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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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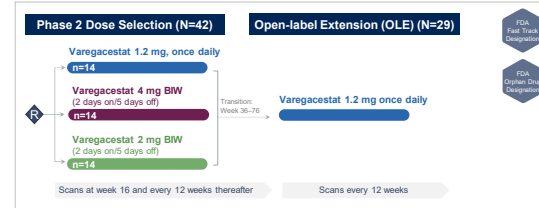
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BACKGROUND

- 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

METHODS

Phase 2 of the RINGSIDE Study (NCT04871282)



Phase 2 Key Inclusion Criteria

- Relapsed/refractory or treatment-naïve desmoid tumors, with tumor growth (by $\geq 10\%$ of SLD) or pain in last 18 months
- Age ≥ 18 years
- Measurable lesion on MRI

OLE Key Inclusion Criteria

- Participating in Phase 2 (with MRI at Week 16)

Study start: Oct. 6, 2021

Data cutoff: Jan. 6, 2025

Primary Endpoint: Safety

Secondary Endpoint: Tumor volume reduction at Week 16

Exploratory Endpoints: ORR by RECIST v1.1 response and T2W signal reduction

RESULTS

Baseline Characteristics

- 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)

| 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) |

Safety Summary

- 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

| 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 |
| Alpecia | 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

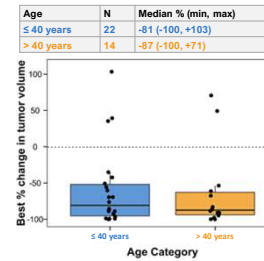
Limitations

- 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

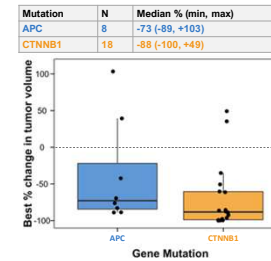
Tumor Volume Reduction Across Subgroups

Best % Change

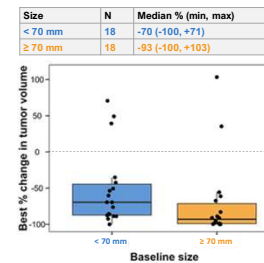
Patient Age



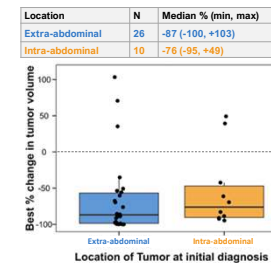
Mutation Type



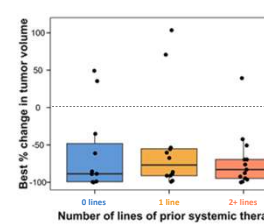
Baseline Tumor Size



Tumor Location



Number of Prior Lines of Therapy



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

ORR and DOR Across Subgroups

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

- ORR by RECIST 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) |

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

CONCLUSIONS

- In the Phase 2 RINGSIDE study of progressive desmoid tumors, responses were seen in patients treated with varegacestat 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)