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Initial Results of Phase 2/3 Trial of AL102 for Treatment of Desmoid Tumors (DT)

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Declaration of Interests (RLJ)

Receipt of grants/research support:

- MSD, GSK

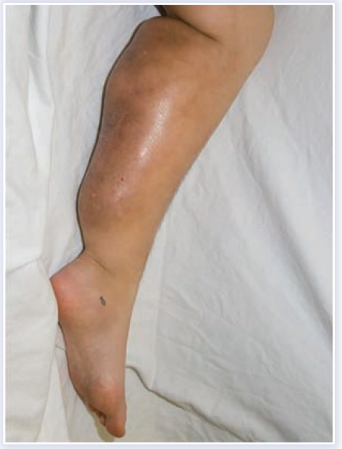
Receipt of consultation fees:

- Adaptimmune, Astex, Athenex, Bayer, Boehringer Ingelheim, Blueprint, Clinigen, Eisai, Epizyme, Daichii, Deciphera, Immunedesign, Immunicum, Karma Oncology, Lilly, Merck, Mundipharma, Pharmamar, Springworks, SynOx, Tracon, UpToDate

Background

Desmoid tumor

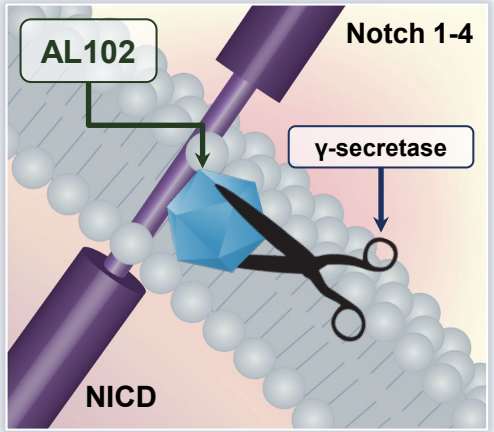
- Locally aggressive tumor
- Variable and unpredictable clinical course with pain, discomfort, and impact on quality of life (QOL)
- 5-6 cases per million people/year
- Peak incidence age 30 (range 15-60) years, female predominance
- 5-10% in the context of familial adenomatous polyposis (FAP)



McDonald, et al., RadioGraphics 2008

Gamma-secretase inhibitor (GSI)

- GSI have antineoplastic activity in DT
- Investigational new drug AL102 - a potent, oral inhibitor of gamma secretase

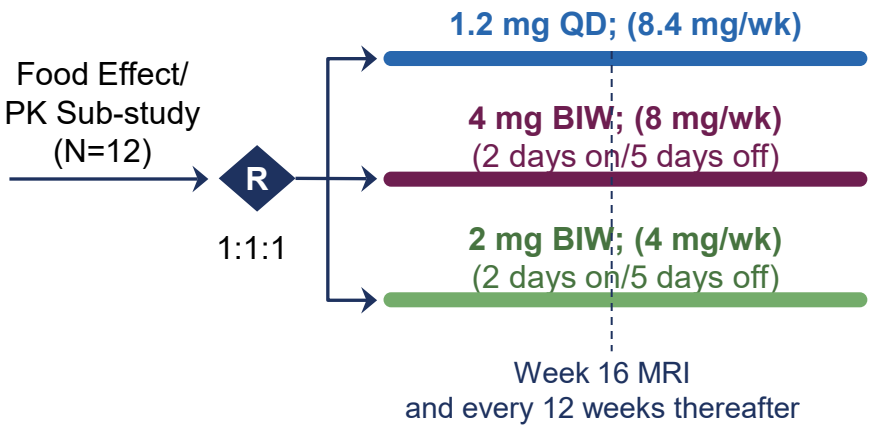


The Desmoid Tumor Working Group, European Journal of Cancer 127 (2020) 96-107; Quintini et al, Ann Surg. 2012; 255(3):511-6; Gounder et al, N Engl J Med 2018;379:2417-28; Trufero et al, Curr. Treat. Options in Oncol. (2017) 18:29

Study Design

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

Part A (N≤36) Regimen Selection



Study Endpoints

Primary:
Safety

Secondary:
Tumor volume reduction

Key Inclusion Criteria:

- R/R or Treatment-naive DT with Progression
  - ≥10% unidimensional growth within 18 months, OR
  - DT-related pain requiring non-opioid med
- Age ≥18

Part B (N=156)
Double-blind Placebo Controlled Study
&
Open-Label Extension at Radiographic Progression

AL102 @ selected regimen vs Placebo

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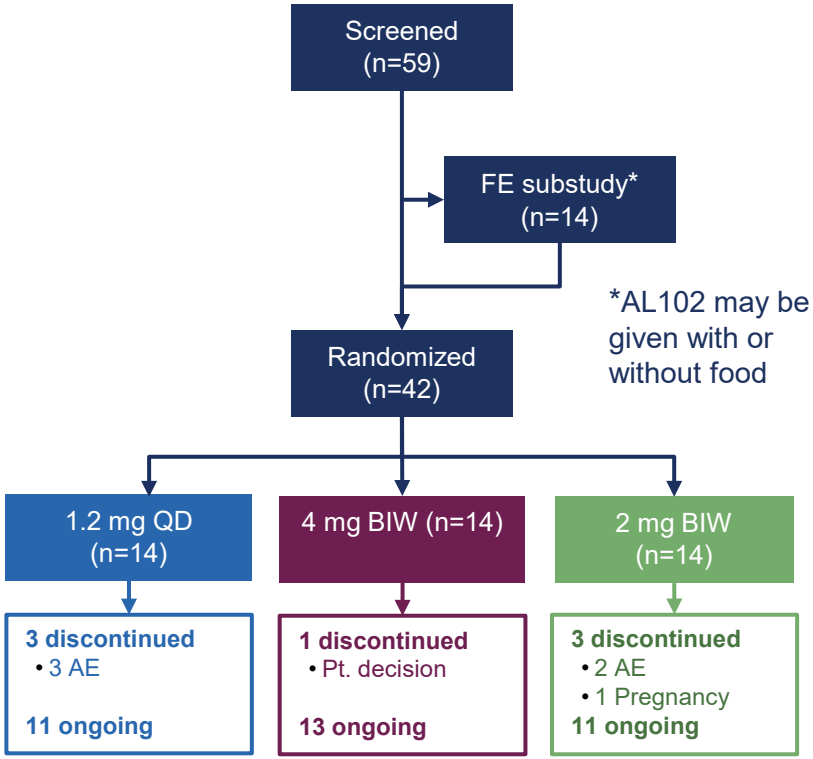
DT, desmoid tumor; BIW, twice weekly; MRI, magnetic resonance imaging; QD, once daily; R, randomization; R/R, relapse/refractory

Disposition, Demographics, and Baseline Characteristics



Baseline characteristics were generally balanced across treatment groups

	Total (N=42)
Age (years), median (range)	38.5 (19,72)
Gender – female n (%)	31 (74)
Location of tumor at diagnosis, n (%)	
Intra Abdominal	11 (26)
Other	31 (74)
Prior DT therapies, n (%)	29 (69)
Prior DT surgeries performed, n (%)	20 (48)
Prior DT radiation therapies, n (%)	4 (10)
Prior therapy treatment type, n (%)	
Chemotherapy	23 (55)
Hormonal Therapy	8 (19)
Targeted Small Molecule	7 (17)
Weeks on study, mean (range)	>23 (4,40)

N, number of patients with data; BIW, twice weekly: 2 days on, 5 days off; QD, once daily; Data Cut Jul 14, 2022

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Safety Profile Consistent with GSIs

- AL102 was generally well tolerated with a manageable safety profile in all dose arms
- Most AEs were grade 1-2
- Grade 3 AEs were uncommon
- No grade 4 or 5 AEs
- 4 SAEs in 3 patients were assessed as unrelated to AL102 by the investigator
- AEs causing discontinuation included diarrhea, stomatitis, ALT elevation and rash
- AEs were consistent with mechanism of action of GSIs

Treatment-related AEs in ≥20% of Subjects

		1.2 mg QD (n=14)		4 mg BIW (n=14)		2 mg BIW (n=14)	
System Organ Class	Preferred Term	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Gastrointestinal disorders	Diarrhoea	11 (79)	1 (7)	8 (57)	1 (7)	7 (50)	-
	Nausea	5 (36)	-	5 (36)	-	3 (21)	-
	Dry mouth	5 (36)	-	5 (36)	-	-	-
	Stomatitis	6 (43)	1 (7)	2 (14)	-	-	-
General disorders	Fatigue	5 (36)	-	5 (36)	-	5 (36)	-
Investigations	AST Increased	2 (14)	-	3 (21)	-	1 (7)	-
Metabolism and nutrition	Hypophosphataemia	4 (29)	-	1 (7)	-	2 (14)	-
Reproductive system	Amenorrhoea	1 (7)	-	3 (21)	-	-	-
Skin and subcutaneous tissue	Alopecia	5 (36)	-	3 (21)	-	1 (7)	-
	Dry skin	6 (43)	-	3 (21)	-	-	-
	Pruritus	6 (43)	-	2 (14)	-	-	-
	Rash maculo-popular	4 (29)	-	1 (7)	-	1 (7)	-
	Rash	-	-	3 (21)	-	2 (14)	1 (7)
	Dermatitis acneiform	4 (29)	-	-	-	1 (7)	-
	Hair colour changes	3 (21)	-	1 (7)	-	-	-

Data cut: Jul 14, 2022. AE, adverse event, N, number of patients with data; BIW, twice weekly; QD, once daily
a. Data on in the table is showed as number of subjects (%)
b. Subjects are counted once at the highest grade per preferred term

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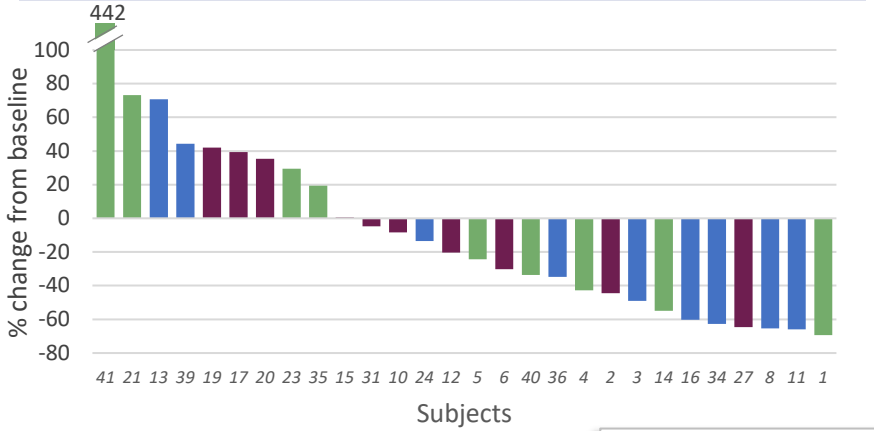
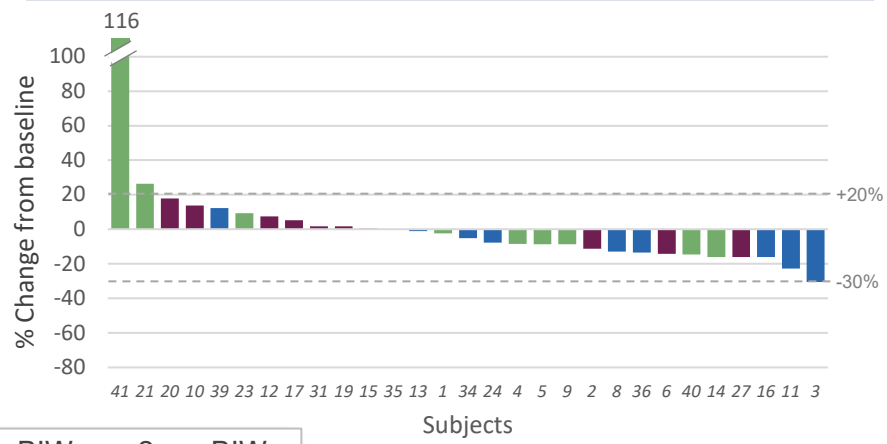
Early Volume and RECIST Response at Week 16

- Activity observed in all dose arms
- PR (central) observed at 16 weeks (confirmed 28 weeks)

Volume (N=28)



Central RECIST (N=29)

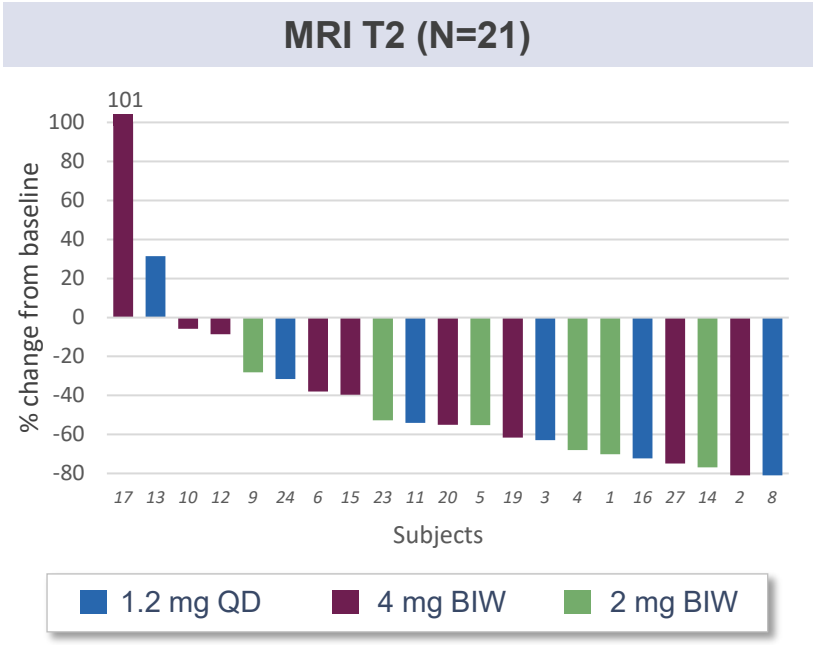


1.2 mg QD 4 mg BIW 2 mg BIW

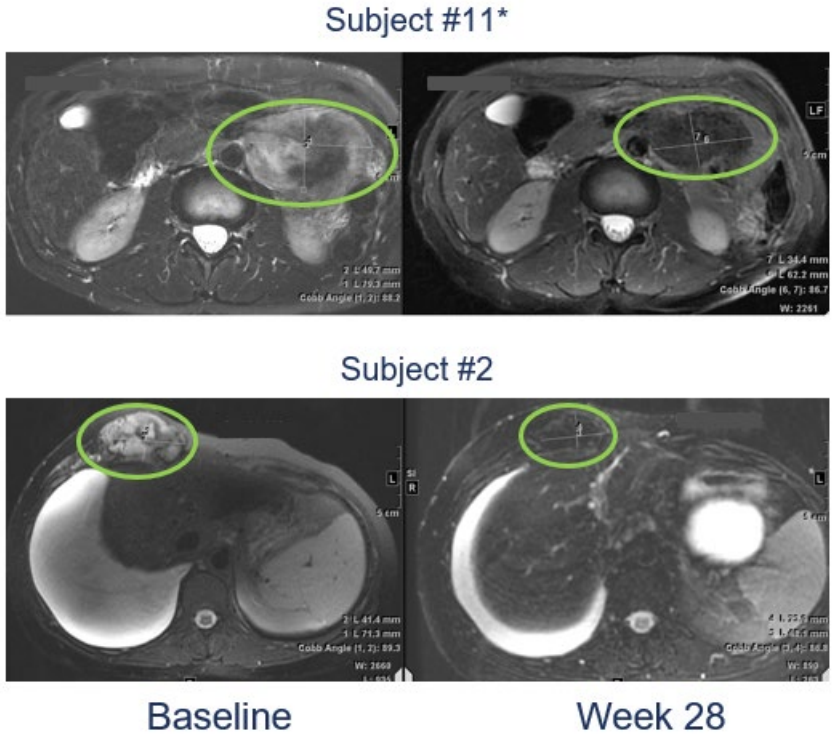
N, number of patients with data; BIW, twice weekly; QD, once daily; Data cut: Jul 14, 2022

T2 Changes Reflect Decrease in Cellularity

- Reduction of T2 intensity in 19 of 21 subjects at Week 16



- Reduction of T2 intensity and size in 2 subjects at Week 28



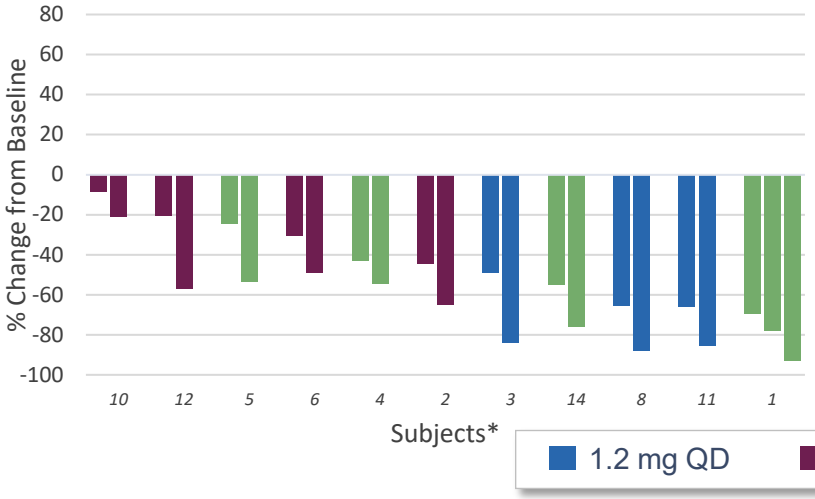
N, number of patients with data; BIW, twice weekly; QD, once daily; Data cut: Jul 14, 2022; * Wk 28 for Subject #11 was obtained post-data cut

MRI Results Beyond 16 Weeks

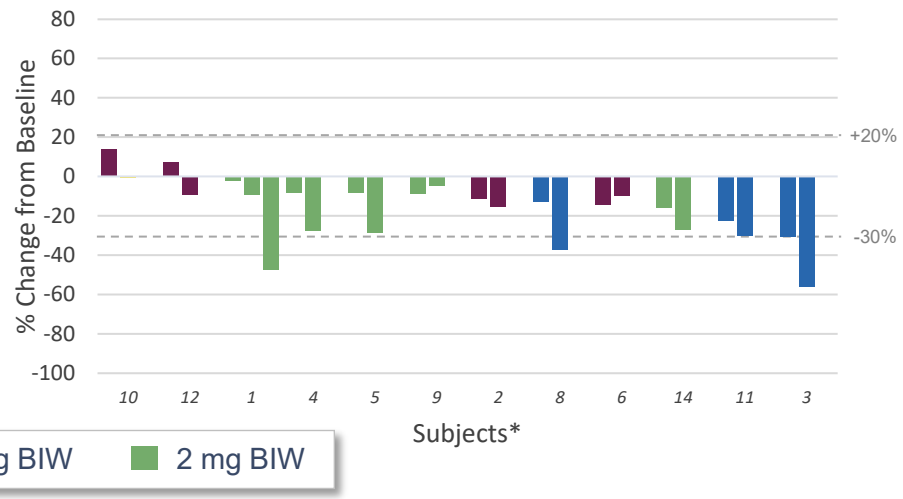
Consistent response across study arms and measures deepening over time

- At data cut, 12 subjects had results for 2 or more MRI scans
- 4 central PRs: 1 at week 16 confirmed at week 28, 2 at week 28, 1 at week 40

Volume (n=11)



Central RECIST (n=12)



1.2 mg QD | 4 mg BIW | 2 mg BIW

* For each subject, set of bars denotes Week 16 & 28 results (and week 40, where applicable)

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BIW, twice weekly, QD, once daily
Data cut: Jul 14, 2022

Conclusions Based on Initial Results from RINGSIDE Part A

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

- Safety is consistent with the MOA and the GSI class of drug
- No Grade 4/5 AEs
- Grade 3 AEs uncommon and similar across dose arms

Efficacy was demonstrated across all arms

- Consistent across measures: Volume, Central/Local RECIST, and T2, T1 (data not shown)
- Responses are seen within 16 weeks and are maintained and deepen over time
- First PR seen at 16 weeks and 3 additional PRs over the follow up period

RINGSIDE Part A results support the initiation of Part B and Open-Label Extension

AE, adverse event; MOA, mechanism of action
Data cut: Jul 14, 2022