RINGSIDE Phase 3 Study of Varegacestat in Desmoid Tumors: Primary Results and T2-weighted Signal Intensity Changes

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BACKGROUND

- Desmoid tumors (DT) are rare, connective tissue tumors that are often locally aggressive and infiltrative.
- Targeted systemic therapies, including gamma-secretase inhibitors (GSIs, nirogacestat), tyrosine kinase inhibitors (TKIs, sorafenib) and chemotherapy, are utilized for the treatment of DT.[1]
- RINGSIDE is a Phase 3 global, randomized, double-blinded, placebo-controlled trial of the investigational GSI varegacestat 1.2 mg once daily in adults with progressing DT.

RINGSIDE Phase 3 Analyses Reported Here

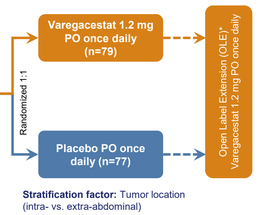
- Primary analysis of efficacy and safety
- Descriptive analysis of change in longitudinal T2-weighted (T2W) signal intensity on MRI—an indicator of cellular activity in DT[2] that may complement size-based response assessments[2-4]

METHODS

RINGSIDE Phase 3 Trial (NCT04871282)

Key Eligibility Criteria

- Adults with histologically confirmed DT that has progressed in the past 12 months per RECIST v1.1
- Treatment-naïve and previously treated patients
- Measurable disease
- ECOG PS score 0-2



Stratification factor: Tumor location (intra- vs. extra-abdominal)

Enrollment: Nov. 15, 2022 – Feb. 14, 2024

Data-cutoff date: Oct. 7, 2025

Endpoints

Primary: PFS by BICR

Key Secondary:

- ORR by BICR
- Change in tumor volume from baseline at Week 24 by BICR
- Change in GODDESS patient-reported worst pain intensity (WPI) from baseline at Week 12

Tumor Assessments by BICR

- Response per RECIST v1.1
- Tumor volume (TV)
- T2W signal intensity

Descriptive Analysis

Change from baseline in RECIST sum of diameters (SOD), TV, and T2W signal intensity

*Crossover to OLE from either arm allowed if progressive disease. BICR: blinded independent central review | DT: desmoid tumors | ECOG PS: Eastern Cooperative Oncology Group performance status | GODDESS: GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale | ORR: objective response rate | RECIST: Response Evaluation Criteria in Solid Tumors | PFS: progression free survival | T2W: T2-weighted

RESULTS

Participant Characteristics

Characteristic, n (%)		Varegacestat (n=79)	Placebo (n=77)
Median age (range), years		42.0 (18–66)	39.0 (20–69)
Sex	Male	26 (32.9)	29 (37.7)
	Female	53 (67.1)	48 (62.3)
	Premenopausal	36 (45.6)	38 (49.4)
Target tumor location†	Extra-abdominal	60 (75.9)	49 (63.6)
	Intra-abdominal	19 (24.1)	28 (36.4)
Medical history of FAP		7 (8.9)	8 (10.4)
Median target tumor size per RECIST (range), mm		75.1 (18.0, 244.9)	84.8 (21.3, 666.3)
Prior therapies	Any prior therapy	52 (65.8)	60 (77.9)
	Surgery	24 (30.4)	33 (42.9)
	Radiation therapy	8 (10.1)	12 (15.6)
	Systemic therapy‡	43 (54.4)	46 (59.7)
Prior systemic therapies	0 lines	36 (45.6)	31 (40.3)
	1 line	25 (31.6)	22 (28.6)
	≥2 lines	18 (22.8)	24 (31.2)

RECIST: Response Evaluation Criteria in Solid Tumors | † Per electronic data capture system | ‡ Includes chemotherapy, tyrosine kinase inhibitors, and hormonal therapy | Percentages may not total 100 because of rounding.

Dose Reductions & Discontinuation

Median Exposure: Varegacestat 20 months | Placebo 11 months

Dose Reduction Due to AEs: Varegacestat 80% | Placebo 9%

- Median time to first dose reduction: Varegacestat 3.5 months | Placebo 5.6 months
- Most common reason: Diarrhea 19%

Discontinuation Due to AEs: Varegacestat 20% | Placebo 6%

- Reasons varied with no single event in >2 participants

Safety Profile

- Among the most common adverse events, incidence of Grade 3+ was low
- No deaths due to adverse events
- Serious adverse events: Varegacestat 25 (32%) | Placebo 7 (9%)
- Of 26 varegacestat participants reporting alopecia, 25 had Grade 1 and one had Grade 2 attributed to another drug associated with alopecia

Adverse Events, n (%)	Varegacestat (n=79) Any grade	Varegacestat (n=79) Grade 3+	Placebo (n=77) Any grade	Placebo (n=77) Grade 3+
Any adverse event	79 (100)	45 (57)	70 (91)	13 (17)
Reported in ≥25% in either arm*				
Diarrhea	65 (82)	8 (10)	21 (27)	0
Fatigue	35 (44)	1 (1)	18 (23)	2 (3)
Rash	34 (43)	2 (3)	9 (12)	0
Nausea	28 (35)	0	20 (26)	0
Cough	27 (34)	0	4 (5)	0
Hypophosphatemia	27 (34)	1 (1)	2 (3)	0
Alopecia	26 (33)	0	3 (4)	0
Dry mouth	24 (30)	0	5 (7)	0
Hair color changes	20 (25)	0	0	0
Pruritus	20 (25)	0	4 (5)	0
Rash maculo-papular	20 (25)	1 (1)	1 (1)	0

*MedDRA preferred terms

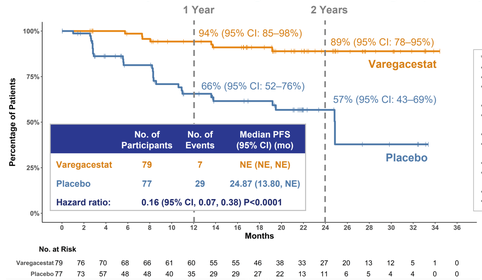
Ovarian Toxicity*

- A known class effect of GSI
- Varegacestat 56% | Placebo 5% (of premenopausal women)
- Resolved in 55% of those who reported it overall and among all who discontinued varegacestat and have follow-up available
- No discontinuations for ovarian toxicity

*Includes the MedDRA preferred terms amenorrhea, premature menopause, menopause, ovarian failure

Progression-free Survival Benefit

- 84% reduction in the risk of radiographic disease progression or death with varegacestat vs placebo (HR: 0.16, P<0.0001)
- PFS consistently favored varegacestat in all subgroups analyzed*

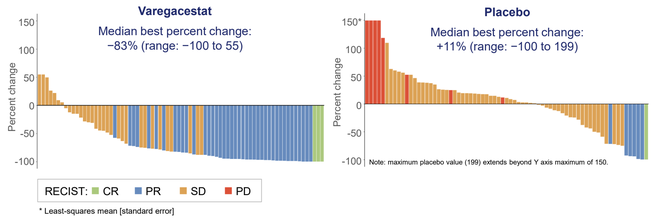


*Subgroup Analyses:
- Male/female
- Age ≤30 / >30 years
- Tumor location intra-/extra-abdominal
- *APC* mutation
- *CTNNB1* mutation (S45F+S45P T41A)
- Baseline tumor size >10 / ≤10 cm
- Baseline pain score (WPI ≥ 2 vs < 2)
- Prior DT surgery (yes/no)
- Prior systemic DT therapy (yes/no)
- Prior DT chemotherapy (yes/no)
- Prior TKI (yes/no)

Tumor Volume Reduction

- Significant tumor volume reduction* at Week 24 with varegacestat (-109.6 [40.64] cm^3) vs placebo (+122.8 [42.72] cm^3) | Difference: −232.4 (57.39) | P<0.0001

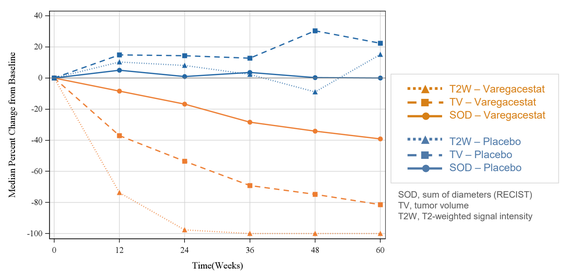
Tumor Volume Best Percent Change with RECIST Category Color-Coding Overlay



* Least-squares mean [standard error]

T2-Weighted Signal Intensity Reduction

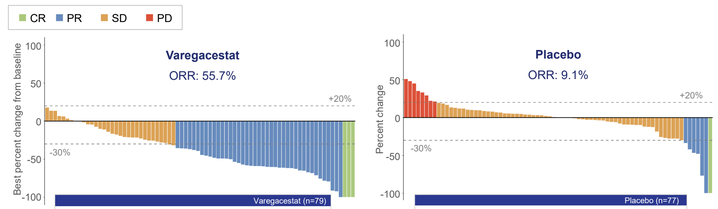
- Median best percent change: varegacestat -100% vs placebo -12%



SOD, sum of diameters (RECIST)
TV, tumor volume
T2W, T2-weighted signal intensity

Objective Response Benefit

- Significantly higher ORR with varegacestat (55.7%) vs placebo (9.1%) | P<0.0001

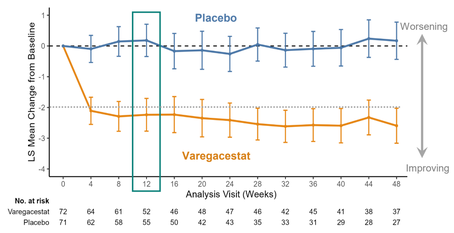


	Varegacestat (n=79)	Placebo (n=77)
Time to objective response (months), median (range)	8.2 (2.6–28.0)	16.7 (8.1–30.2)
Duration of response (months), median (95% CI)*	NE (NE, NE)	NE (NE, NE)
Best overall response, n (%)		
Complete response (CR)	3 (3.8)	1 (1.3)
Partial response (PR)	41 (51.9)	6 (7.8)
Stable disease (SD)	32 (40.5)	59 (76.6)
Progressive disease (PD)	0	10 (13.0)
Not available	3 (3.8)	1 (1.3)

*Kaplan-Meier estimate

Worst Pain Intensity Reduction

- Significant reduction in worst pain intensity score* at Week 12 with varegacestat (−2.24 [0.27]) vs placebo (+0.18 [0.27]) | Difference: −2.42 (0.37) | P<0.0001



- Clinically significant difference (>2 points) in favor of varegacestat as early as first evaluation at Week 4
- Assessed by Item 1 of the Gounder/ Desmoid Tumor Research Foundation Desmoid Tumor Symptom/Impact Scale

* Least-squares mean [standard error]

CONCLUSIONS

- RINGSIDE Phase 3 study of varegacestat 1.2 mg once daily vs placebo in progressing DT met its primary and all alpha-controlled secondary endpoints.
- Varegacestat benefits vs placebo:
  - 84% reduction in the risk of a PFS event
  - 55.7% ORR
  - Significant reduction in tumor volume at Week 24
  - Significant improvement in worst pain intensity at Week 12
- Early, marked decreases in T2W provide additional rationale for rapid clinical benefit and depth of response observed with varegacestat.
- Findings add to a growing body of work showing T2W may play a role in evaluating treatment response in DT.
- Once-daily varegacestat safety profile was consistent with the GSI class and manageable with dose modifications.
- Varegacestat has the potential to become a standard-of-care treatment for DT.

References: **1.** Kasper B, et al. *JAMA Oncol.* 2024;10(8):1121–1128. | **2.** Souza FF, et al. *Front Oncol.* 2023;13:1286807. | **3.** Sundaram M, et al. *AJR Am J Roentgenol.*1987;148(6):1247–50. | **4.** Vandevenne JE, et al. *Eur Radiol.* 1997;7(7):1013–9.

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