

Subgroup Analysis of the Phase 2 Part of the RINGSIDE Phase 2/3 Trial of Varegacestat for Treatment of Desmoid Tumors

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Key Takeaway Points

1

In the Phase 2 part of the RINGSIDE trial of progressive desmoid tumors, varegacestat demonstrated deep responses in all subgroups examined

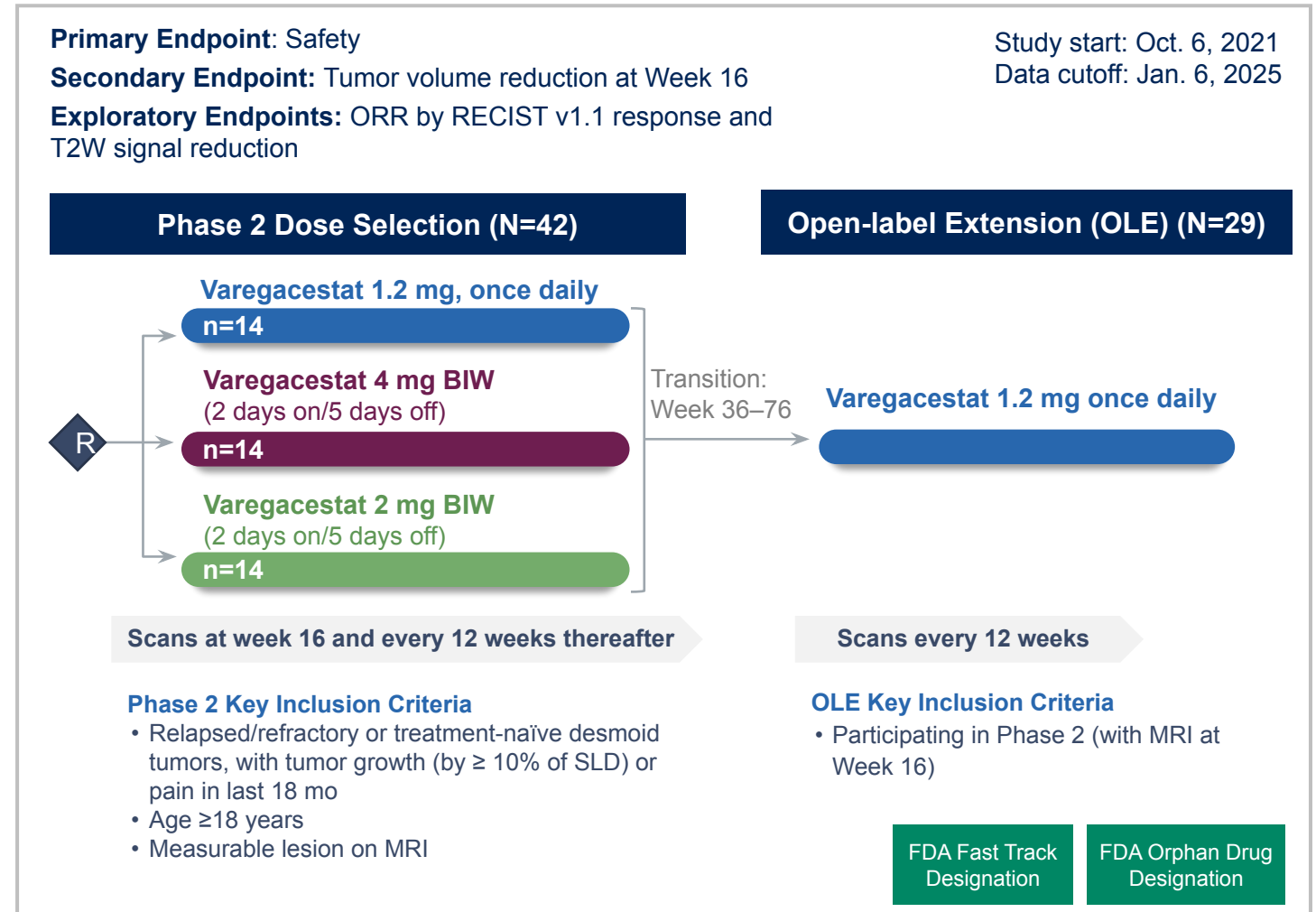
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RINGSIDE Phase 2 results support continued evaluation of varegacestat in the double-blind, randomized, placebo-controlled RINGSIDE Phase 3 study

Background & Methods: Phase 2 of the RINGSIDE Study

- Desmoid tumors (DTs) are rare locally aggressive connective tissue tumors with variable clinical presentations and behavior and different underlying pathogenic mutations
- Gamma secretase inhibitors (GSIs) have biological rationale and have shown anti-tumor activity in DTs
- RINGSIDE Phase 2 demonstrated safety and responses in patients with DTs when treated with the GSI varegacestat (AL102)¹
- We evaluated treatment responses in key patient subgroups to determine if signals of activity were broad or limited

1. Kasper B, et al. European Society for Medical Oncology Annual Meeting, Sep.13-17, 2024, Barcelona, Spain.



Baseline Characteristics & Safety Summary

- 42 participants (pts) enrolled, 29 (69%) entered the OLE
- 12 pts (29%) still on treatment
- Median time on treatment: 23.3 months (0.7 – 38.8)

- 8 pts (19%) had a serious adverse event (AE)
- 9 pts (21%) discontinued due to an AE
- 14 (33%) pts had treatment-related Grade 3 AEs | No Grade 4-5 AEs

Characteristics	All patients all doses (N=42)	
Age (years), median (min, max)	38.5 (19-72)	
Sex, n (%)	Female	31 (73.8)
	Male	11 (26.2)
ECOG Performance Status, n (%)	0	35 (83.3)
	1	7 (16.7)
Tumor Location at Screening, n (%)		
	Intra Abdominal	12 (28.6)
	Extra Abdominal	30 (71.4)
Tumor size at baseline by BICR, (mm) median (min, max)	69.40 (17.0, 156.2)	
Prior DT Therapy, n (%)	Systemic	29 (69.0)
	Surgery	19 (45.2)
	Radiation	4 (9.5)

Most Common Adverse Events, n (%)	All patients all doses (N=42)	
	All Grades	Grade ≥3*
Diarrhoea	35 (83.3)	5 (11.9)
Nausea	23 (54.8)	0
Fatigue	22 (52.4)	2 (4.8)
Hypophosphatemia	15 (35.7)	0
Stomatitis	15 (35.7)	1 (2.4)
Cough	14 (33.3)	1 (2.4)
Headache	14 (33.3)	0
Rash	14 (33.3)	0
Alopecia	13 (31.0)	0
Dry mouth	13 (31.0)	0
Dry skin	13 (31.0)	0

*No Grade 4 or Grade 5 events were reported

ORR and DOR Across Subgroups

Across age, tumor size, prior therapy, tumor location and mutation (APC vs CTNNB1) subgroups:

- ORR ranged from 50% to 78%
- Median DOR ranged from 37.1 to 79.8 weeks
- Responses were seen in all subgroups examined

Subgroups		ORR n (%)	DOR (weeks) Median (min, max)
All MRI-evaluable patients (n=37)		24 (65)	58.9 (12.1, 120.6)
Age	≤40 years (n=22)	13 (59)	66.1 (22.1, 110.0)
	>40 years (n=15)	11 (73)	37.1 (12.1, 120.6)
Tumor size	<70 mm (n=19)	10 (53)	52.1 (22.1, 99.0)
	≥70 mm (n=18)	14 (78)	78.4 (12.1, 120.6)
Prior lines of therapy	0 (n=11)	6 (55)	79.8 (22.1, 95.9)
	1 (n=13)	9 (69)	37.1 (12.1, 120.6)
	2+ (n=13)	9 (69)	56.0 (12.1, 110.0)
Tumor location	Intra-abdominal (n=10)	5 (50)	46.1 (12.1, 99.0)
	Extra-abdominal (n=27)	19 (70)	61.9 (12.1, 120.6)
Mutation*	APC (n=8)	4 (50)	55.4 (12.1, 66.1)
	CTNNB1 (n=19)	13 (68)	79.6 (22.1, 120.6)
	S45F (n=3)	2 (67)	31.0 (24.9, 37.1)
	T41A (n=5)	2 (40)	88.2 (55.9, 120.6)
	Other (n=11)	9 (82)	82.0 (22.1, 110.0)

ORR, objective response rate; DOR, duration of response

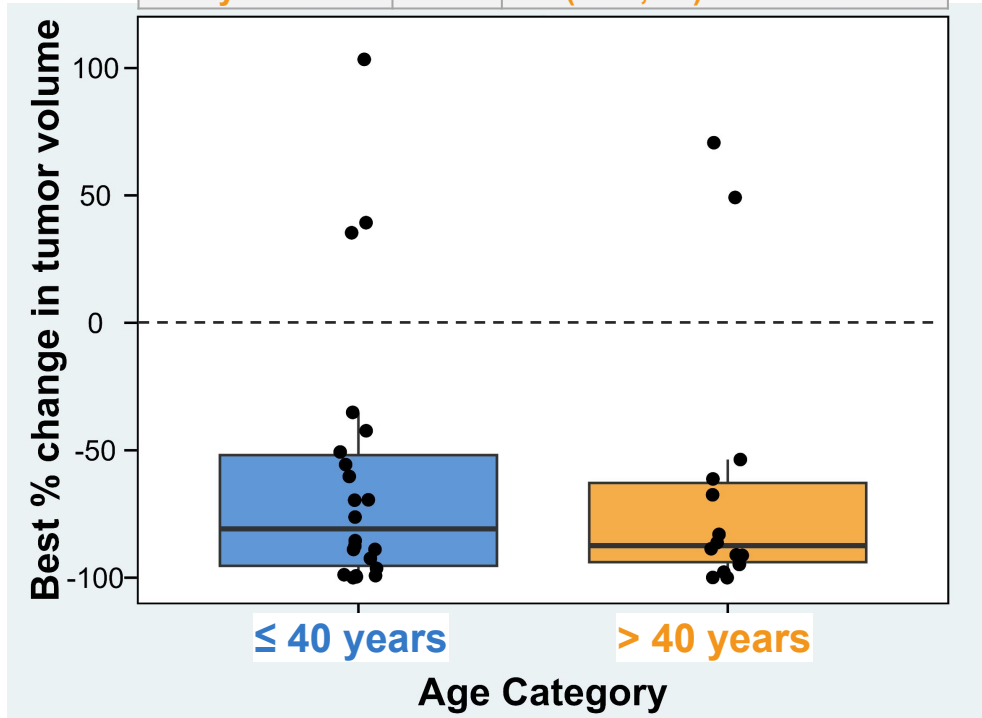
*10 subjects with both APC and CTNNB1 categorized as “no” or “unknown” were excluded from the analysis

Tumor Volume Reduction by Age and Mutation Type

Best % Change

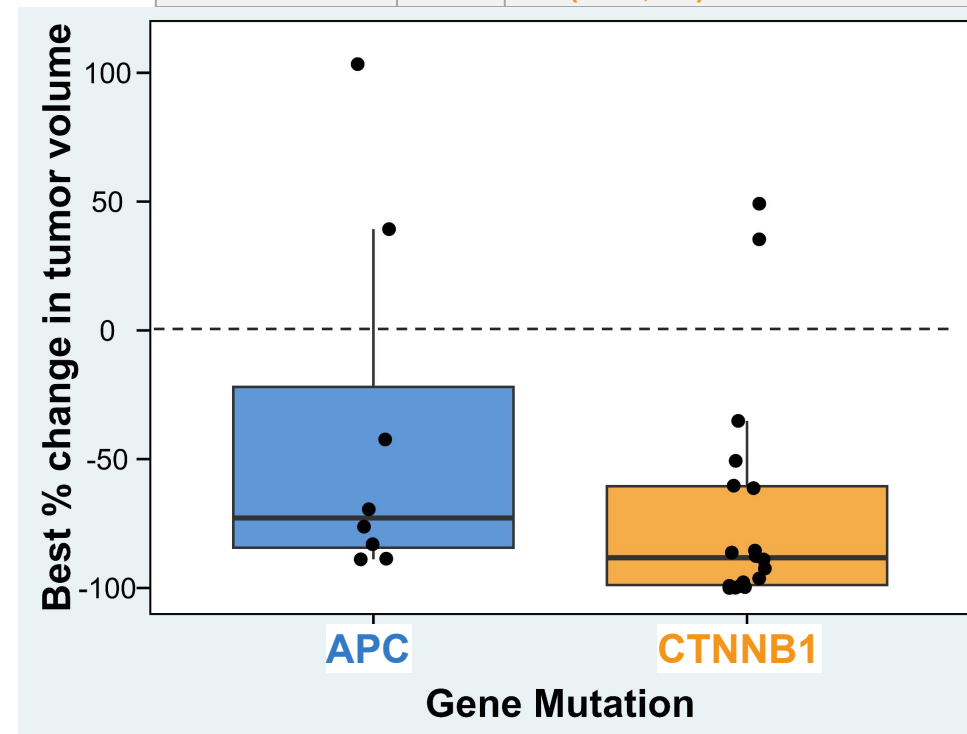
Patient Age

Age	N	Median % (min, max)
≤ 40 years	22	-81 (-100, 103)
> 40 years	14	-87 (-100, 71)



Mutation Type

Mutation	N	Median % (min, max)
APC	8	-73 (-89, 103)
CTNNB1	18	-88 (-100, 49)



N=36 for tumor volume reduction. Volume results were per blinded independent central review and was missing for one patient with PR

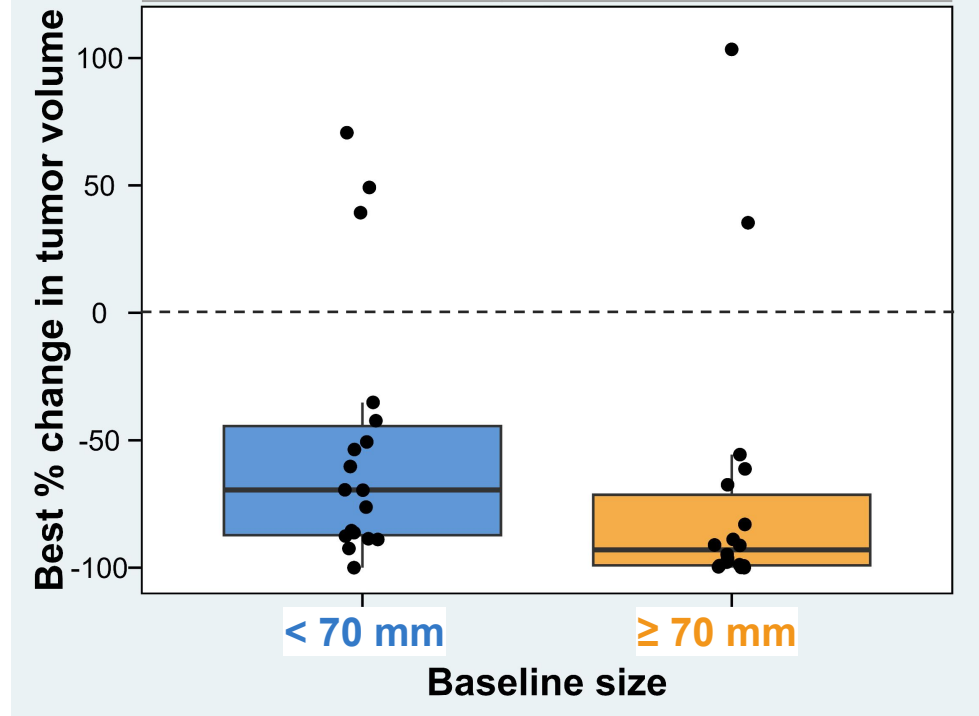
Abstract #40.
Gounder et al.
T2-Weighted Signal Intensity, Tumor Volume, and Exposure-Response Analysis in RINGSIDE Study

Tumor Volume Reduction by Size and Location

Best % Change

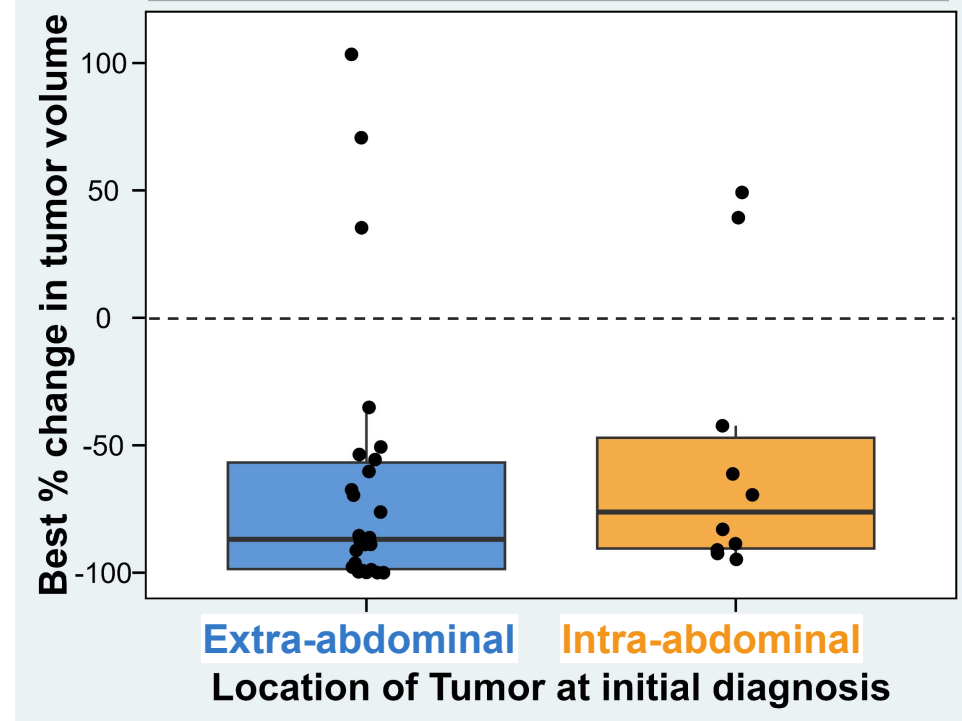
Baseline Tumor Size

Size	N	Median % (min, max)
< 70 mm	18	-70 (-100, 71)
≥ 70 mm	18	-93 (-100, 103)



Tumor Location

Location	N	Median % (min, max)
Extra-abdominal	26	-87 (-100, 103)
Intra-abdominal	10	-76 (-95, 49)

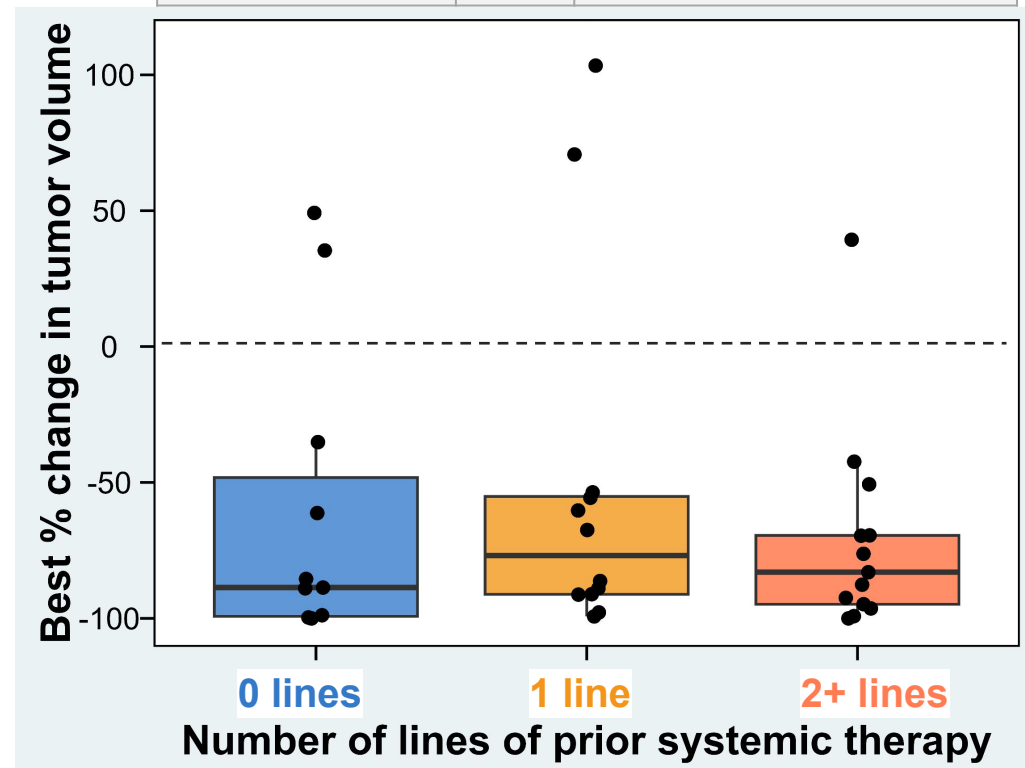


N=36 for tumor volume reduction. Volume results were per blinded independent central review and missing for one patient with PR.

Tumor Volume Reduction by Number of Prior Lines of Therapy

Best % Change

# of therapies	N	Median % (min, max)
0 lines	11	-89 (-100, 49)
1 line	12	-77 (-99, 103)
2+ lines	13	-83 (-100, 39)



N=36 for tumor volume reduction. Volume results were per blinded independent central review and missing for one patient with PR.

Limitations

- This is a post hoc analysis of outcomes in different patient subgroups
- The sample sizes in each subgroup are relatively small
- We limited our analysis to subgroups with at least 5 patients
- The dosing regimen for patients on 2/4 mg intermittent* changed to 1.2 mg once daily when they entered the OLE, per the study design

*2 days on/5 days off
OLE, open-label extension

Conclusions

- In the **Phase 2** RINGSIDE study of progressive desmoid tumors, varegacestat demonstrated deep responses in all subgroups examined
- RINGSIDE **Phase 2** results support continued evaluation of varegacestat for desmoid tumors in the double-blind, randomized, placebo-controlled RINGSIDE **Phase 3** study (NCT04871282)

Acknowledgements

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Lay Summary Slide

What did this research tell us?

- In the Phase 2 part of the RINGSIDE study, varegacestat reduced desmoid tumor size in most patients regardless of age, mutation type, tumor size, tumor location, and number of prior therapies

Who does this research impact?

- Adults with desmoid tumors

What does this mean for patients right now?

- Varegacestat is still being studied for treatment of desmoid tumors
- The Phase 3 part of the RINGSIDE trial is evaluating varegacestat compared with a placebo in patients with desmoid tumors