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

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*At the time of the analysis.

INTRODUCTION

- Nirogacestat, an oral, targeted gamma secretase inhibitor, is the only US FDA- and European Commission-approved treatment for adults with progressing desmoid tumors (DT) who require systemic treatment[1-3]
- The safety and efficacy of nirogacestat were assessed in DeFi (NCT03785964), a global, randomized, multicenter, phase 3 clinical trial, which included a double-blind (DB), placebo-controlled phase and an open-label extension (OLE) phase[4]
- In the primary analysis of DeFi, nirogacestat demonstrated a favorable safety profile and significant, clinically meaningful improvement vs placebo in progression-free survival (hazard ratio, 0.29; 95% CI: 0.15–0.55; [*P*<.001]), objective response rate (41% vs 8%; [*P*<.001]), and patient-reported outcomes (PROs) for pain, symptom burden, physical and role functioning, and health-related quality of life (all *P*≤.01)[4]
- Long-term results from DeFi indicated that treatment with nirogacestat was associated with continued tumor size reductions, durable objective responses, and sustained PRO benefits[5]
- Understanding the timing of nirogacestat's efficacy and safety may facilitate optimization of treatment outcomes

OBJECTIVE

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

METHODS

- In DeFi, patients were randomized in the DB phase to receive either placebo or nirogacestat 150 mg twice daily. This analysis includes 69 patients treated with nirogacestat in the DB phase and includes data collected through the end of the OLE phase
- The incidence and timing of first onset were reported for treatment-related adverse events (TRAEs)
  - TRAEs were defined as any treatment-emergent adverse event (TEAE) deemed by the investigator to be related to study treatment that emerged or worsened from the time of the first dose of nirogacestat through 30 days after the last dose or the last dose date if starting another treatment for DT
- Time until first dose reduction was calculated as the date of the first dose reduction minus the date of the first dose of nirogacestat

METHODS (CONT.)

- PRO measurements were assessed according to protocol[4] and included:
  - Brief Pain Inventory–Short Form (BPI-SF) for average worst pain intensity score
  - Gounder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale (GODDESS®) Desmoid Tumor Symptom Scale (DTSS) pain and total symptom scores
  - GODDESS Desmoid Tumor Impact Scale (DTIS) physical function domain score
  - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) role and physical functioning scores
- Time to symptomatic improvement in PRO scores was calculated as the date of the first score improvement minus the date of the first dose of nirogacestat plus 1 day
- Tumor responses were defined according to Response Evaluation Criteria in Solid Tumors (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

RESULTS

- Median duration of nirogacestat treatment was 33.6 months

SAFETY

- For most of the TRAEs reported by ≥20% of patients the onset of first occurrence was during the first month after initiating nirogacestat treatment (**Figure 1, Table 1**); 74% of patients reported TRAEs in the first month that were grade 1 or 2

DOSE REDUCTIONS AND TREATMENT DISCONTINUATIONS

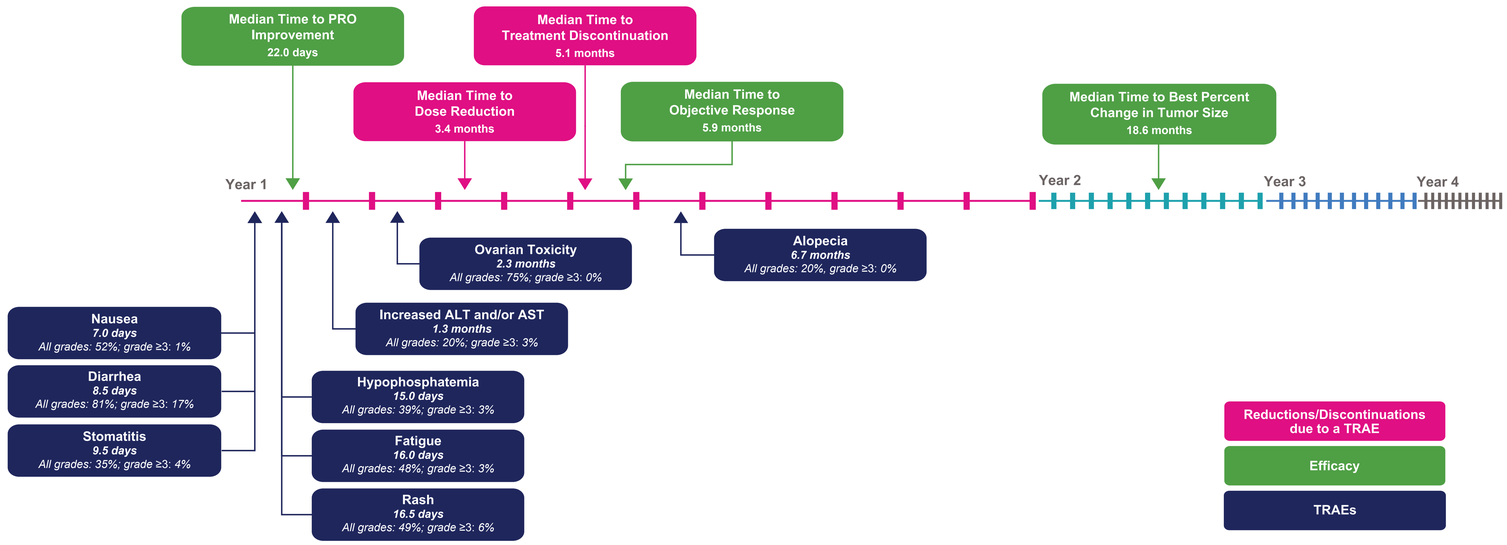
- Of the 34 patients with a dose reduction due to a TEAE, 33 (97%) were deemed to be related to study treatment
  - Median duration of treatment after dose reduction due to a TEAE was 24.0 months
  - Of these 33 patients with a dose reduction due to a TRAE, only 3 (9%) went on to discontinue treatment due to the same TRAE
  - The median time to dose reduction due to a TRAE was 3.4 months **(Figure 1)**
- In total, 20 patients (29%) receiving nirogacestat experienced a TEAE that led to treatment discontinuation; of these, 18 (90%) discontinued treatment due to a TRAE
  - The median time to treatment discontinuation due to a TRAE was 5.1 months **(Figure 1)**

EFFICACY

- Median time to objective response was 5.9 months, and median time to best percent change in tumor size was 18.6 months **(Figure 1)**
- Patients experienced improvement in PROs as early as the first visit after starting treatment **(Table 2)**; this benefit was sustained throughout treatment

RESULTS (CONT.)

Figure 1. Timeline of dose reductions and treatment discontinuations due to a TRAE, efficacy outcomes, and frequently reported TRAEs



TRAE data represent the incidence and median time until first onset for TRAEs reported by ≥20% of patients.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; PRO, patient-reported outcomes; TRAE, treatment-related adverse event.

Table 1. 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	N/A
Alopecia	14 (20)	6.7 months	0	N/A

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

Table 2. Timing of symptomatic improvement in PROs

Assessment	Patients, n/N (%)[a]	Median time to symptomatic improvement[b]
BPI-SF API[c]	43/46 (94)	22.0 days
DTSS TSS[c]	57/66 (86)	22.0 days
DTSS Pain[c]	58/64 (91)	22.0 days
DTIS PF	61/69 (88)	28.0 days
EORTC QLQ-C30 PF	44/52 (85)	29.0 days
EORTC QLQ-C30 RF	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.
API, average pain intensity; 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; PF, physical functioning; PRO, patient-reported outcome; RF, role functioning; TSS, total symptom score.

CONCLUSIONS

- Clinical benefit with nirogacestat is often experienced early, but TEAEs often precede radiologic evidence of response
- Pain is one of the most frequent and debilitating symptoms that patients with DT experience; based on these data from DeFi, 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 and for continuing treatment long enough to experience maximum benefit (median of approximately 18 months in the DeFi study)
- The first onset of most TRAEs was within the first month, but median time to dose reductions was not until after month 3, suggesting 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

DISCLOSURES: ***Emanuela Palmerini*** *discloses serving on advisory boards for Daiichy Sankyo, Deciphera Pharmaceuticals, Eusa Pharma, SynOx Therapeutics, Ipsen Biopharmaceuticals and Servier; receiving research funding from Bristol-Myers Squibb, Pfizer and PharmaMar; and receiving travel support from Lilly, Pharmamar, and Takeda.* ***Gabriel Tinoco*** *discloses acting in a consulting or advisory role for SynOx, Deciphera, Servier, and Merck Serono.*

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