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Phase 2 Results from the RINGSIDE Phase 2/3 Trial of AL102 for Treatment of Desmoid Tumors

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BACKGROUND

Desmoid Tumors (DTs) Are Rare, Highly Debilitating Soft Tissue Tumors with No Approved Therapies

Aggressive, invasive connective tissue tumors that infiltrate surrounding tissues and affect function of organs and nerves[1]

- DTs can occur in any anatomic location

Associated with significant disease impacts

- Tumors can cause severe, chronic pain, deformity, swelling, loss of function, bowel obstruction or perforation, and/or threat to vital organs

Substantial burden of illness

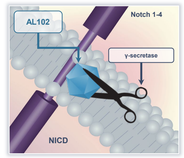
- Symptoms are chronic and quality of life is reduced[2]

No approved therapies and no effective systemic treatment options available

- Local therapies, such as surgery or radiation, are associated with frequent recurrence and toxicity
- Chemotherapy (e.g., doxorubicin) and tyrosine kinase inhibitors (e.g., sorafenib) show limited and inconsistent efficacy with high toxicity rates

DT Pathophysiology Is Driven by Wnt Pathway

- DT are driven by CTNNB1 (somatic) mutations (~85%) or APC (germline) mutations (10-15%)—both result in activation of the Wnt Pathway[3]
- There is overlap as well as direct cross talk between Notch target gene activation and Wnt Pathway[4]
- γ-secretase inhibitors (GSIs) are potent modulators of Notch, providing a mechanistic rationale for GSI therapy in DT[4]
- Investigational AL102 is a selective inhibitor of γ-secretase-mediated Notch signaling in vitro

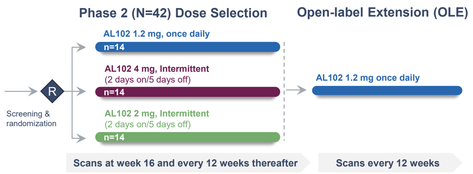


METHODS

RINGSIDE Phase 2 Study & Open-Label Extension

Primary Endpoint: Safety
Secondary Endpoint: Tumor volume reduction
Exploratory Endpoints: RECIST and T2W signal reduction

FDA Fast Track Designation



Phase 2 Key Inclusion Criteria

- Relapsed/refractory or treatment-naïve DT, with tumor growth (by ≥ 10% of SLD) or pain in last 18 mo
- Age ≥18 years
- Measurable Lesion on MRI

OLE Key Inclusion Criteria

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

MRI, magnetic resonance imaging | OLE, open-label extension | SLD, sum of largest diameters

Current Analysis

- Data cut-off July 5, 2023
- **Phase 2 fully enrolled in March 2022**
  - 88% of patients had progressive disease per RECIST criteria at enrollment
- **Open-label extension**
  - 29 patients rolled over between Oct 2022 – May 2023
  - 27 still on study
- **Median (range) time on treatment:**
  - On Phase 2 (42 enrolled patients): 11.9 (1-17.5) months
  - On Open-label extension (28 patients rolled over from Phase 2): 4.0 (1.2-8.3) months
  - Phase 2 and OLE: 16.6 months

RESULTS

Efficacy in Phase 2 and Open-Label Extension

Patient Population Is Representative of Patients with DTs

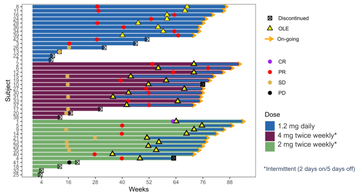
Baseline characteristics were generally balanced across treatment groups

Baseline Patient and Disease Characteristics	Total (N=42) n (%)
Age (years), Median (range)	38.5 (19-72)
Gender	
Female	31 (73.8)
Male	11 (26.2)
Location of Tumor at Initial Diagnosis	
Intra Abdominal	12 (28.6)
Extra Abdominal	31 (71.4)
Size of Tumor, Measured (n)	39
Median in mm (min, max)	61.0 (0, 169)
Prior Desmoid Cancer Therapies	29 (69.0)
Prior Desmoid Cancer Surgeries	20 (47.6)
Prior Desmoid Radiation Therapies	4 (9.5)

Treatment Duration and Time to Response

Half of the responses in the 1.2 mg arm occurred by Week 28

- Four additional patients from the twice weekly dosing arms achieved a response or confirmation of response (3 PRs and 1 CR) after switching to once daily dosing of 1.2 mg

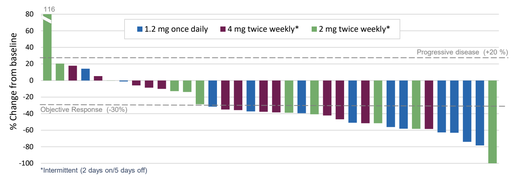


*Intermittent (2 days on/5 days off)

Best Overall Response by RECIST per BICR[1]

1.2 mg once daily achieved ORR of 83% per RECIST criteria in the evaluable population (N=12)

- Efficacy results demonstrate a dose-response pattern favoring the 1.2 mg daily arm
- The twice weekly 2 and 4 mg arms achieved lower ORRs than the 1.2 mg daily arm
- The ORR was 64% across the 3 dose arms (n=36)



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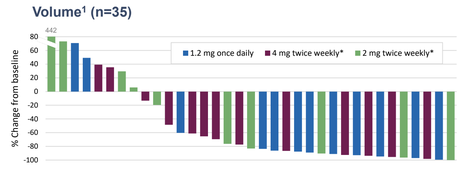
Objective Response [2] per RECIST	1.2 mg once daily Evaluable[2] (n=12)	1.2 mg once daily ITT (n=14)	4 mg twice weekly* Evaluable[2] (n=13)	4 mg twice weekly* ITT (n=14)	2 mg twice weekly* Evaluable[2] (n=11)	2 mg twice weekly* ITT (n=14)	All Evaluable[2] (n=36)	All ITT (n=42)
Objective Response Rate (CR + PR), n (%)	**10 (83)**	**10 (71)**	**8 (62)**	**8 (57)**	**5 (45)**	**5 (36)**	**23 (64)**	**23 (55)**
Best Overall Response								
Complete Response (CR)	0	0	0	0	**1 (9)**	**1 (7)**	**1 (3)**	**1 (2)**
Partial Response (PR)	**10 (83)**	**10 (71)**	**8 (62)[3]**	**8 (57)[3]**	**4 (36)**	**4 (29)**	**22 (61)**	**22 (52)**
Stable Disease (SD)	2 (17)	2 (14)	5 (38)	5 (36)	5 (45)	5 (36)	12 (33)	12 (29)
Progressive Disease (PD)	0	0	0	0	1 (9)	1 (7)	1 (3)	1 (2)
Disease Control Rate (DCR)	12 (100)	12 (86)	13 (100)	13 (93)	10 (91)	10 (71)	35 (97)	35 (83)
Time to objective response, median (range), months	8.1 (3.8, 15)		12 (9, 18)		9.2 (6.4, 9.2)		9.4 (3.8, 18)	

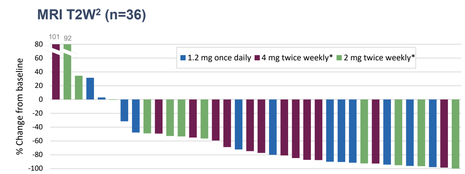
*Intermittent (2 days on/5 days off)
1. Change from baseline in tumor shrinkage as measured on MRI by Blinded independent Central Review (BICR)
2. Evaluable population defined as patients with at least 1 post-baseline scan
3. Three PRs in the 4 mg twice weekly arm were achieved after rolling over to 1.2 mg daily

Reductions in Volume and in T2W Are Consistent with RECIST Responses

These changes preceded RECIST responses across all arms but were deeper in the 1.2 mg daily arm

- A decrease in T2 signal intensity, as measured by MRI, reflects a decrease in tumor cellularity and in DT is considered an indicator of anti-tumor activity and symptomatic improvement

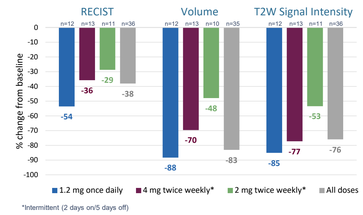




*Intermittent (2 days on/5 days off)
1. Change from baseline in tumor volume as measured on MRI by Blinded independent Central Review (BICR)
2. Change from baseline T2 weighted signal intensity on MRI by BICR

Median Best Response Across Dose Arms by BICR

Greatest reductions in tumor size and T2 signal intensity in the 1.2 mg daily arm



*Intermittent (2 days on/5 days off)

Consistent Pattern of Deeper, More Rapid and Persistent Tumor Responses for 1.2 mg Once Daily

Reductions in volume and T2 signal intensity were also observed across twice weekly dose arms

- Early and significant volume (-52%) and T2 (-58%) reductions were observed at 16 weeks in the 1.2 mg arm
- Tumor volume shrinkage consistently deepens over time and some patients continue to PR or CR by RECIST with longer follow-up

Median % change from baseline over time

Parameter	Study Visit	1.2 mg once daily (n= 12)[1]	4 mg twice weekly* (n=13)[1]	2 mg twice weekly* (n=11)[1]
RECIST (sum of diameters)	Week 16	-13	2	-7
	Week 28	-26	-10	-7
	Week 40	-23	-17	-22
	Week 52	-37	-35	-23
	Week 64	-40	-34	-29
Volume	Week 16	-52	-10	-15
	Week 28	-76	-36	-51
	Week 40	-76	-63	-61
	Week 52	-84	-74	-70
	Week 64	-82	-77	-44
T2W Signal Intensity (cellularity)	Week 16	-58	-38	-28
	Week 28	-79	-42	-50
	Week 40	-76	-59	-55
	Week 52	-87	-77	-93
	Week 64	-90	-80	-90

*Intermittent (2 days on/5 days off)
1. n, represents all evaluable patients in that arm. Percentage of results per week and modality may vary based on availability of result per patient/modality/visit

Abbreviations: BICR, Blinded independent Central Review | CR, complete response | ITT, intention to treat | MRI, magnetic resonance imaging | SD, stable disease | OLE, open-label extension | ORR, objective response rate | PR, partial response | PD, progressive disease | RECIST, Response Evaluation Criteria in Solid Tumors | T2W, T2-weighted

Safety in Phase 2 and Open-Label Extension

Safety Profile Overall and in 1.2 mg Once-Daily Group Is Consistent with GSI Class

Safety Population[a], n (%)	1.2 mg once daily (n=14)	4 mg twice weekly* (n=14)	2 mg twice weekly* (n=14)
One or more TEAEs at any grade	14 (100%)	14 (100%)	14 (100%)
One or more grade ≥3 TEAEs	5 (35.7%)	7 (50%)	9 (64.3%)
TEAEs leading to discontinuation	4 (28.6%)	0 (0.0%)	3 (21.4%)
Any serious TEAE	1 (7.1%)	1 (7.1%)	5 (35.7%)
Treatment-related serious TEAEs	0 (0%)	0 (0%)	0 (0%)
TEAEs leading to death	0 (0%)	0 (0%)	0 (0%)
Months on the study (median range), months	16.1 (2.1, 19.3)	16.8 (2.9, 20.6)	16.6 (1, 20.9)

a. Showing the number (%) of patients in each category
*Intermittent (2 days on/5 days off).

AL102 was generally well tolerated with a manageable safety profile across all dose arms

- Regardless of dose regimen, adverse events (AEs) were predominantly Grade 1 (~69%) or Grade 2 (~26%); Most common were diarrhea, nausea, fatigue dry skin and stomatitis
- There were no grade 5 AEs
- There was one grade 4 unrelated AE (acute pancreatitis secondary to gall stones)
- Serious AEs were reported in 7/42 patients (17%) and assessed as unrelated to AL102 by investigators
- Discontinuation due to AEs occurred in 7/42 of patients (17%)

Ovarian dysfunction† was reported in pre-menopausal women across all dose arms

- 5/9 (56%) with 1.2 mg once daily
- 6/8 (75%) and 3/6 (50%) with 4 and 2 mg twice weekly,* respectively

†Ovarian dysfunction defined as premature menopause, menopause, ovarian failure, amenorrhea, and irregular menstruation

TEAEs reported in ≥25% of patients at 1.2 mg QD and Across All Dose Arms

Study Population, n (%)	1.2 mg once daily (n=14)	
	All Grades	Grade 3
Diarrhoea	13 (92.8)	2 (14.3)
Nausea	8 (57.1)	–
Fatigue	7 (50)	–
Alopecia	7 (50)	–
Dry skin	7 (50)	–
Stomatitis	7 (50)	1 (7.1)
Dermatitis acneiform	6 (42.9)	–
Dry mouth	6 (42.9)	–
Hypophosphatemia	6 (42.9)	–
Rash maculo-papular	5 (35.7)	–
Aspartate aminotransferase increased	4 (28.6)	–

Study Population, n (%)	All Patients All Doses (N=42)	
	All Grades	Grade 3
Diarrhoea	33 (78.6)	4 (9.5)
Nausea	23 (54.8)	–
Fatigue	18 (42.9)	1 (2.4)
Dry skin	14 (33.3)	–
Stomatitis	14 (33.3)	1 (2.4)
Alopecia	13 (31.0)	–
Dry mouth	13 (31.0)	–
Headache	12 (28.6)	–
Hot flush	12 (28.6)	–
Hypophosphataemia	12 (28.6)	–
Cough	11 (26.2)	–
Rash	11 (26.2)	1 (2.4)
Rash maculo-popular	11 (26.2)	1 (2.4)
Vomiting	11 (26.2)	1 (2.4)

CONCLUSIONS

AL102 was generally well tolerated with a manageable safety profile in all dose arms

- Safety is consistent with MOA and the GSI class of drug
- Most treatment-emergent AEs were Grade 1 or 2 (95%)

Phase 2 efficacy was demonstrated across all dose arms

- Deepest, more rapid and persistent tumor responses in volume reduction, T2W signal intensity and RECIST with AL102 1.2 mg daily than with intermittent doses
  - RECIST ORR was 83% in the 1.2 mg daily arm with median best reduction in volume (-88%) and T2W (-85%)
  - RECIST ORR was 64% across all 3 dose arms
  - Early and deep volume (-52%) and T2 (-58%) reductions within 16 weeks of starting 1.2 mg daily may correlate with symptomatic improvements[5]

1.2 mg once daily was selected for the currently enrolling Phase 3, double-blind, placebo-controlled trial (NCT04871282)

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References: 1. Gounder MM, et al. J Clin Oncol. 2018, 36(2):202-209. **| 2.** Fernandez M, et al., Burden of illness of desmoid tumors. Poster presented at 2022 CTOS Annual Meeting, November 16, 2022, Vancouver, Canada, and 2022 Desmoid Tumor Research Foundation Annual Meeting. **| 3.** Lazar AJ, et al. Am J Pathol. 2008, 173:1518. **| 4.** Ungerbäck J, et al. PLoS One. 2011, 6:e17957. **| 5.** Zanchetta E, et al. Cancer Medicine. 2021;10:4356–4365.

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