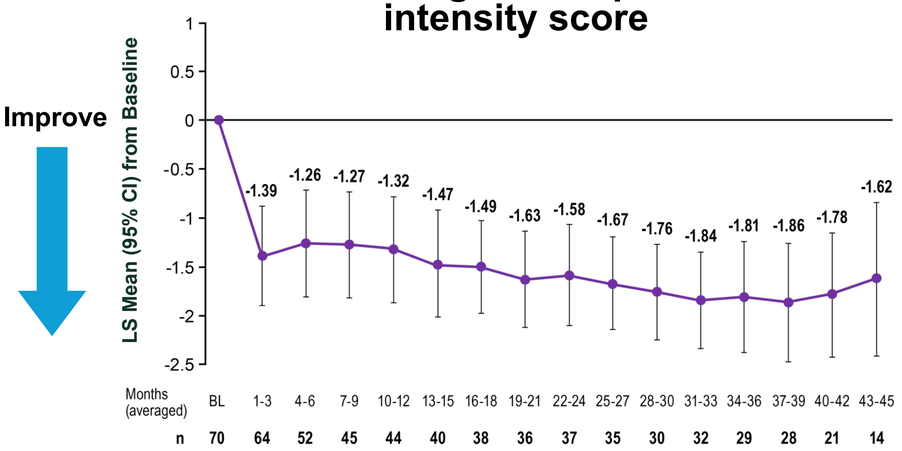
Patients Who Remained on Nirogacestat Treatment Reported Sustained Overall Improvement in PROs Up to 45 Months

BPI-SF

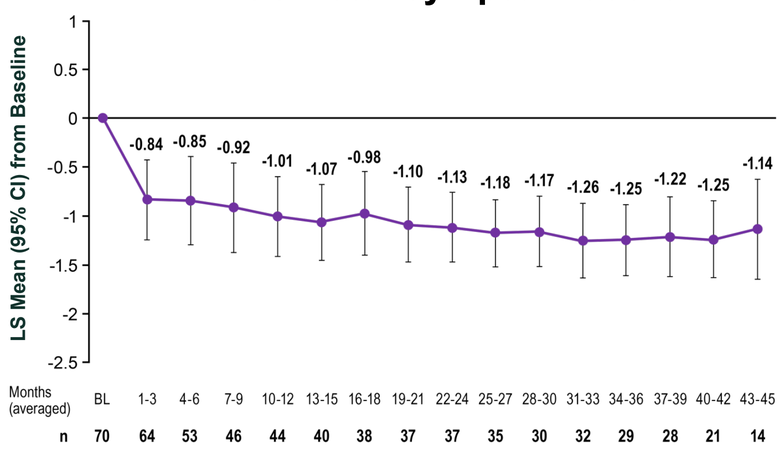
Average worst pain intensity score



LS mean change from baseline in BPI-SF average worst pain intensity score
ranged from −1.86 to −1.26
on a 0–10 scale

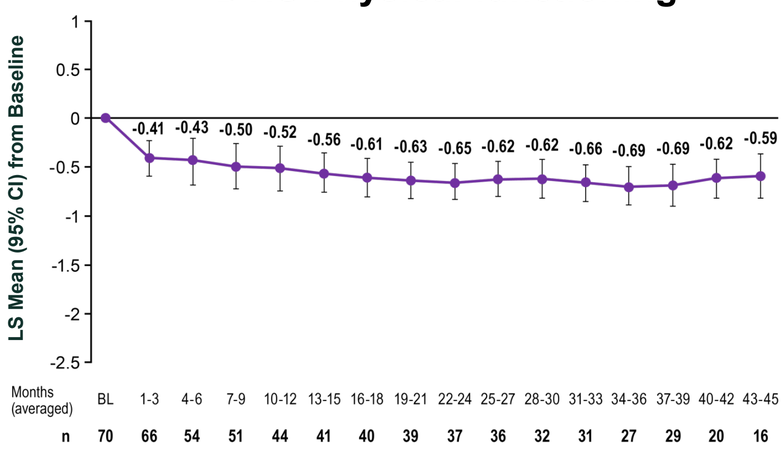
GODDESS

DTSS Total symptom score



LS mean change from baseline for DTSS total symptom score
ranged from −1.26 to −0.84
on a 0–10 scale

DTIS Physical functioning



LS mean change from baseline for DTIS physical functioning
ranged from −0.69 to −0.41
on a 5-point Likert scale

Based on the averaged results of 3-month intervals with DB and OLE data combined. For the subjects with DB phase last dose and OLE phase first dose gap > 5 days, the gap was deducted for re-windowing. Average worst pain intensity score was up to a 7-day average of BPI-SF question #3: worst pain in last 24 hours (on a scale of 0–10). Total symptom score on a scale of 0–10 (24-hour recall, weekly summary scores based on 7-day average prior to each visit). Physical functioning domain score utilized a 5-point Likert for frequency (7-day recall).
BL, baseline; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; DB, double blind; DT, desmoid tumor; DTIS, Desmoid Tumor Impact Scale; DTSS, Desmoid Tumor Symptom Scale; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; LS, least squares; OLE, open-label extension; PROs, patient-reported outcomes.

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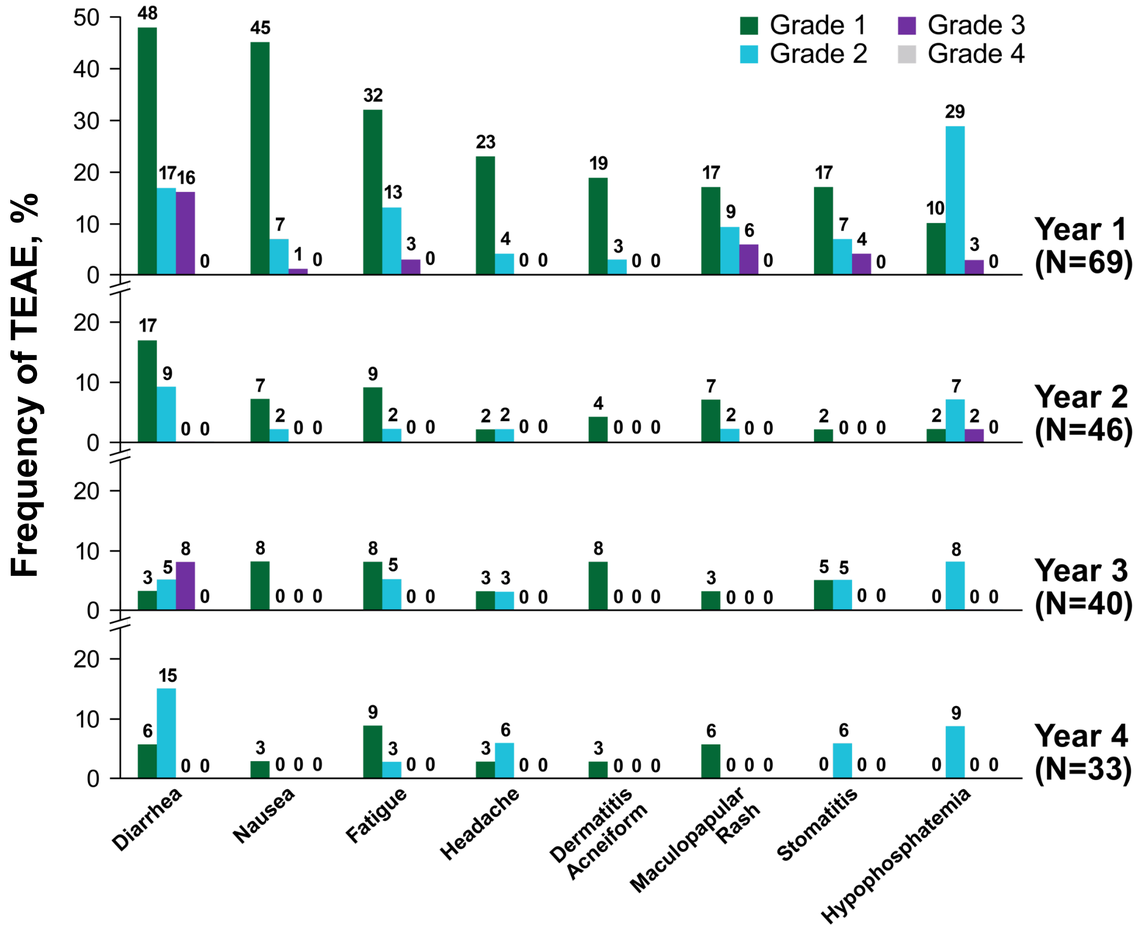
Safety Profile of Longer-Term Nirogacestat Treatment and Follow-up Consistent with Primary Analysis

Safety Population, N=69[a]

- Most frequently reported all-grade TEAEs were diarrhea, nausea, fatigue, hypophosphatemia, and headache
- Most events were Grade 1 or 2 with first onset occurring in the first year of the treatment course for most patients
- Decreased incidence and severity of frequently reported TEAEs in years 2, 3, and 4 of treatment
- Ovarian toxicity (OT) reports were consistent with the primary analysis[b]
  - 3 patients who had previously reported an OT event reported an additional event while continuing nirogacestat
  - 1 OT event in a patient who had not previously reported an OT event



TEAEs: New Onset Per Year by Greatest Severity with Nirogacestat Treatment

[a]Patients (N=69) who received at least one dose of nirogacestat. [b]OT was identified by investigators in females of reproductive potential based on abnormal reproductive hormone values or perimenopausal symptoms or both; the verbatim terms for these events were coded to the MedDRA (version 24.0) preferred terms of ovarian failure, premature menopause, amenorrhea, menopause, oligomenorrhea, and ovarian disorder. TEAEs were defined as events occurring or worsening after the initiation of nirogacestat through 30 days after the last dose or the date of the patient's last dose before starting another treatment. MedDRA, Medical Dictionary for Regulatory Activities; OT, ovarian toxicity; TEAEs, treatment-emergent adverse events.

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Conclusion

- These results show the longer-term efficacy and safety of continuous use of nirogacestat with median exposure of 33.6 months, extended from 20.6 months at the primary analysis[1]
- Longer-term treatment with nirogacestat was associated with:
  - further reduction in tumor size
  - 3 new complete responses and 3 new partial responses
  - durable objective responses
  - early improvement and sustained benefit in PROs
    - pain, DT-specific symptom severity, and DT-specific physical functioning
- Safety profile of longer-term nirogacestat treatment in this analysis was consistent with the primary analysis

1. Gounder MM, et al. *N Engl J Med*. 2023;388(10):898-912.
DT, desmoid tumor; PROs, patient-reported outcomes.

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Sarcoma Patient Advocacy Global Network (SPAGN)

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