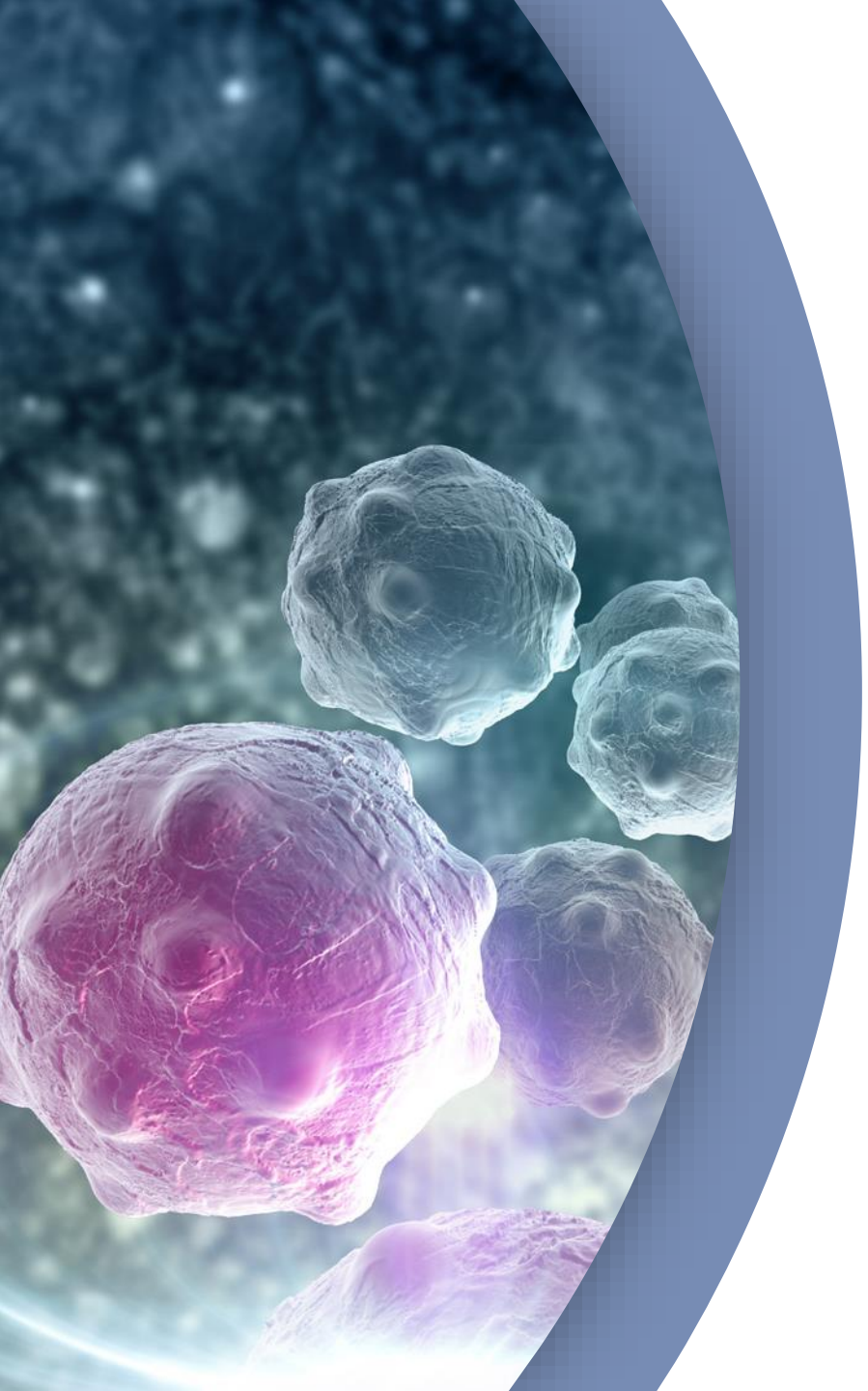


Emerging Treatments for Desmoid Tumors

Key Opinion Leader Insights

October 6, 2022

Disclaimer

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including statements relating to our development of AL101 and AL102, the promise and potential impact of our preclinical or clinical trial data, the timing of and plans to initiate additional clinical trials of AL101 and AL102, the timing and results of any clinical trials or readouts, the sufficiency of cash to fund operations, and the anticipated impact of COVID-19, on our business. These forward-looking statements are based on management's current expectations. The words ”may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “estimate,” “believe,” “predict,” “potential” or “continue” or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: we have incurred significant losses since inception and anticipate that we will continue to incur losses for the foreseeable future. We are not currently profitable, and we may never achieve or sustain profitability; we will require additional capital to fund our operations, and if we fail to obtain necessary financing, we may not be able to complete the development and commercialization of AL101 and AL102; we have a limited operating history and no history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability; we are heavily dependent on the success of AL101 and AL102, our most advanced product candidates, which are still under clinical development, and if either AL101 or AL102 does not receive regulatory approval or is not successfully commercialized, our business may be harmed; due to our limited resources and access to capital, we must prioritize development of certain programs and product candidates; these decisions may prove to be wrong and may adversely affect our business; the outbreak of COVID-19, may adversely affect our business, including our clinical trials; our ability to use our net operating loss carry forwards to offset future taxable income may be subject to certain limitations; our product candidates are designed for patients with genetically defined cancers, which is a rapidly evolving area of science, and the approach we are taking to discover and develop product candidates is novel and may never lead to marketable products; we were not involved in the early development of our lead product candidates; therefore, we are dependent on third parties having accurately generated, collected and interpreted data from certain preclinical studies and clinical trials for our product candidates; enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be made more difficult or rendered impossible by multiple factors outside our control; if we do not achieve our projected development and commercialization goals in the timeframes we announce and expect, the commercialization of our product candidates may be delayed and our business will be harmed; our product candidates may cause serious adverse events or undesirable side effects, which may delay or prevent marketing approval, or, if approved, require them to be taken off the market, require them to include safety warnings or otherwise limit their sales; the market opportunities for AL101 and AL102, if approved, may be smaller than we anticipate; we may not be successful in developing, or collaborating with others to develop, diagnostic tests to identify patients with Notch-activating mutations; we have never obtained marketing approval for a product candidate and we may be unable to obtain, or may be delayed in obtaining, marketing approval for any of our product candidates; even if we obtain FDA approval for our product candidates in the United States, we may never obtain approval for or commercialize them in any other jurisdiction, which would limit our ability to realize their full market potential; we have been granted Orphan Drug Designation for AL101 for the treatment of ACC and may seek Orphan Drug Designation for other indications or product candidates, and we may be unable to maintain the benefits associated with Orphan Drug Designation, including the potential for market exclusivity, and may not receive Orphan Drug Designation for other indications or for our other product candidates; although we have received Fast Track designation for AL101, and may seek Fast Track designation for our other product candidates, such designations may not actually lead to a faster development timeline, regulatory review or approval process; we face significant competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively; we are dependent on a small number of suppliers for some of the materials used to manufacture our product candidates, and on one company for the manufacture of the active pharmaceutical ingredient for each of our product candidates; and any future collaborations will be, important to our business. If we are unable to maintain our existing collaboration or enter into new collaborations, or if these collaborations are not successful, our business could be adversely affected; enacted and future healthcare legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates, if approved, and may affect the prices we may set; if we are unable to obtain, maintain, protect and enforce patent and other intellectual property protection for our technology and products or if the scope of the patent or other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and we may not be able to compete effectively in our markets; we may engage in acquisitions or in-licensing transactions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources; risks related to our operations in Israel could materially adversely impact our business, financial condition and results of operations.

These and other important factors discussed under the caption “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2020 filed with the U.S. Securities and Exchange Commission (SEC) on March 24, 2021 and our other filings with the SEC, could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. New risk factors and uncertainties may emerge from time to time, and it is not possible to predict all risk factors and uncertainties. While we may elect to update such forward-looking statements at some point in the future, except as required by law, we disclaim any obligation to do so, even if subsequent events cause our views to change. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.
Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and we make no representation as to the adequacy, fairness, accuracy or completeness of any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Neither we nor our affiliates, advisors or representatives makes any representation as to the accuracy or completeness of the data included in this presentation or undertake to update such data after the date of this presentation. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

Agenda

Introduction	**Dr. Roni Mamluk** CEO, Ayala
Challenges in Exploiting Medical Therapies for Desmoid Tumors	**Prof. Dr. med. Bernd Kasper** Mannheim University Medical Center
AL102 in Desmoid Tumors	**Dr. Gary Gordon** CMO, Ayala
RINGSIDE Initial Results	**Prof. Robin Jones** The Royal Marsden
AL102 Commercial Opportunity	**Dr. Roni Mamluk** CEO
Q&A	**All**
Closing	**Dr. Roni Mamluk** CEO

Bernd Kasper, MD

- Professor at the Sarcoma Unit of the Mannheim Cancer Center (MCC), Mannheim University Medical Center
- Head of the study center of the German Interdisciplinary Sarcoma Group (GISG) and active in national and international study groups (AIO, EORTC)
- Principal Investigator of several national and international trials on STS, DF and GIST
- Chair of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG)
- Member of the Board of Directors of the Connective Tissue Oncology Society (CTOS)
- Board member to patient organizations dealing with STS, DF and GIST (SPAEN, NLMSF and DTRF)
- MD degree from Heidelberg University
- Studied at Imperial College School of Medicine (London), Jules Bordet Institute, Medical Oncology Clinic (Brussels)

ayala pharmaceuticals

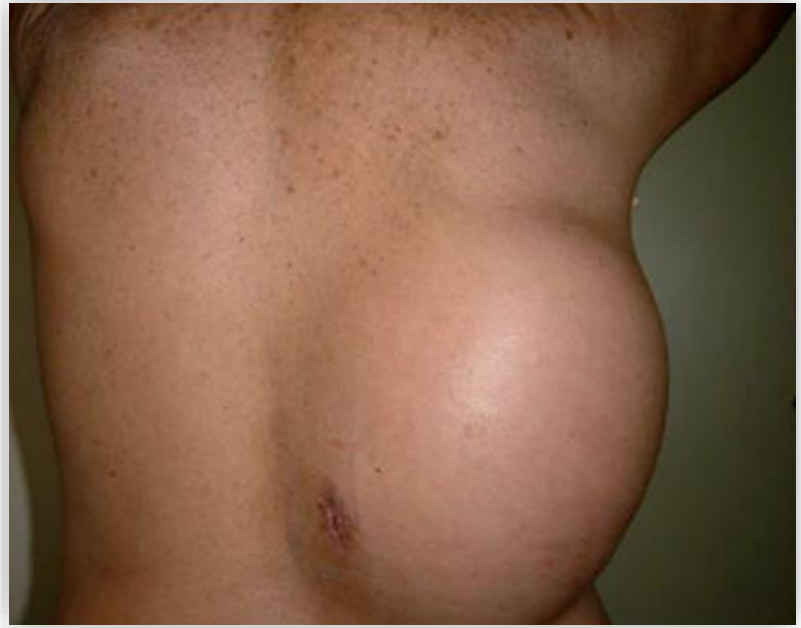
CHALLENGES IN EXPLOITING MEDICAL THERAPIES FOR DESMOID TUMORS

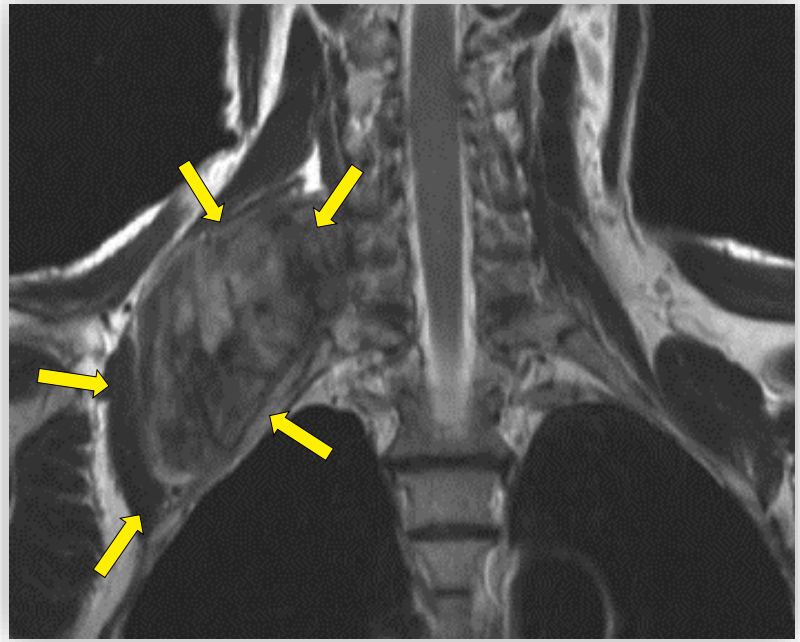
Prof. Dr. med. Bernd Kasper

University of Heidelberg, Mannheim University Medical Center, Mannheim, Germany

Background (1)

- Desmoid tumor (DT) is an invasive proliferative disease of the connective tissue characterized by a variable and often unpredictable clinical course.
- ~5-6 cases per 1 million of the population per year, a peak age at ~30 years and more often in women.*
- Annual incidence of 1700 cases in the United States with prevalence being much higher.
- 90-95% DT are sporadic, while 5-10 % arise in the context of familial adenomatous polyposis (FAP).
- Driven by mutations in *CTNNB1* (beta-catenin) or in *APC*.

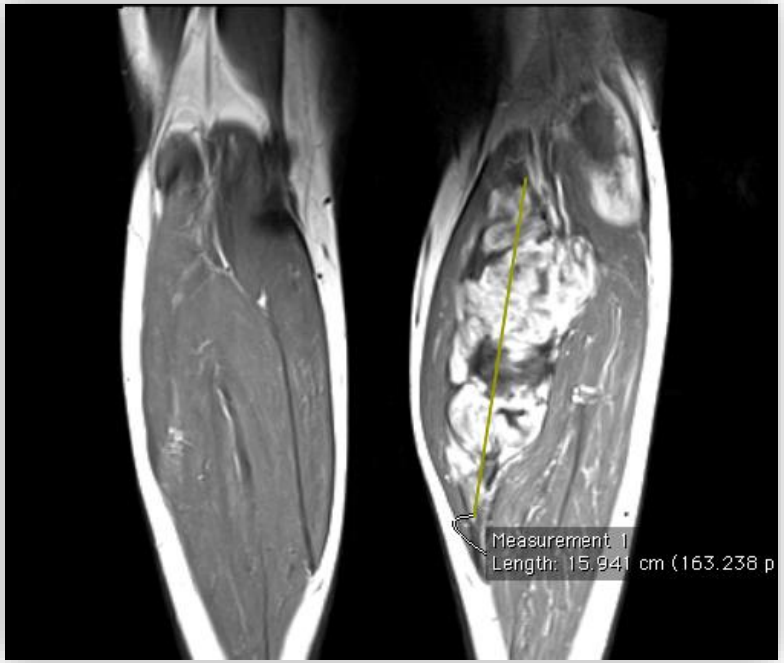


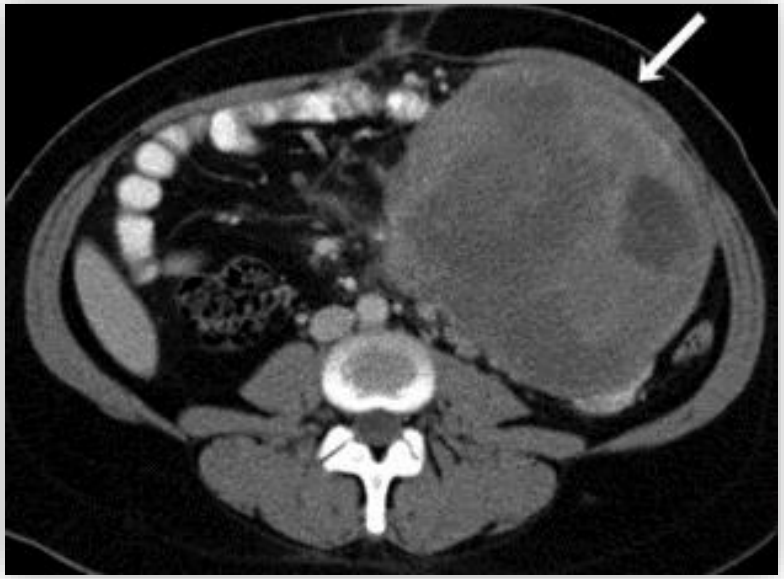


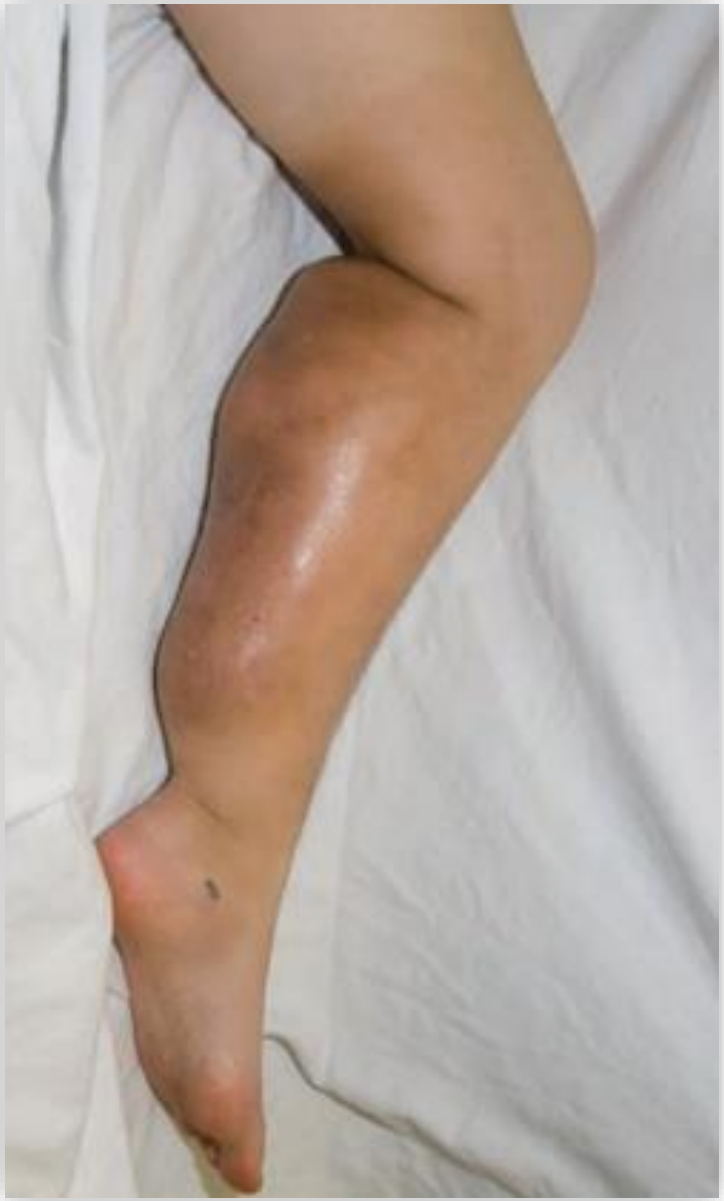
* Kasper B et al. Eur J Cancer 2015; 51: 127-136

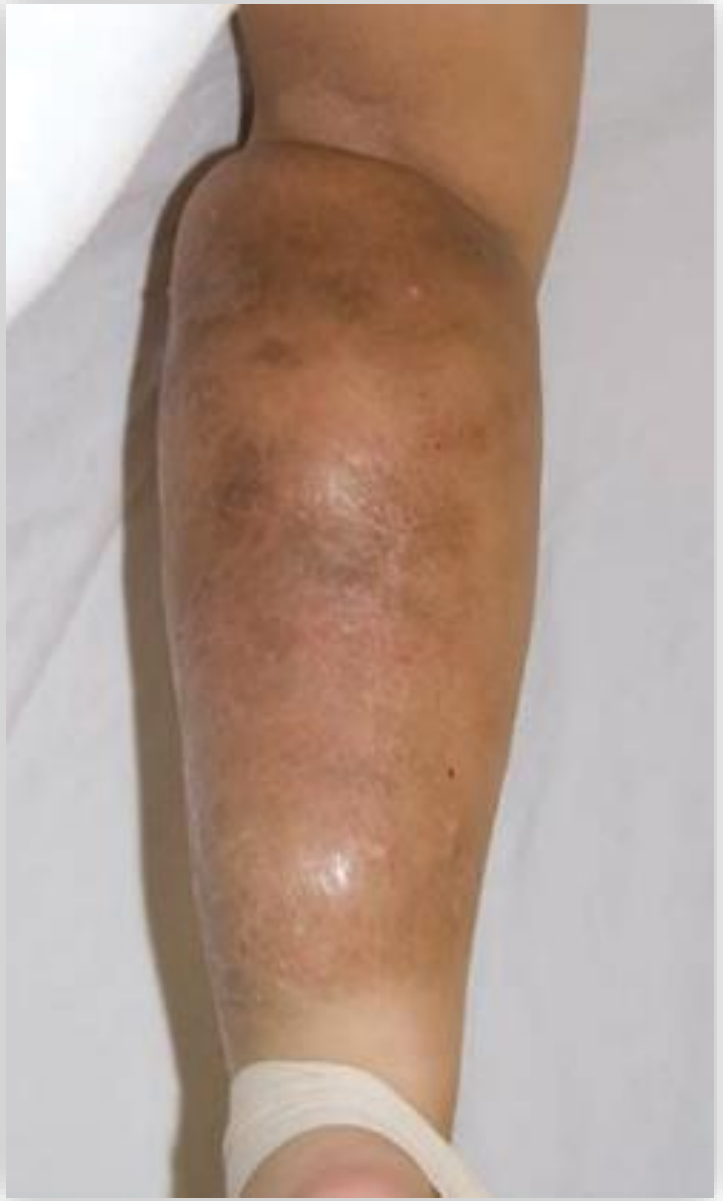
Background (2)

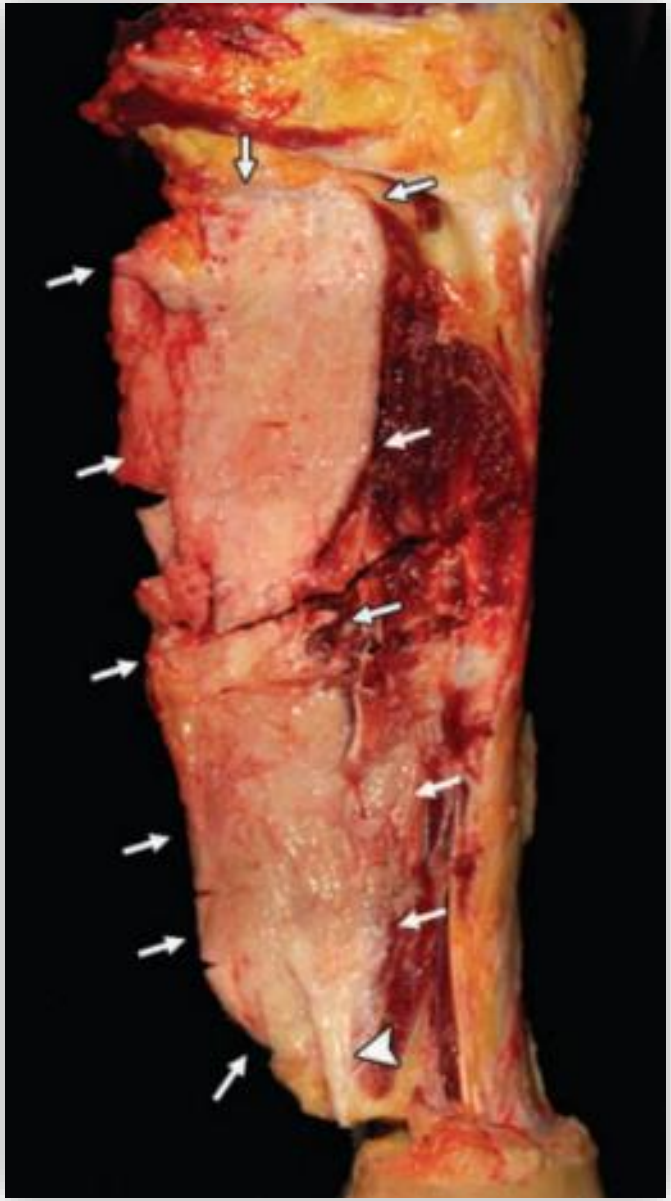
- DT starts as a painless or minimally painful mass with a history of slow growth.
- DT usually grows as a single lesion and can result in tissue/ organ infiltration, but without metastases.
- DT can lead to:
  - chronic pain
  - functional deficits and debility
  - disfiguration
  - psychological problems
  - general decrease in quality of life
  - and even sometimes death











McDonald ES et al. Radiographics 2008; 28: 901-906

Global Guidelines Exist

- Global consensus initiative involving medical experts as well as patients/patient advocates from Europe, North America, and Japan
- Under the auspices of, and supported by:
  - European Reference Network for rare solid adult cancers (EURACAN)
  - European Organisation for Research and Treatment of Cancer (EORTC) / Soft Tissue and Bone Sarcoma Group (STBSG)
  - Sarcoma Patients Advocacy Global Network (SPAGN)
  - The Desmoid Tumor Research Foundation (DTRF)

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Review

The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients

The Desmoid Tumor Working Group[1]

Received 6 October 2019; received in revised form 15 November 2019; accepted 16 November 2019
Available online 28 January 2020

KEYWORDS
Desmoid tumour;
β-catenin;
CTNNB1;
Gardner syndrome;
Medical therapy;
Radiotherapy;
Surgery;
Patient advocacy groups;
SPAEN;

Abstract Desmoid tumor (DT; other synonymously used terms: Desmoid-type fibromatosis, aggressive fibromatosis) is a rare and locally aggressive monoclonal, fibroblastic proliferation characterised by a variable and often unpredictable clinical course. Previously surgery was the standard primary treatment modality; however, in recent years a paradigm shift towards a more conservative management has been introduced and an effort to harmonise the strategy amongst clinicians has been made. We present herein an evidence-based, joint global consensus guideline approach to the management of this disease focussing on: molecular genetics, indications for an active treatment, and available systemic therapeutic options. This paper follows a one-day consensus meeting held in Milan, Italy, in June 2018 under the auspices of the European Reference Network for rare solid adult cancers, EURACAN, the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) as well as Sarcoma Patients EuroNet (SPAEN) and The Desmoid tumour Research Foundation (DTRF). The meeting brought

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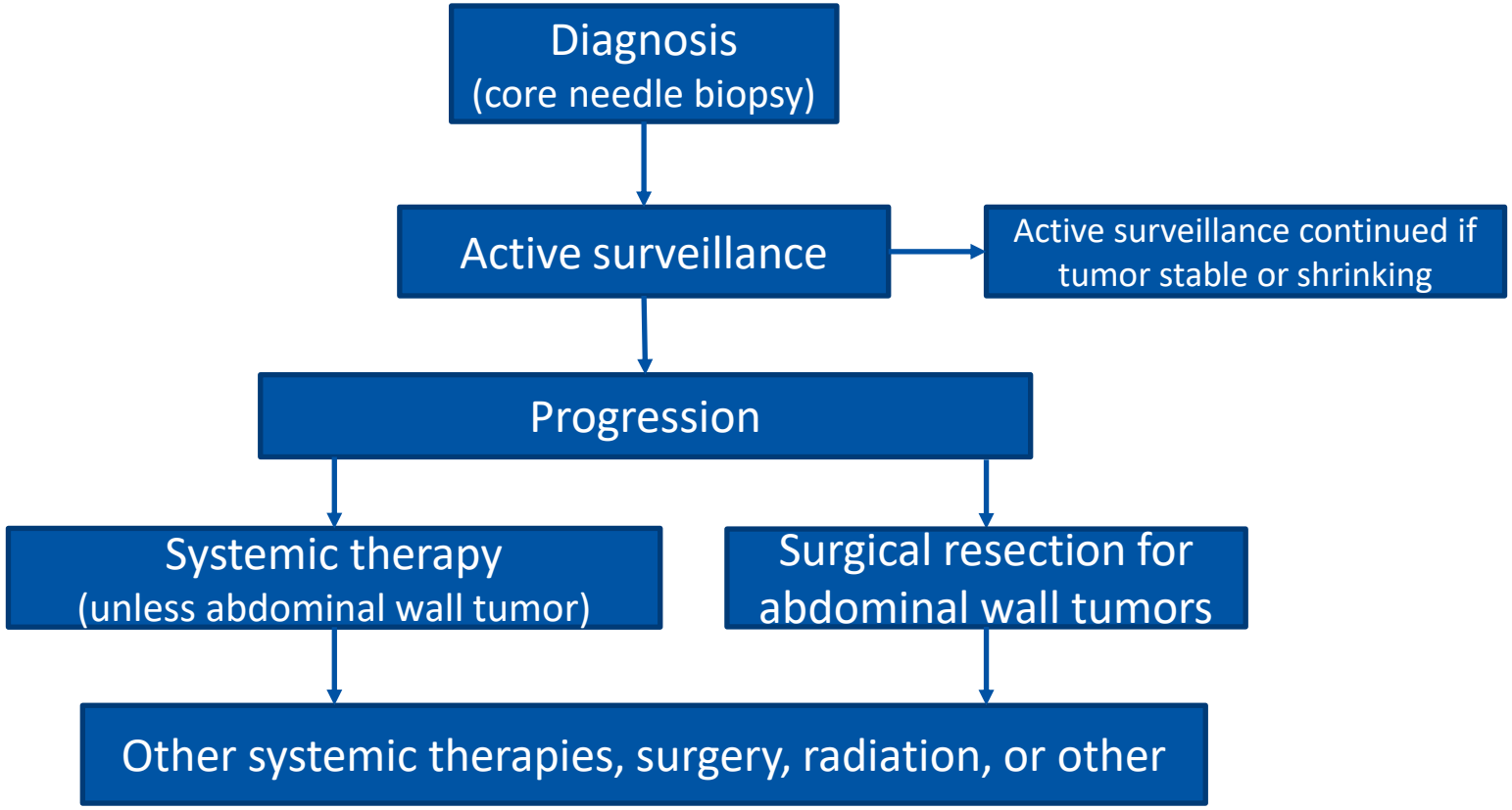
** *Corresponding author*: Bernd Kasper, MD, Sarcoma Unit, Interdisciplinary Tumor Center, Mannheim University Medical Center, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.
E-mail addresses: bernd.kasper@umm.de (B. Kasper), alessandro.gronchi@istitutotumori.mi.it (A. Gronchi).
[1] THE Desmoid tumor Working Group: Ben Alman, Steven Attia, Christina Baumgarten, Charlotte Benson, Jean-Yves Blay, Sylvie Bonvalot, Jessica Breuing, Ken Cardona, Paolo G. Casali, Frits van Coevorden, Chiara Colombo, Angelo P. Dei Tos, Palma Dileo, Andrea Ferrari, Marco Fiore, Anna M. Frezza, Jesica Garcia, Rebecca Gladdy, Mrinal Gounder, Alessandro Gronchi, Rick Haas, Sam Hackett, Florian Haller, Peter Hohenberger, Olga Husson, Robin L. Jones, Ian Judson, Bernd Kasper, Akira Kawai, Vlada Kogosov, Alex J. Lazar, Robert Maki, Tim Mathes, Christina Messiou, Fariba Navid, Yoshihiro Nishida, Elena Palassini, Nicolas Penel, Robert Pollock, Dawid Pieper, Marlene Portnoy, Chandrajit P. Raut, Evelyne Roets, Sergio Sandrucci, Marta Sbaraglia, Silvia Stacchiotti, Katherine A. Thornton, Winette van der Graaf, Kim van der Zande, Winan J. van Houdt, Victor Villalobos, Andrew J. Wagner, Eva Wardelmann, Markus Wartenberg, Sarah Watson, Aaron Weiss, Nikolaos Zafiropoulos.

https://doi.org/10.1016/j.ejca.2019.11.013

Eur J Cancer 2020; 127: 96-107

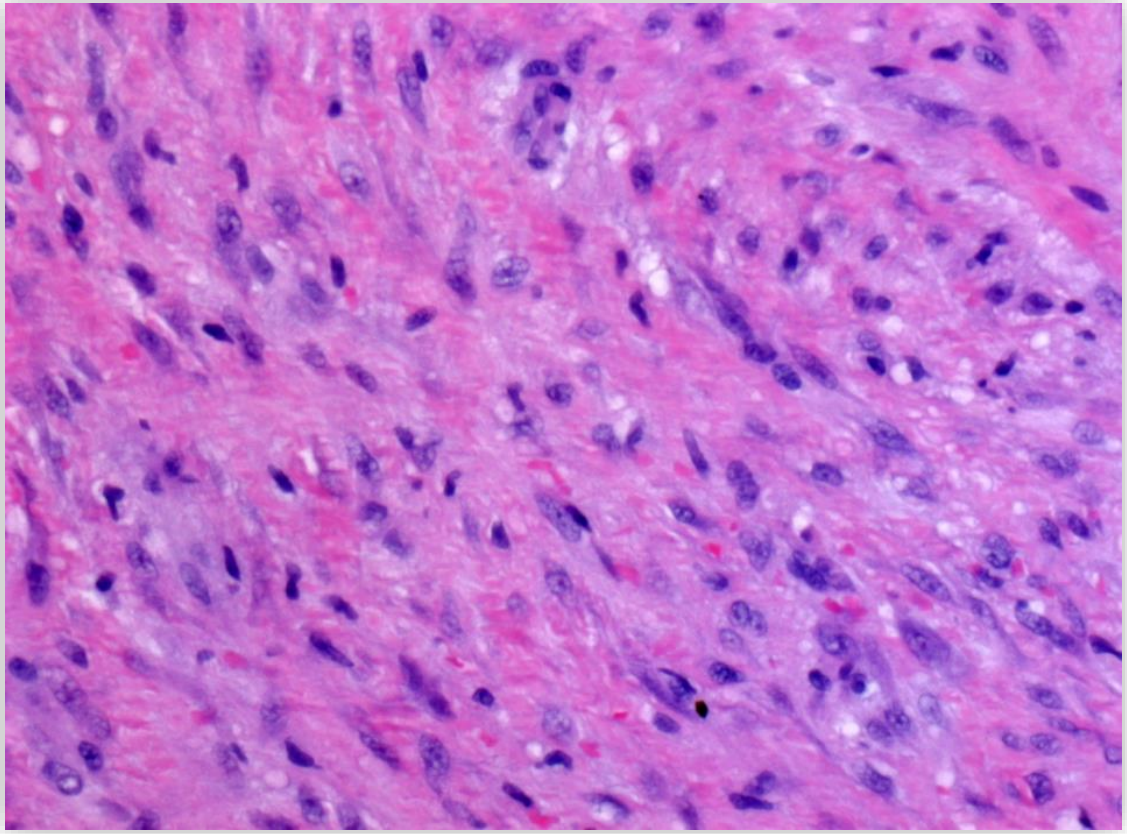
Desmoid Consensus Initiative: Current Treatment Paradigm



Adapted from The Desmoid Tumor Working Group. Eur J Cancer 2020; 127: 96-107

The Systemic Treatment Landscape for Desmoid Tumors

- Active Surveillance
- Surgery
- Radiotherapy
- Indications for treatment
  - Threats to life
  - Organ function
  - Pain
  - Limitations in movement
  - Tumour growth
- **Systemic Treatment Options**
  - Antihormonal Therapy (+ NSAID)
  - Chemotherapy
  - Targeted Therapy (TKIs)
  - γ-Secretase Inhibitor Therapy



Kasper B et al. Oncologist 2011; 16: 682-693

Chemotherapy

- MTX / Vinblastine[1]
- MTX / Vinorelbine[2] or Vinorelbine alone[3]
- Anthracycline-based regimens[4]
- Pegylated liposomal doxorubicin (PLD)[5,6,7]

Indication: Non-resectable, rapidly growing and / or symptomatic or even life-threatening DT should preferably be treated with chemotherapy

[1] *Skapek SX et al. J Clin Oncol 2007; 25: 501-506*
[2] *Palassini E et al. Cancer J 2017; 23: 86-91*
[3] *Mir O et al. J Clin Oncol 2016; 34 (suppl; abstr 11050)*
[4] *De Camargo VP et al. Cancer 2010; 116: 2258-2265*
[5] *Constantinidou A et al. Eur J Cancer 2009; 45: 2930-2934*
[6] *Constantinidou A et al. Acta Oncol 2011; 50: 455-461*
[7] *Pang A et al. J Clin Oncol 2016; 34 (suppl; abstr 11032)*

Chemotherapy (selected regimens)

No randomized studies!

Reference	Chemotherapy regimen	Number of patients	Response	Follow-up [months]
Patel	Doxorubicin 60-90 mg/m² + dacarbazine 750-1000 mg/m²	12	2 CR 4 PR 2 SD	28-235
Gega	Doxorubicin 20 mg/m² d1-4 + dacarbazine 150 mg d1-4, d28	7	3 CR 4 PR	33-108
Constantinidou	Pegylated liposomal doxorubicin 50 mg/m², d28	12	4 PR 7 SD	7-39
Wehl	Pegylated liposomal doxorubicin 50 mg/m², d28	4	4 PR	NR
Azzarelli	Vinblastine 6 mg/m² + methotrexate 30 mg/m², weekly	27	4 OR 19 SD	6-96
Weiss	Vinorelbine 20 mg/m² + methotrexate 50 mg/m², weekly	13	NR	< 12
Skapek	Vinblastine 5 mg/m² + methotrexate 30 mg/m², weekly	27	8 PR 10 SD	5-37
Pilz	VAIA, VAC, cyclophosphamide + ifosfamide	19	4 CR 5 PR	NR

Kasper B et al. Oncologist 2011; 16: 682-693

Efficacy Summary: TKIs & GSI

	n*	Inclusion Criteria	Treatment Dose [mg]	Treatment Duration	ORR [%]	6-month-PFS [%]	12-month-PFS [%]	24-month-PFS [%]
Heinrich et al. ***J Clin Oncol 2006***	19	"heavily pretreated patients"	Imatinib 800 mg	325 days	16	53	37	n.e.
Penel et al. ***Ann Oncol 2010***	35	"radiological evidence for PD"	Imatinib 400 mg	1 year	11	80	67	55
Chugh et al. ***Clin Cancer Res 2010***	49	"locally advanced disease"	Imatinib 200-600 mg	until PD 9 pts. > 3 years	6	84	66	n.e.
Kasper et al. ***Eur J Cancer 2017***	38	**RECIST PD**	Imatinib 800 mg	2 years	19	65	59	45
Gounder et al. ***NEJM 2018***	50	"progressive or symptomatic"	Sorafenib 400 mg	until PD	33	n.e.	89	81
Toulmonde et al. ***Lancet Oncol 2019***	48	**RECIST PD**	Pazopanib 800 mg	1 year	37	84	86	67
Kasper et al. ***ESMO 2022***	72	**RECIST PD**	Nirogacestat 300 mg	until PD	41	mPFS niro = not estimable mPFS pbo = 15.1 months		

*n = number of drug treated subjects in trial

DeFi: Phase 3 Study of Nirogacestat vs Placebo in Adult Patients With DT

Trial Summary

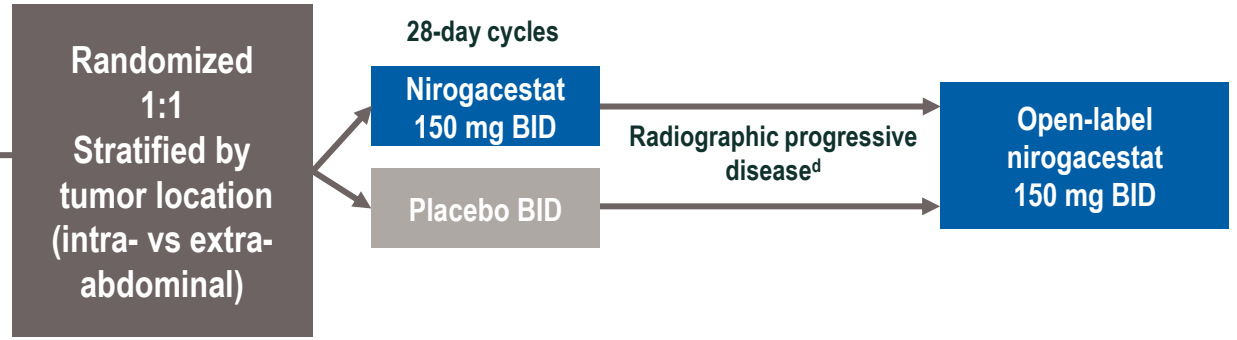
- Global, randomized, double-blind, placebo-controlled, Phase 3 trial comparing the efficacy, safety, and tolerability of nirogacestat vs placebo in adult patients with progressing DT
- 142 patients randomized across 37 sites in North America and Europe

Key Endpoints

- **Primary:** Progression-free survival[b]
- **Secondary:** Objective response rate and patient-reported outcomes, including symptom burden, physical/role function, and overall quality of life[c]

Adult Eligible Patients

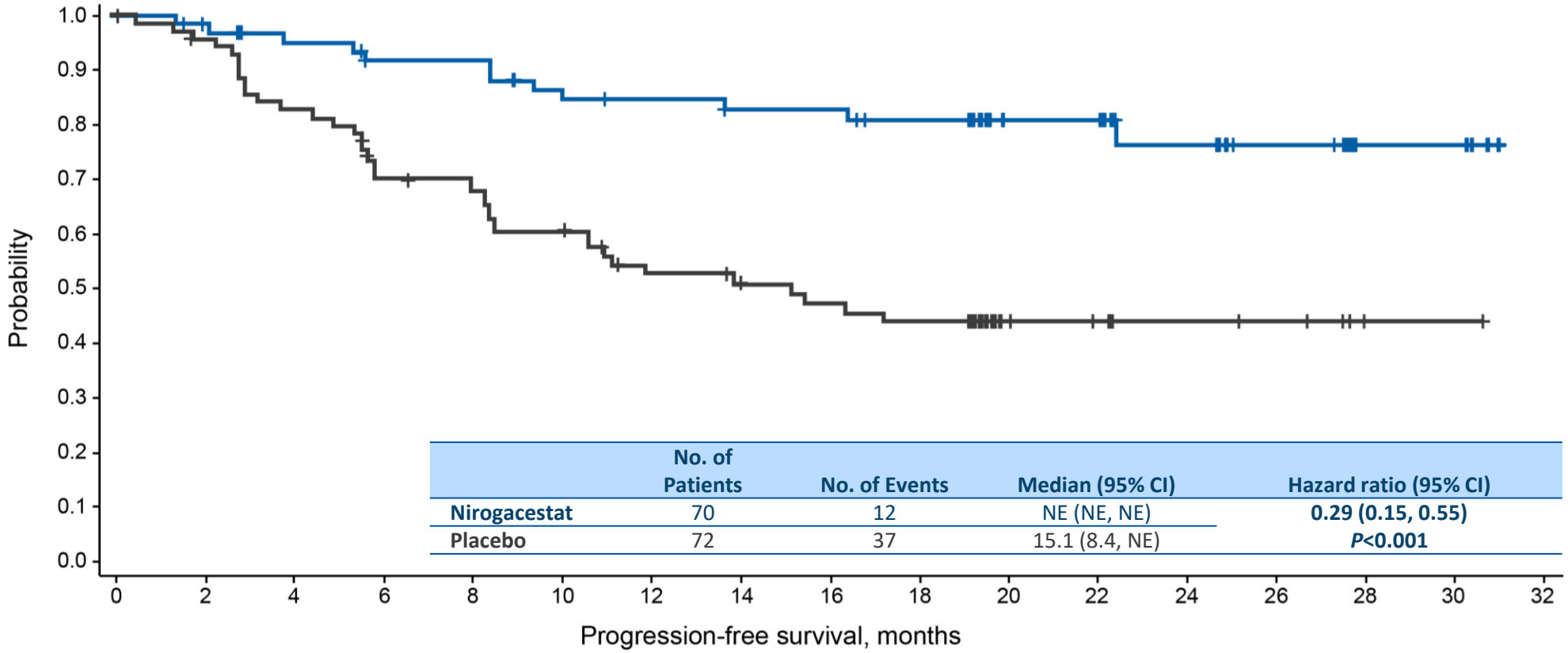
- Histologically confirmed DT with progressive disease per RECIST v1.1[a]
  - Treatment-naïve with DT not amenable to surgery, or
  - Refractory or recurrent disease (after ≥1 line of therapy)



Primary Analysis Data Cutoff: April 7, 2022

[a]Progressive disease defined by histologically confirmed DT that has progressed ≥20% within the past 12 months by RECIST v1.1. Target tumors identified at screening by the Investigator.
[b]Progression-free survival was calculated from the time of randomization until disease progression or death due to any cause. Progression was determined via blinded, independent, central review and included radiographic progression per RECIST v1.1 and clinical progression.
[c]As assessed by change from baseline for BPI-SF, GODDESS DTSS, GODDESS DTIS, and EORTC QLQ-C30 at Cycle 10.
[d]Radiographic disease progression or once the required number of events have been observed and the primary progression-free survival analysis has been completed.
BID, twice-daily dosing; BPI-SF, Brief Pain Inventory–Short Form; DT, desmoid tumor; DTIS, GODDESS DT Impact Scale; DTSS, GODDESS DT Symptom Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; RECIST, Response Evaluation Criteria in Solid Tumors.
ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03785964. Accessed August 24, 2022.

Nirogacestat Significantly Reduced the Risk of Disease Progression



	No. of Patients	No. of Events	Median (95% CI)	Hazard ratio (95% CI)
Nirogacestat	70	12	NE (NE, NE)	**0.29 (0.15, 0.55)**
Placebo	72	37	15.1 (8.4, NE)	***P*<0.001**

No. of Participants at Risk:

Nirogacestat	**70**	**63**	**56**	**52**	**52**	**47**	**46**	**44**	**44**	**41**	**26**	**26**	**17**	**12**	**4**	**4**	**0**
Placebo	**72**	**67**	**58**	**47**	**45**	**40**	**32**	**29**	**27**	**25**	**10**	**8**	**6**	**5**	**1**	**1**	**0**

Median follow-up time was 19.2 months for nirogacestat and 10.9 months for placebo.
NE, not estimable.

Nirogacestat Safety Profile

Safety population, n (%)	Nirogacestat (n=69)		Placebo (n=72)	
Duration of study drug exposure, median (range), mo	20.6 (0.3, 33.6)		11.4 (0.2, 32.5)	
Dose intensity, median (range), mg/d	288.3 (169, 300)		300.0 (239, 300)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	69 (100)	39 (57)	69 (96)	12 (17)
TEAEs of any grade reported in ≥25% of patients in either arm				
Diarrhea	58 (84)	11 (16)	25 (35)	1 (1)
Nausea	37 (54)	1 (1)	28 (39)	0
Fatigue	35 (51)	2 (3)	26 (36)	0
Hypophosphatemia	29 (42)	2 (3)	5 (7)	0
Rash, maculopapular	22 (32)	4 (6)	4 (6)	0
Headache	20 (29)	0	11 (15)	0
Stomatitis	20 (29)	3 (4)	3 (4)	0
TEAEs leading to death	0		1 (1)[a]	
Dose reductions due to TEAEs	29 (42)		0	
Discontinuations due to TEAEs	14 (20)[b]		1 (1)[b]	

- **95% of TEAEs were Grade 1 or 2; the first onset of TEAEs in most patients occurred during Cycle 1**

[a]Death due to sepsis.
[b]TEAEs leading to discontinuations in ≥1 patient include gastrointestinal disorders (n=5 [4%]), ovarian dysfunction (n=4 [3%]), alanine aminotransferase increase (n=3 [2%]), aspartate aminotransferase increase (n=2 [1%]), and metabolism/nutritional disorders (n=2 [1%]).
TEAE, treatment-emergent adverse event.

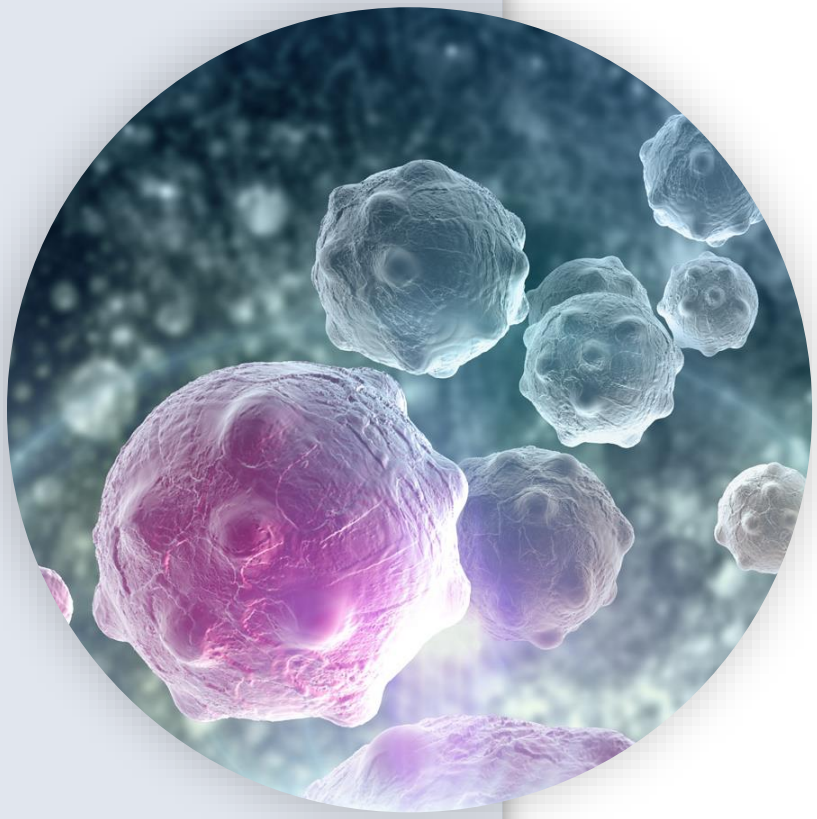
Usual Medical Treatment Options for DT - Summary

- No recommendation for **Antihormonal Therapies**
- **Chemotherapy** may be indicated in rapidly growing and/or symptomatic or even life-threatening DT
  - MTX + Vinblastine is the chemotherapy of choice in the paediatric patient population
  - For young (AYA) patients, pegylated liposomal doxorubicin may be preferred
  - Consider long-term toxicity of some agents
- **TKIs** (sorafenib, pazopanib) have clinical activity in randomized settings and are used but tolerability is limited and there are other side effects
- Emerging **GSIs** promise to be effective agents

- **CAVEAT:** All of drugs mentioned above are not registered for DT and, therefore, are not available or reimbursed in any country!

Thank you!

Bernd Kasper, University of Heidelberg, Mannheim University Medical Center,
Sarcoma Unit, Mannheim, Germany; bernd.kasper@umm.de
Chair EORTC / Soft Tissue and Bone Sarcoma Group (STBSG)
Board of Directors Connective Tissue Oncology Society (CTOS)



AL102 Clinical Development Program

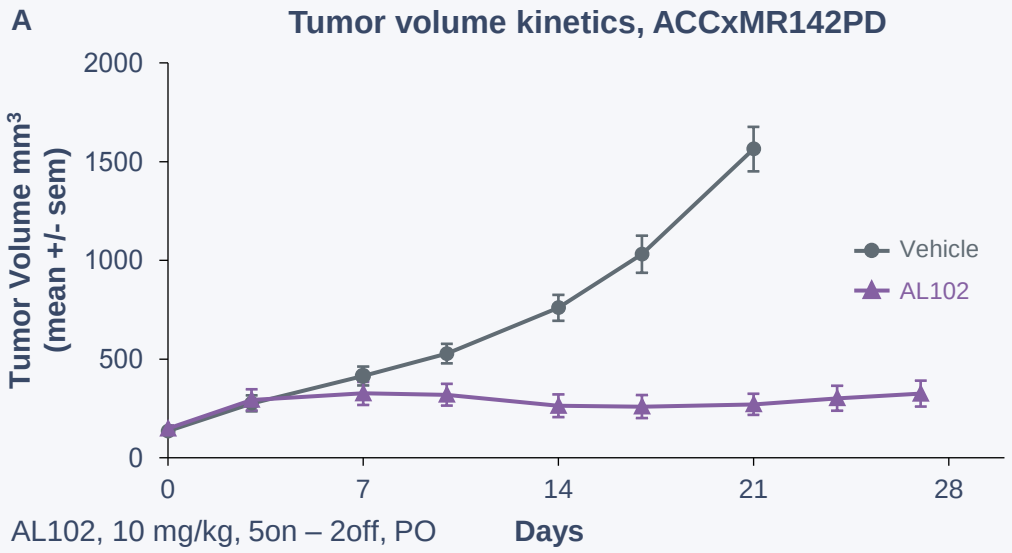
Gary Gordon MD PhD

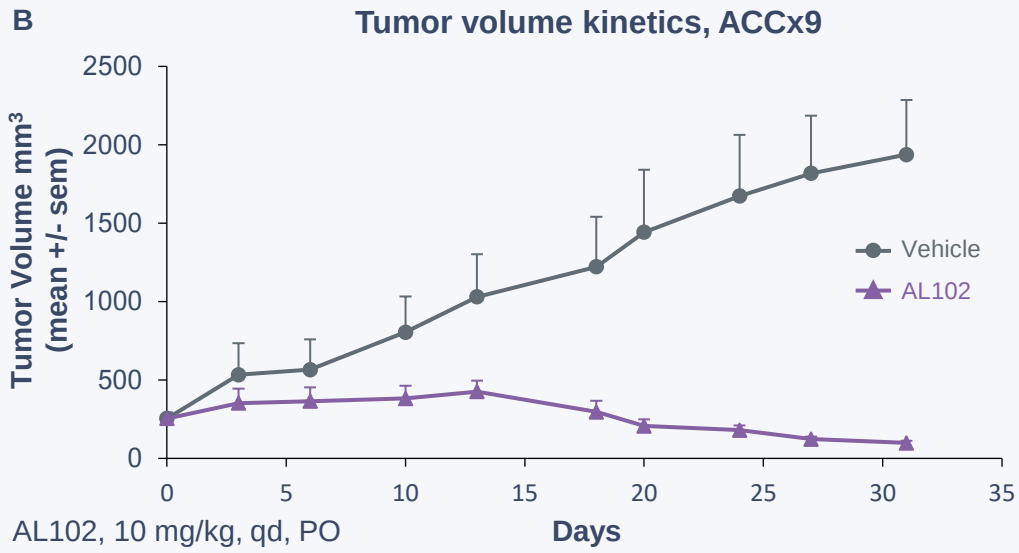
AL102 – Preclinical Work

Inhibition of Constitutive Notch Signaling: IC50 (nM)[1]

	AL102 (BMS-986115)	Nirogacestat[2] (PF-03084014)	RO-4929097[3]	MK-0752[4]
Notch1	6.1	13	3.8	354
Notch2	2.9	15	4.4	403
Notch3	8.1	17	22	955
Notch4	4.4	16	12	874

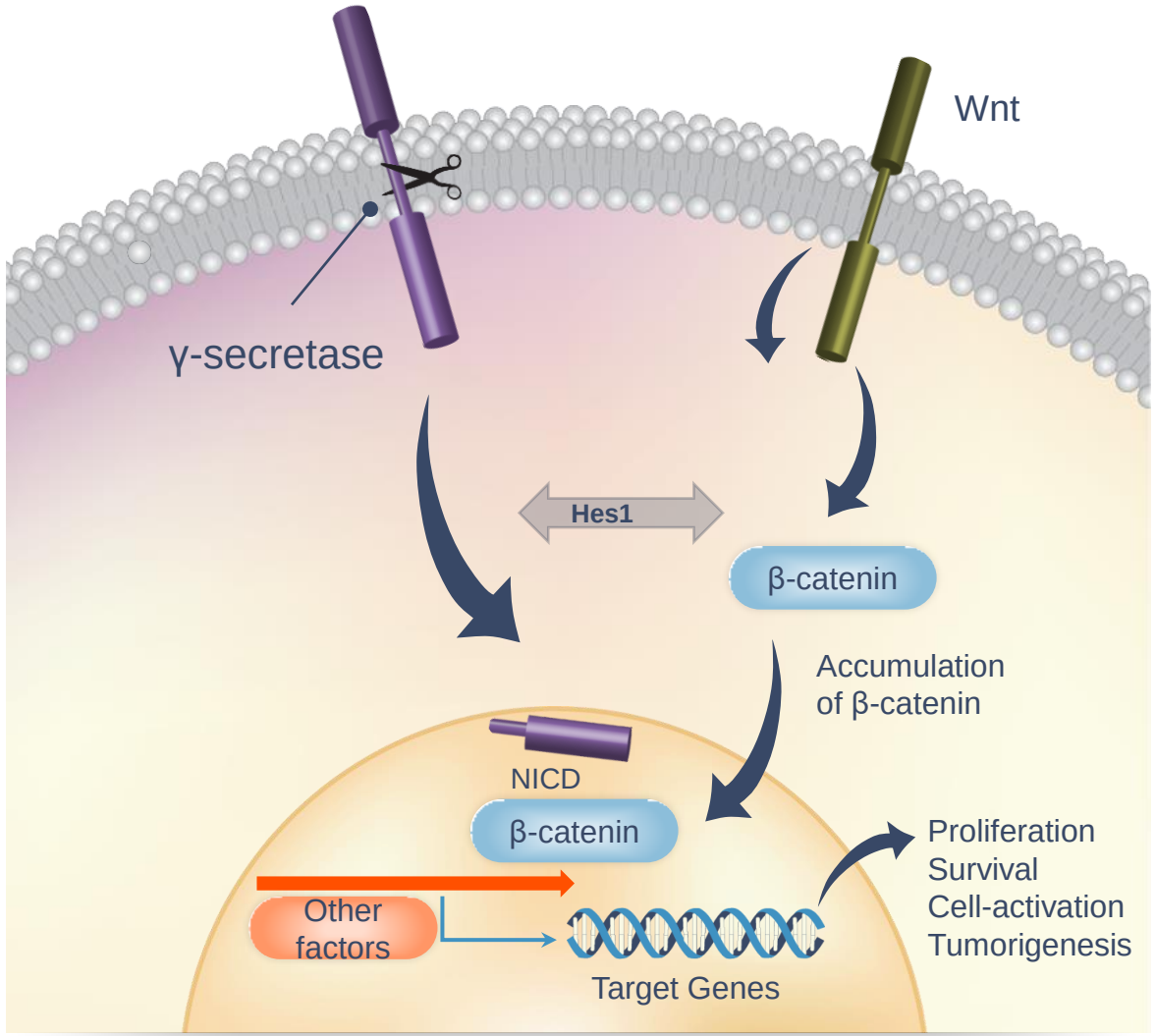
AL102 Inhibits Notch-Activated ACC Tumor Growth

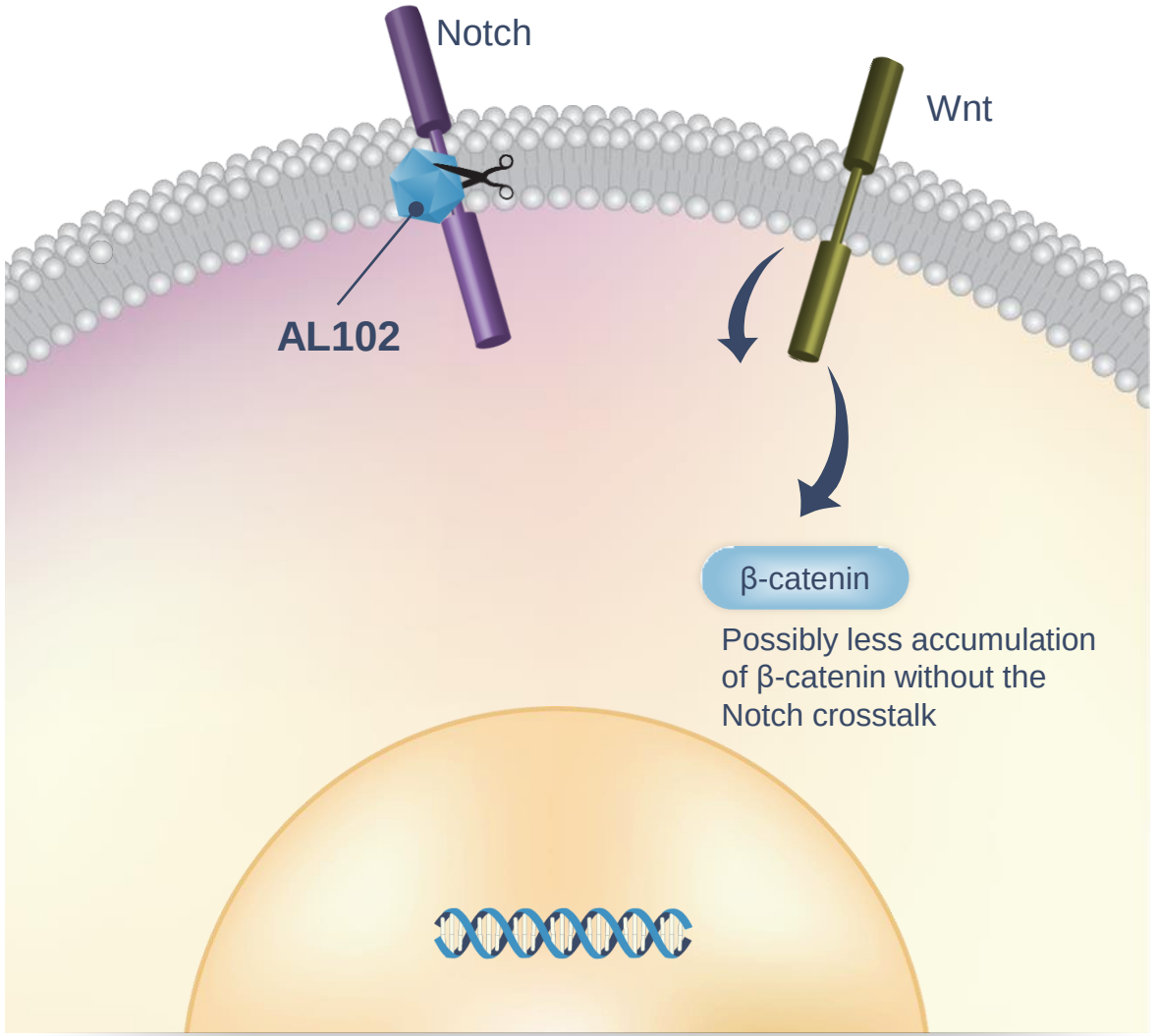




[a]MTD. [b]%TGI = % tumor growth inhibition; active result is defined as %TGI >50.
1 BMS scientific report 930069425
2 Nirogacestat is being developed by SpringWorks Therapeutics, Inc.
3 RO-4929097 was developed by F. Hoffmann-La Roche Ltd. and is not under active development
4 MK-0752 was developed by Merck & Co., Inc. and is not under active development

Potential Mechanisms for GSI Effect on Desmoid Tumors*





CD44-ICD: CD44 intracellular domain; NICD: Notch intracellular domain

Figure adapted from Gounder MM. Cancer. Published online 2015:3933-3937. doi:10.1002/cncr.29562; Bui N, Kummar S. Oncotarget. 2017;8(53):90608-90609; Malla RR, Kiran P. Genes Dis. 2020;9(2):310-324. doi:10.1016/j.gendis.2020.11.015

AL102 Phase 1 Clinical Trial

AL102 Phase 1 Dose Escalation (N = 36)
(NCT01986218)

- Evaluated safety, PK and PD in patients with advanced solid tumors
- Daily and twice weekly doses were tested; 3 doses were tolerated and advanced to Phase 2/3

Safety:

- AL102 was generally observed to be well tolerated at the doses chosen for our Phase 2/3 study
- AE profile as expected for GSIs, diarrhea and nausea being the most frequent, mostly of Grade 1/2

Efficacy:

- Target engagement evidenced by continuous inhibition of Notch pathway genes on both schedules
- Eleven (31%) subjects achieved best response of SD; 5 of these lasted >6 months
- Desmoid tumor patient achieved SD: 16.5% shrinkage in tumor size after 9 months of treatment

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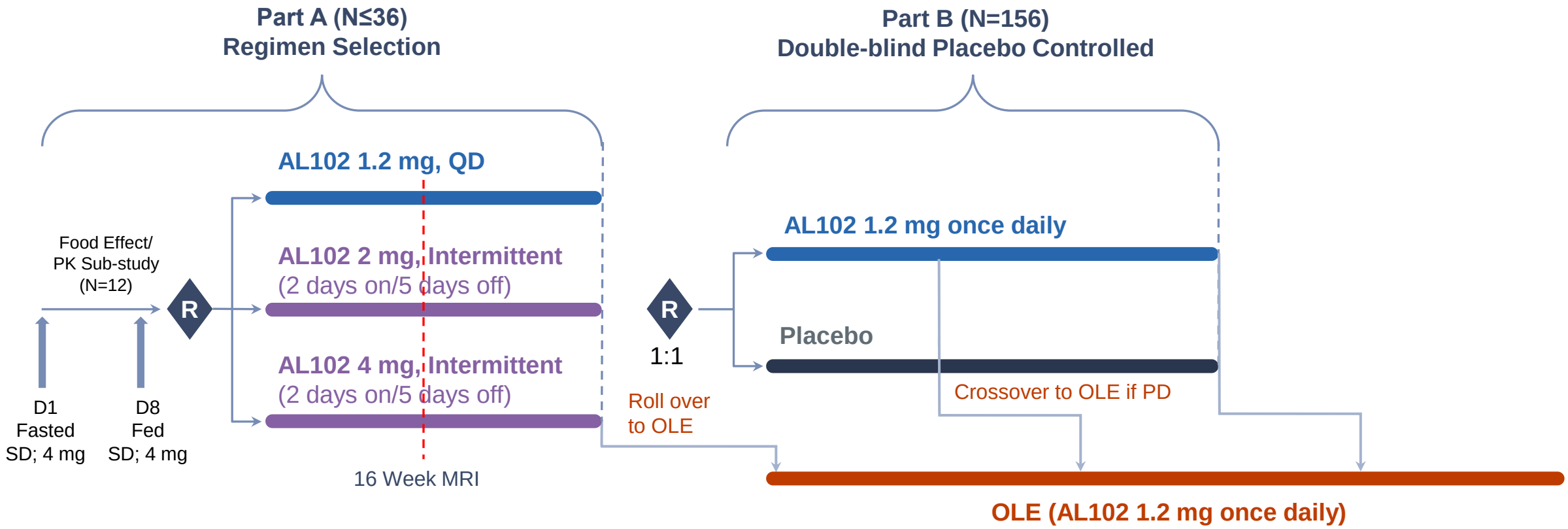
Aung et al, Invest New Drugs, 2018
AE = adverse event; DLT = Dose Limiting Toxicity; GSI – gamma secretase inhibitor; SD = stable disease

RINGSIDE: Pivotal Phase 2/3 Trial Evaluating AL102 in Desmoid Tumors

Part A completed; Part B initiated



CT, computed tomography; DOR, duration of response; D, day; DT, desmoid tumor; MRI, magnetic resonance imaging; OLE, open-label extension; ORR, objective response rate; PFS, progression free survival; PK, pharmacokinetics; QD, once daily; QOL, quality of life; R, randomization, R/R, relapse/refractory; RECIST, Response Evaluation Criteria in Solid Tumors; TN, treatment-naive

Summary

- AL102 is a unique chemical entity
- Potent notch inhibitor
- Significant anti tumor activity in numerous animal models
- Studied in Phase 1, activity seen in a patient with desmoid tumor
- Safe doses were determined
- RINGSIDE Phase 2/3 ongoing; positive initial results reported from Part A

Robin Jones, MD

- Head of the Sarcoma Unit at The Royal Marsden, London UK
- Professor at The Institute of Cancer Research, UK
- Principal investigator for Phase I, II and III trials and translational studies in sarcomas
- Previously Director of the Sarcoma Program at the University of Washington and Fred Hutchinson Cancer Research Center, Seattle
- Member of the Board of Directors of the Connective Tissue Oncology Society (CTOS)
- Board member to patient organizations (SPAEN, NLMSF and GIST UK, EHE Patient Group)
- Postgraduate research at the Institute of Cancer Research evaluated potential predictive and prognostic factors in breast cancer patients treated with neoadjuvant chemotherapy
- Completed medical training at Guy's and St Thomas' Hospital, and oncology training at The Royal Marsden

Initial Results of RINGSIDE, a Phase 2/3 Trial of AL102 for the Treatment of Desmoid Tumors

Mrinal Gounder, Robin L Jones, Rashmi Chugh, Mark Agulnik, Arun Singh, Brian A. Van Tine, Vladimir Andelkovic, Edwin Choy, Jeremy Lewin, Ravin Ratan, Atrayee Basu-Mallick, Bruce Brockstein, Nam Bui, Sant Chawla, Shadi Hadaddin, Hyo Song Kim, Alexander Lee, Javier Martin-Broto, Christopher Ryan, Gary Schwartz, Winette T. A. van der Graaf, Jason Kaplan, Jonathan Yovell, Gary Gordon, Bernd Kasper

Professor Robin Jones, MD
Team Leader in Sarcoma Clinical Trials, The Institute of Cancer Research, UK
Consultant Medical Oncologist, The Royal Marsden, UK

DTRF's Virtual Weekend, Research Workshop
Sept 23, 2022

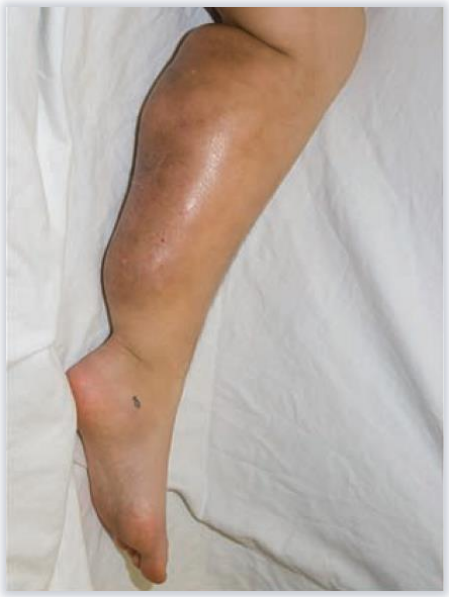
Background

Desmoid tumor

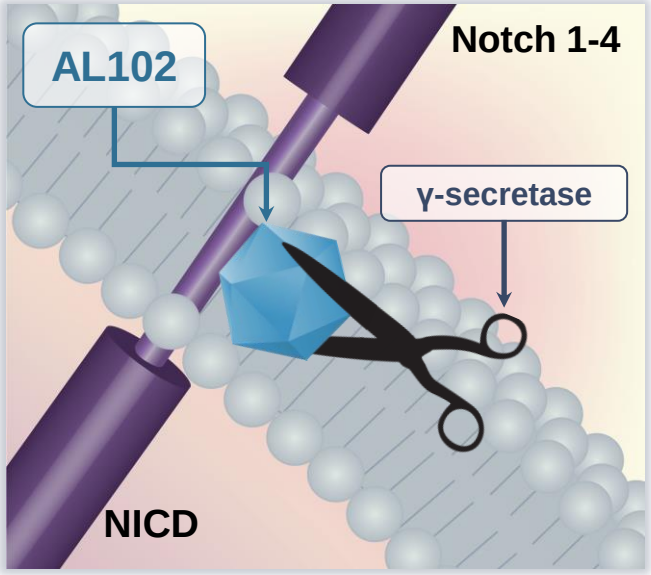
- Locally aggressive tumor
- Variable and unpredictable clinical course with pain, discomfort, and impact on quality of life (QOL)
- 5-6 cases per million people/year
- Peak incidence age 30 (range 15-60) years, female predominance
- 5-10% in the context of familial adenomatous polyposis (FAP)

Gamma-secretase inhibitor (GSI)

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



McDonald, et al., RadioGraphics 2008

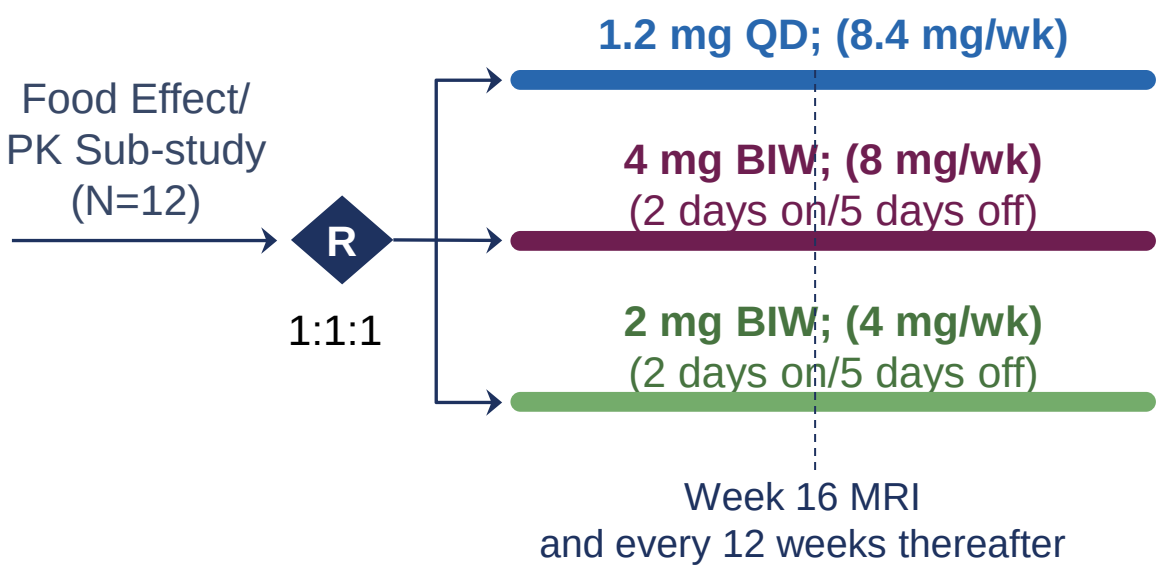


The Desmoid Tumor Working Group, European Journal of Cancer 127 (2020) 96-107; Quintini et al, Ann Surg. 2012; 255(3):511-6; Gounder et al, N Engl J Med 2018;379:2417-28; Trufero et al, Curr. Treat. Options in Oncol. (2017) 18:29

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:

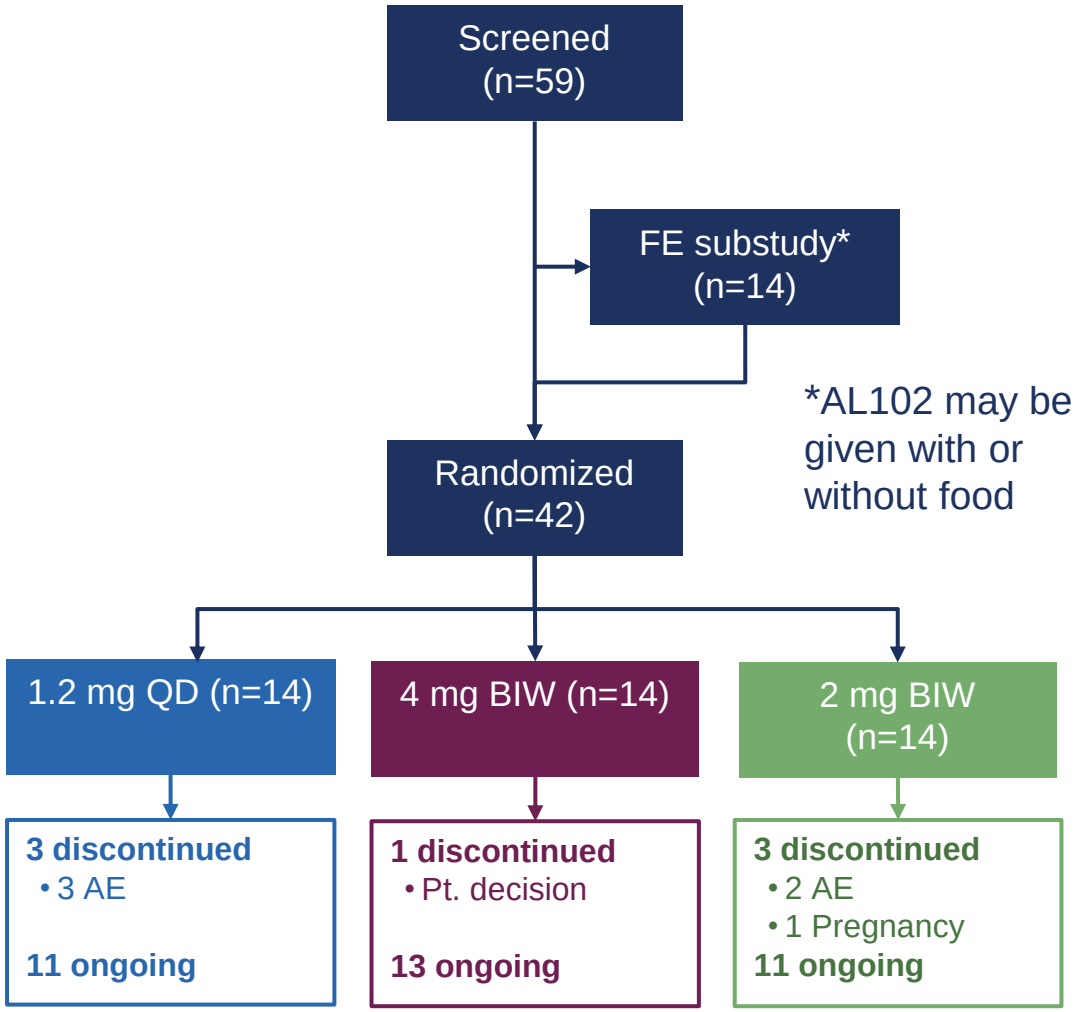
- R/R or Treatment-naive DT with Progression
  - ≥10% unidimensional growth within 18 months, OR
  - DT-related pain requiring non-opioid med
- Age ≥18

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

AL102 @ selected regimen vs Placebo

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

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
- Across all doses, ovarian dysfunction was seen in 22% of patients (N = 23)[c]
- AEs were consistent with mechanism of action of GSIs

Treatment-related AEs in ≥20% of Subjects

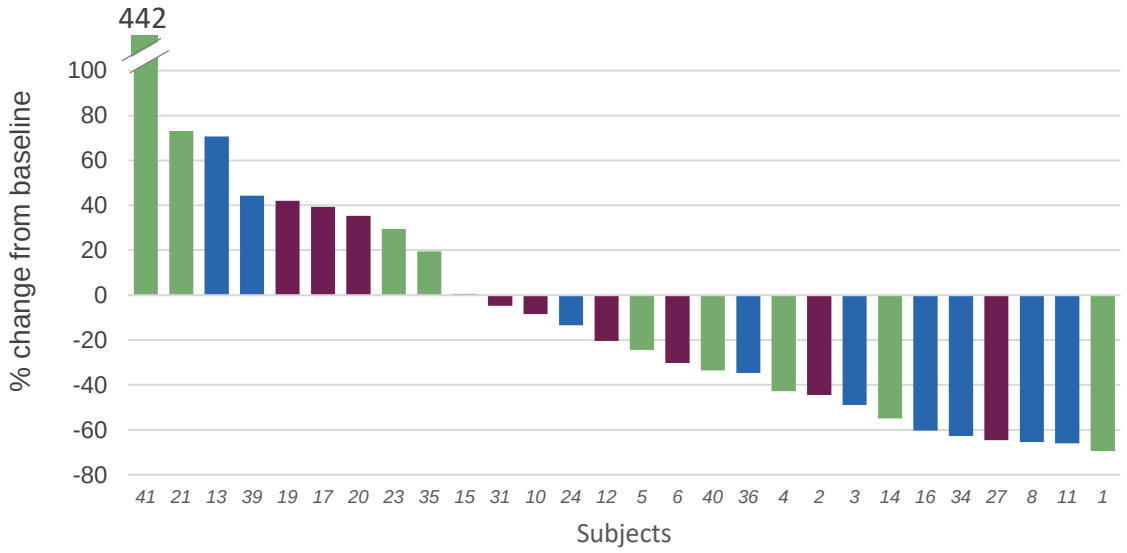
		1.2 mg QD (n=14)		4 mg BIW (n=14)		2 mg BIW (n=14)	
System Organ Class	Preferred Term	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Gastrointestinal disorders	Diarrhoea	11 (79)	1 (7)	8 (57)	1 (7)	7 (50)	-
	Nausea	5 (36)	-	5 (36)	-	3 (21)	-
	Dry mouth	5 (36)	-	5 (36)	-	-	-
	Stomatitis	6 (43)	1 (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; c. ovarian dysfunction defined as premature menopause, menopause, ovarian failure, amenorrhea, and irregular menstruation

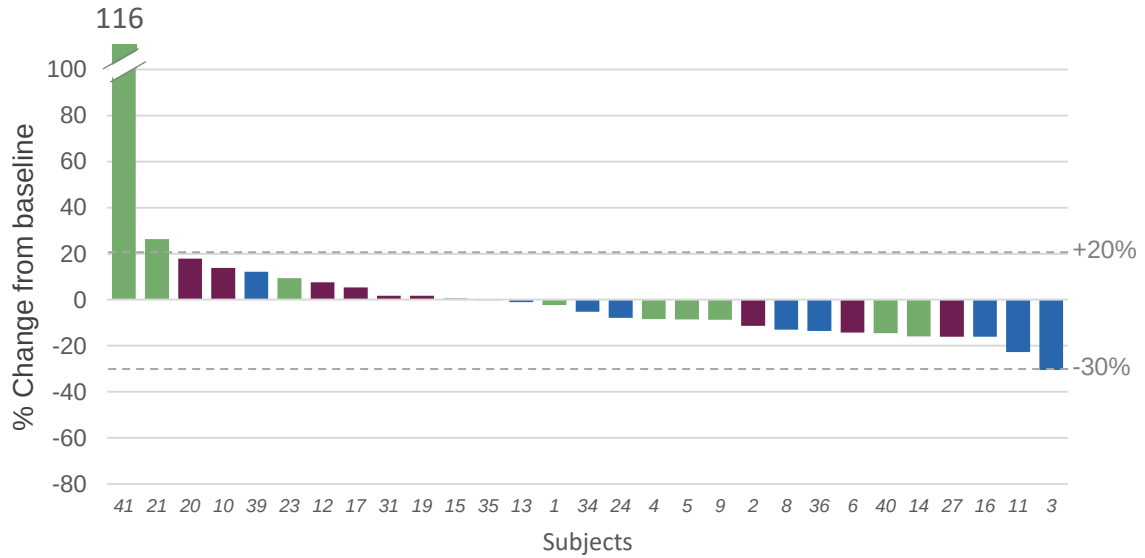
Early Volume and RECIST Response at Week 16

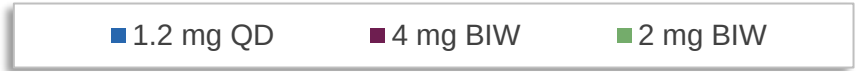
- Activity observed in all dose arms
- PR (central) observed at 16 weeks (confirmed 28 weeks)

Volume (N=28)



Central RECIST (N=29)

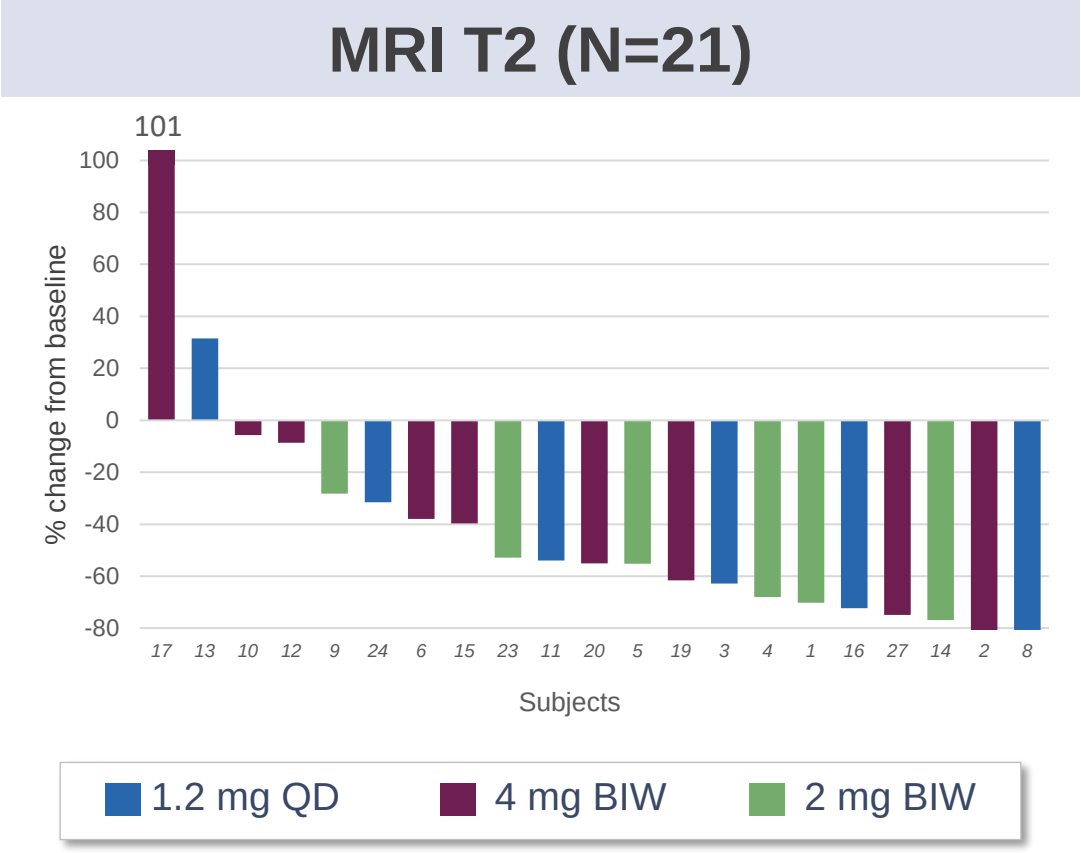




N, number of patients with data; Data cut: Jul 14, 2022

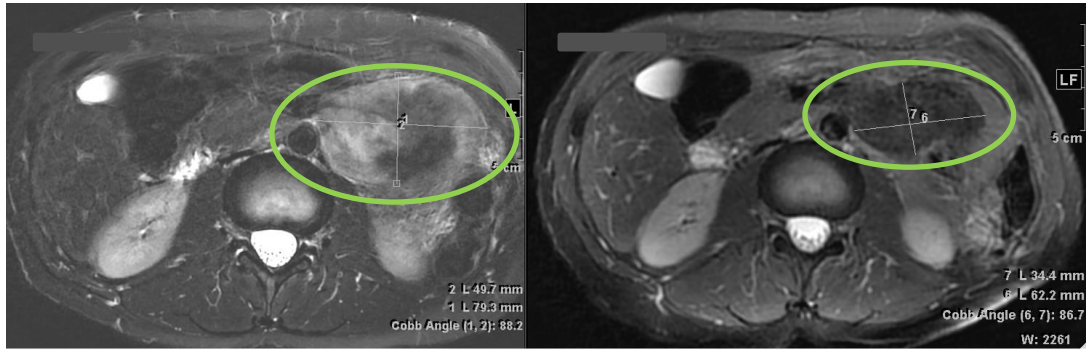
T2 Changes Reflect Decrease in Cellularity

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

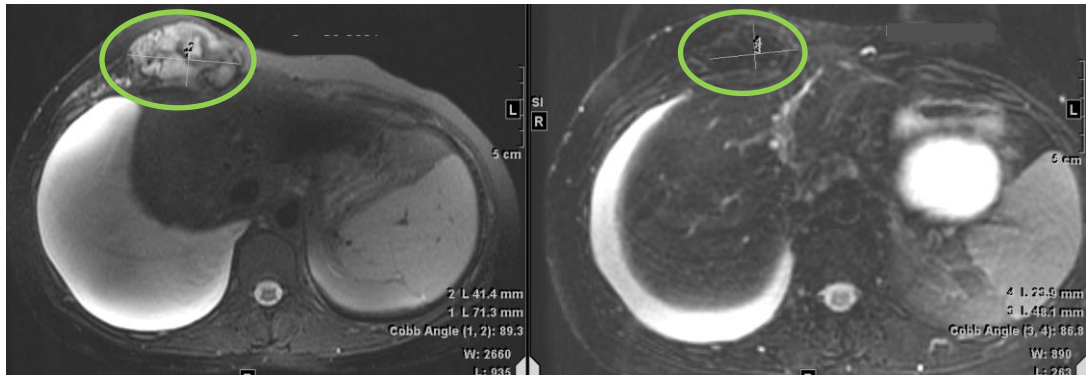


- Reduction of T2 intensity and size in 2 subjects at Week 28

Subject #11*



Subject #2



Baseline Week 28

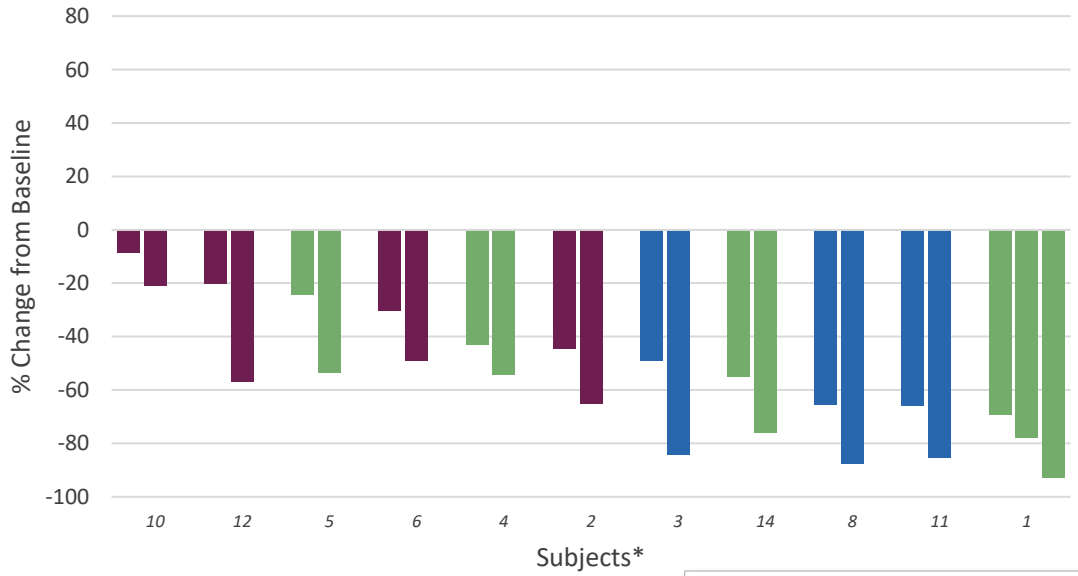
N, number of patients with data; Data cut: Jul 14, 2022; * Wk 28 for Subject #11 was obtained post-data cut

MRI Results Beyond 16 Weeks

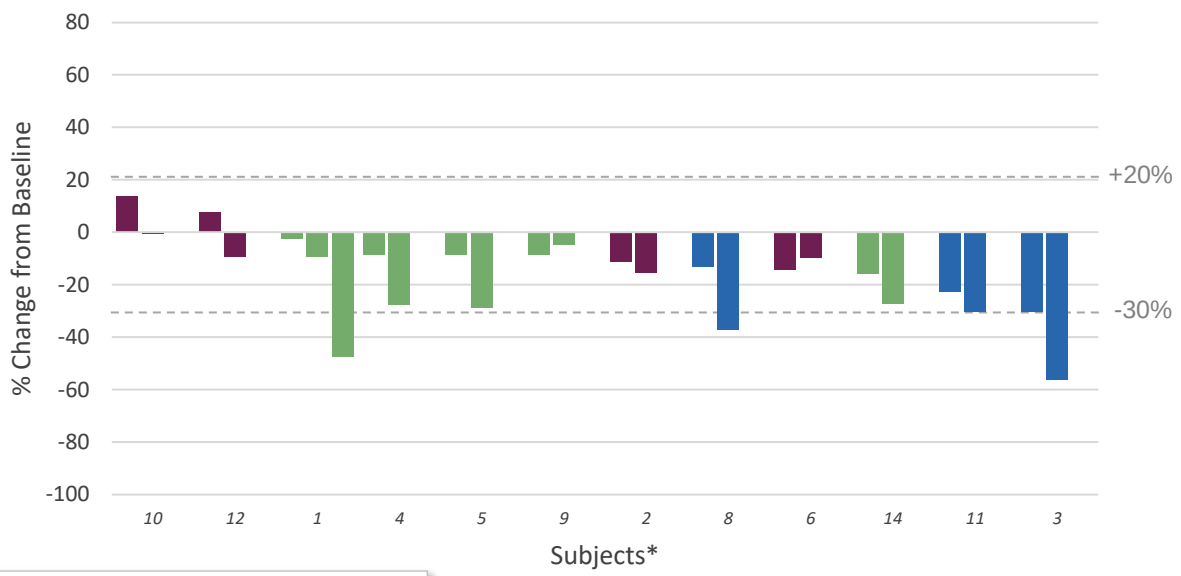
Consistent response across study arms and measures deepening over time

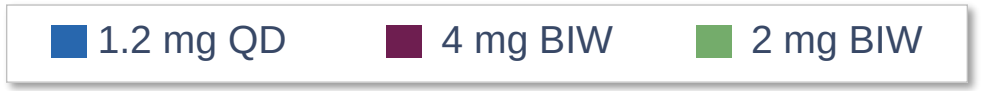
- At data cut, 12 subjects had results for 2 or more MRI scans
- 4 central PRs: 1 at week 16 confirmed at week 28, 2 at week 28, 1 at week 40

Volume (n=11)



Central RECIST (n=12)





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

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

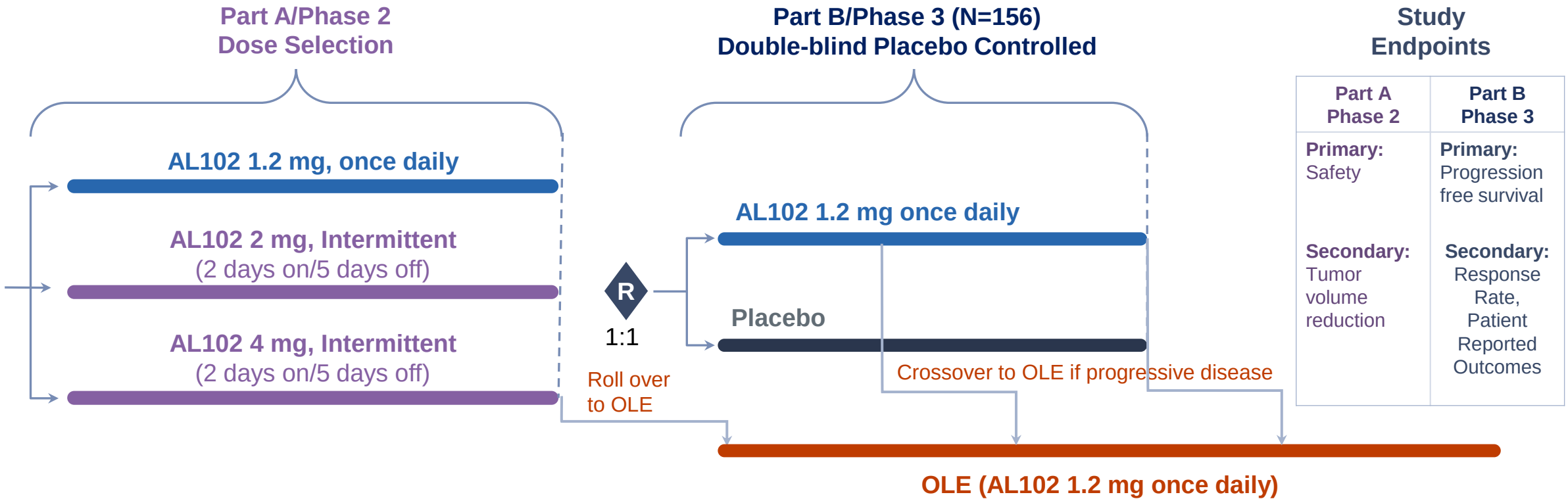
- Consistent across measures: Volume, Central/Local RECIST, and T2, T1 (data not shown)
- Responses are seen within 16 weeks and are maintained and deepen over time
- First PR seen at 16 weeks and 3 additional PRs over the follow up period

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

RINGSIDE: Pivotal Phase 2/3 Trial Evaluating AL102 in Desmoid Tumors

Part A fully enrolled, treatment ongoing; Part B initiated



Study Endpoints

Part A Phase 2	Part B Phase 3
Primary: Safety	**Primary:** Progression free survival
Secondary: Tumor volume reduction	**Secondary:** Response Rate, Patient Reported Outcomes

Part A Key Inclusion Criteria

- Relapsed/refractory or treatment-naïve, with tumor growth or pain in the last 18 mos
- Age ≥18
- Measurable Lesion on MRI

Part B Key Inclusion Criteria

- Relapsed/refractory or treatment-naïve, with tumor growth in the last 12 months
- Age ≥12
- Measurable Lesion on MRI or CT

OLE Key Inclusion Criteria

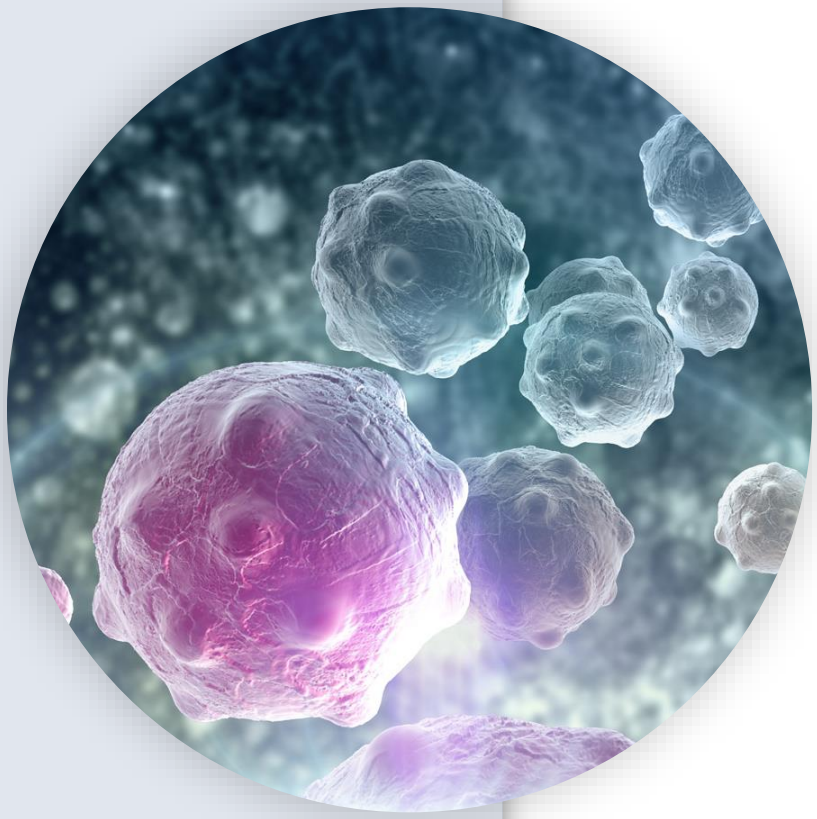
- Participating in Part A (MRI at Week 16)
- Participating in Part B and were noted to have progressive disease by central review
- Still on study after completion of Part B

CT, computed tomography; MRI, magnetic resonance imaging; OLE, open-label extension; R, randomization

RINGSIDE Part B / Phase 3 Enrollment is Open!

- USA
- UK
- Australia
- Netherlands
- Spain
- South Korea
- Israel
- Belgium
- France
- Germany
- India
- Italy
- Poland

US sites are enrolling
Other sites gradually opening



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AL102 Commercial Opportunity

Roni Mamluk PhD

AL102 for the Potential Treatment of Desmoid Tumors

Market Opportunity

- No FDA-approved therapies for desmoid tumors
- Annual incidence of ~1,700 in US[1]
- 5,500 to 7,000 patients actively seeking treatment in the US
- 5Y survival rates >95%
- Responses to different treatment options are most often modest and not durable[2]
- Clear unmet need for more effective systemic therapies to treat recurrent/ progressive tumors and prevent recurrence

Competitive Positioning

- AL102 has good activity in desmoid tumors at safe doses
- Less pill burden for AL102 → Important for chronic treatment

1 Penel, N., et al. Curr Opin Oncol, 2021; Broekhoven, D.L., et al. Ann Surg Oncol. 2015;22(9): 2817-23; Desmoid Tumor Working Group, Eur J Cancer 2020;127:96–107
2 Janinis, J. Annals of Oncology, 2003;14:181-190; Shang, H, et al. Cancer 2015;121:4088-96

Ayala Upcoming Potential Milestones

- 4Q 2022 – Enroll 1st Patient in Part B of RINGSIDE
- Mid 2023 – Present longer-term data from Part A of RINGSIDE with AL102
- Early 2023 – Gain clarity on registration for AL101 in R/M ACC

ACC = Adenoid Cystic Carcinoma; DT = Desmoid Tumor; R/R T-ALL = Relapsed / Refractory T-cell Acute Lymphoblastic Leukemia


Questions?
Answers.

Thank you.

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