Abstract #11515

RINGSIDE Phase 2/3 Trial of AL102 for Treatment of Desmoid Tumors (DT): Updated Phase 2 Results

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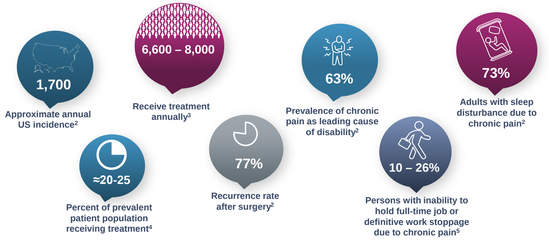
BACKGROUND

Desmoid Tumors

- DTs are locally aggressive, invasive connective tissue tumor associated with a high recurrence rate but with no metastatic potential
- DTs infiltrate surrounding tissues and affect organs and nerves[1]
- Substantial burden of illness due to chronic symptoms, decreased quality of life, and increased financial burden[2]
- No approved therapies
- Move away from surgery leaves a treatment gap/opportunity

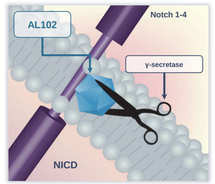
DTs are associated with[1]

- Long-lasting pain due to nerve compression or tumor pressure
- Restricted range-of-motion
- Lesion ulceration
- Organ dysfunction
- Amputation
- Disfigurement
- Significant morbidity



AL102: Potential Treatment for DT

- DTs are characterized by CTNNB1 (somatic) mutations (~85%) or APC (germline) mutations (10-15%), both result in activation of the Wnt pathway[6]
- There is overlap and direct cross talk between Notch target gene activation and Wnt pathway[7]
- Gamma secretase inhibitors (GSIs) are potent modulators of Notch, providing a mechanistic rationale for GSI therapy in DT[7]
- Strong clinical evidence supports the role of GSI class in DT
- Tumor shrinkage (per RECIST criteria) and volume reduction (on MRI) have been documented with Ayala's GSIs AL101 and AL102[8-10] in clinical studies, as well as with nirogacestat in late-stage clinical studies[6,7]



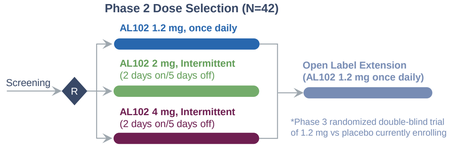
METHODS

RINGSIDE: Pivotal Phase 2/3* Trial Evaluating AL102 in DT

NCT04871282

Phase 2 fully enrolled (March 2022) | Treatment ongoing | Data cut: 03 Jan 2023

Phase 2 Dose Selection (N=42)



Phase 2 Endpoints

Primary: Safety

Secondary : Tumor volume reduction

Phase 2 Key Inclusion Criteria

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

OLE Key Inclusion Criteria

- Rollover patients from Phase 2 (active on treatment when Phase 2 ends)
- Crossover patients from Phase 3 (were noted to have progressive disease by central review)

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

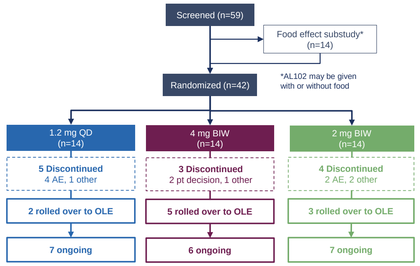
RESULTS

Baseline Characteristics

- Baseline characteristics were generally balanced across treatment groups

Baseline Patient and Disease Characteristics	1.2 mg QD (N=14) n (%)	4 mg BIW (N=14) n (%)	2 mg BIW (N=14) n (%)	Total (N=42) n (%)
Age (years), median (range)	44 (24-61)	36 (24-69)	32.5 (19-72)	38.5 (19-72)
Gender				
Female	11 (78.6)	11 (78.6)	9 (64.3)	31 (73.8)
Male	3 (21.4)	3 (21.4)	5 (35.7)	11 (26.2)
Location of Tumor at Initial Diagnosis				
Intra Abdominal	4 (28.6)	3 (21.4)	4 (28.6)	11 (26.2)
Extra Abdominal	10 (71.4)	11(78.6)	10(71.4)	31 (73.8)
Size of Tumor (mm)	14	13	12	39
Median (min, max)	62.0 (35, 169)	65 (11, 110)	55.5 (0, 120)	61.0 (0, 169)
Prior Desmoid Cancer Therapies	9 (64.3)	7 (50.0)	13 (92.9)	29 (69.0)
Chemotherapy	7 (50)	4 (28.6)	9 (64.3)	20 (47.6)
Targeted small molecule	2 (14.3)	4 (28.6)	6 (42.9)	12 (28.6)
Hormonal therapy	3 (21.4)	2 (14.3)	4 (28.6)	9 (21.4)
Prior Desmoid Cancer Surgeries	7 (50.0)	5 (35.7)	8 (57.1)	20 (47.6)
Prior Desmoid Radiation Therapies	1 (7.1)	1 (7.1)	2 (14.3)	4 (9.5)

Subject Disposition

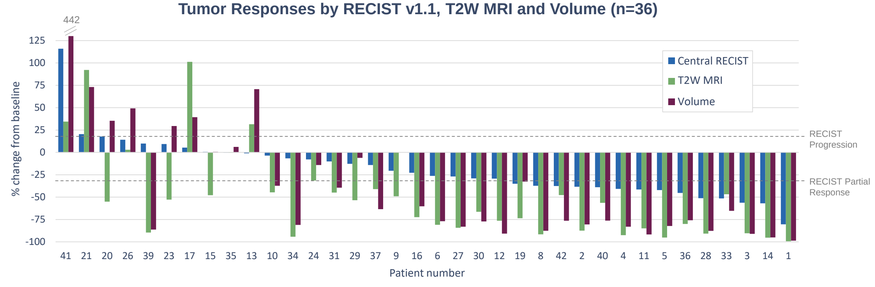


OLE, open-label etexnsion

Efficacy Outcomes

Substantial Reductions in Tumor Size – Consistent Among All Measures

Tumor Responses by RECIST v1.1, T2W MRI and Volume (n=36)



Best Overall Response by BICR

- 1.2 mg once daily achieved ORR of 50% in the evaluable population
- Current median time on treatment is 10.3 months and the study is ongoing
- Changes in tumor volume and T2W MRI (tumor cellularity) typically preceded RECIST responses and were deeper than those in the RECIST evaluation
- A decrease in T2W, as measured by MRI, reflects a decrease in tumor cellularity and in DT is considered a strong indicator of anti-tumor activity
- Tumor volume shrinkage consistently deepens over time and some patients continue to PRs by RECIST with longer follow-up

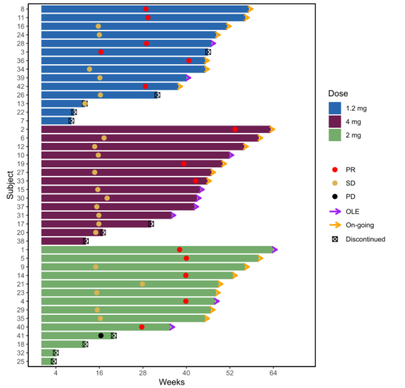
Evaluable population	1.2 mg QD (n= 12)	4 mg BIW (n=13)	2 mg BIW (n=11)
ORR (CR + PR), n (%)	**6 (50)**	**3 (23.1)**	**5 (45.5)**
Complete Response (CR)	0	0	• 0
Partial Response (PR)	**6 (50)**	**3 (23.1)**	**5 (45.5)**
Stable Disease (SD)	6 (50)	10 (76.9)	4 (36.4)
Progressive Disease (PD)	0	0	2 (18.1)
Disease Control Rate	100%	100%	81.9%
Time to objective response (months), median (range)	6.7 (3.8-9.4)	9.8 (9.0-12.3)	9.2 (6.4-9.2)

BICR, blinded independent central review | ORR, objective response rate | RECIST, Response Evaluation Criteria in Solid Tumors v1.1 by BICR | T2W MRI, T2-weighted signal intensity on MRI by BICR

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

Study Visit	Median % Change from Baseline: 1.2 mg QD (n= 12)	4 mg BIW (n=13)	2 mg BIW (n=11)
Tumor Volume			
Week 16	**-51.9**	-9.5	-15.2
Week 28	**-76.4**	-35.5	-51.2
Week 40	**-75.9**	-63.4	-61.2
T2W Signal Intensity (cellularity)			
Week 16	**-58.4**	-37.9	-28.2
Week 28	**-77.8**	-42.1	-50.2
Week 40	**-85.2**	-56.6	-54.9
RECIST (sum of diameters)			
Week 16	**-13.3**	1.7	-7.2
Week 28	**-29.4**	-9.6	-7.0
Week 40	**-22.8**	-16.7	-22.0

Most PRs in 1.2 mg Arm Achieved at 16 to 28 Weeks



Safety Outcomes

Summary

- 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 (~70%) or Grade 2 (~20%) | Most common were diarrhea, nausea, fatigue, alopecia, and dry skin
  - There were no Grade 4-5 related AEs
  - Serious AEs were reported in 6/42 patients (14%) and assessed as unrelated to AL102 by investigators
- Discontinuation due to AEs occurred in 6/42 of patients (14%)
  - These were Grade 2 rash, keratitis, stomatitis, diarrhea, ALT elevation
  - All occurred within 3 months of treatment initiation
- Ovarian dysfunction was reported in 11/23 (48%) women of childbearing potential across all dose arms, but only in 3/9 (33%) with 1.2 mg once daily

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

Adverse Events Reported in ≥20% of Patients

Preferred Term	1.2 mg QD (N=14) n (%)				4 mg BIW (N=14) n (%)				2 mg BIW (N=14) n (%)			
	Grade 1	Grade 2	Grade 3	Total	Grade 1	Grade 2	Grade 3	Total	Grade 1	Grade 2	Grade 3	Total
Diarrhea	8 (57.1)	3 (21.4)	2 (14.3)	13 (92.9)	6 (42.9)	3 (21.4)	1 (7.1)	10 (71.4)	5 (35.7)	1 (7.1)	1 (7.1)	7 (50)
Nausea	5 (35.7)	3 (21.4)	—	8 (57.1)	6 (42.9)	3 (21.4)	—	9 (64.3)	4 (28.6)	—	—	4 (28.6)
Fatigue	7 (50)	—	—	7 (50)	4 (28.6)	2 (14.3)	—	6 (42.9)	3 (21.4)	2 (14.3)	—	5 (35.7)
Alopecia	7 (50)	—	—	7 (50)	4 (28.6)	—	—	4 (28.6)	2 (14.3)	—	—	2 (14.3)
Dry skin	7 (50)	—	—	7 (50)	4 (28.6)	—	—	4 (28.6)	1 (7.1)	—	—	1 (7.1)
Hypophosphataemia	3 (21.4)	2 (14.3)	—	5 (35.7)	2 (14.3)	—	—	2 (14.3)	1 (7.1)	3 (21.4)	—	4 (28.6)
Hotflush	3 (21.4)	—	—	3 (21.4)	4 (28.6)	—	—	4 (28.6)	4 (28.6)	—	—	4 (28.6)
Dry mouth	5 (35.7)	1 (7.1)	—	6 (42.9)	2 (14.3)	3 (21.4)	—	5 (35.7)	—	—	—	—
Stomatitis	3 (21.4)	3 (21.4)	1 (7.1)	7 (50)		2 (14.3)	—	2 (14.3)	1 (7.1)	1 (7.1)	—	2 (14.3)
Headache	1 (7.1)	—	—	1 (7.1)	3 (21.4)	2 (14.3)	—	5 (35.7)	4 (28.6)	1 (7.1)	—	5 (35.7)
Cough	3 (21.4)	—	—	3 (21.4)	4 (28.6)	—	—	4 (28.6)	3 (21.4)	—	—	3 (21.4)
Vomiting	2 (14.3)	1 (7.1)	—	3 (21.4)	1 (7.1)	1 (7.1)	1 (7.1)	3 (21.4)	4 (28.6)	—	—	4 (28.6)
Aspartate aminotransferase increased	4 (28.6)	—	—	4 (28.6)	2 (14.3)	1 (7.1)	—	3 (21.4)	2 (14.3)	—	—	2 (14.3)
Alanine aminotransferase increased	3 (21.4)	—	—	3 (21.4)	2 (14.3)	—	—	2 (14.3)	2 (14.3)	1 (7.1)	1 (7.1)	4 (28.6)

— Not reported by patients taking this dose

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

Phase 2 efficacy was demonstrated across all dose arms

- First PR at 16 weeks and 13 additional PRs across all dose arms over the follow-up period
- Most responses with AL 102 1.2 mg daily occurred as early as 16-28 weeks
- Consistent pattern of deeper, more rapid and persistent tumor responses in volume reduction, T2W signal intensity and RECIST with AL102 1.2 mg daily than with intermittent doses

RINGSIDE Phase 2 results support initiation of Phase 3 and Open-Label Extension

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

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Email: gounderm@mskcc.org

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