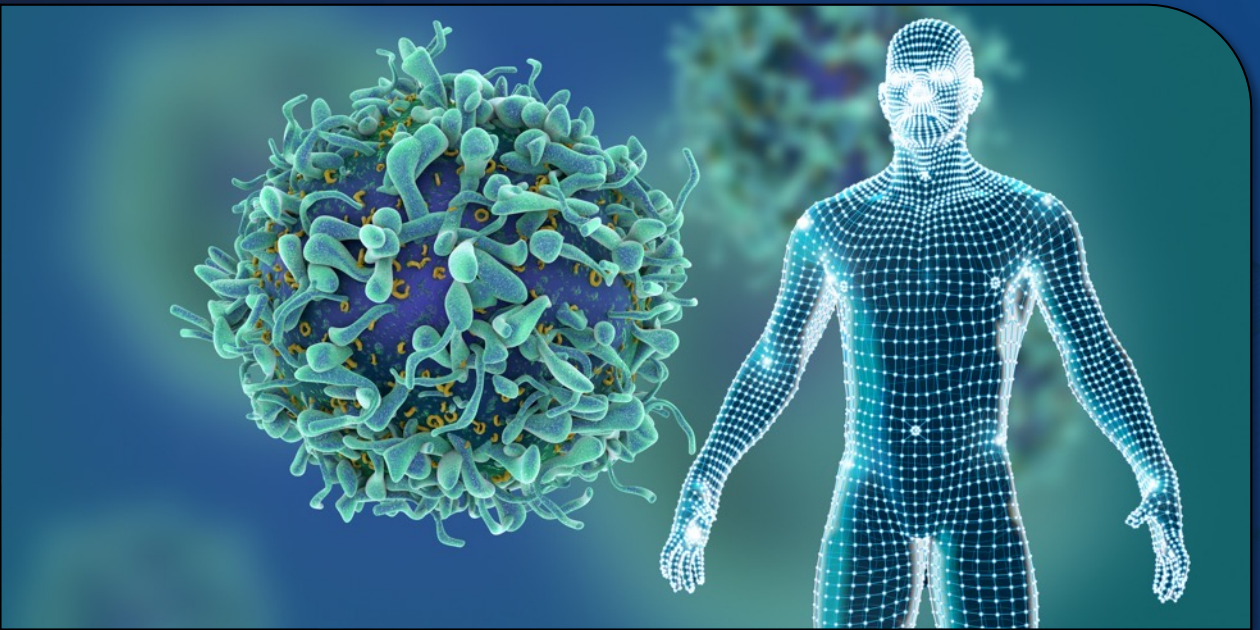
Patient-Centric Frameworks in Desmoid Tumors

Integrating Emerging Science on Gamma-Secretase Inhibitors for Progressive Disease

PeerView Live

Desmoid Tumor Research Foundation

SARC



Our Goals for Today

Prof. Dr. Patrick Schöffski, MD, MPH
Leuven Cancer Institute
University Hospitals Leuven
KU Leuven
Leuven, Belgium

- **Enhance your knowledge** of utilizing gamma-secretase inhibitors for the management of desmoid tumors
- **Improve your skills** for selecting personalized systemic treatment options that consider clinical trial evidence and guidelines
- **Equip you with strategies** to address practical aspects of care, including shared decision-making and adverse event management

Gaps and Challenges in the Diagnosis and Treatment of Desmoid Tumors

Desmoid tumors are rare

They have a variable presentation, clinical course, andoutcomes

Initial misdiagnosis is common

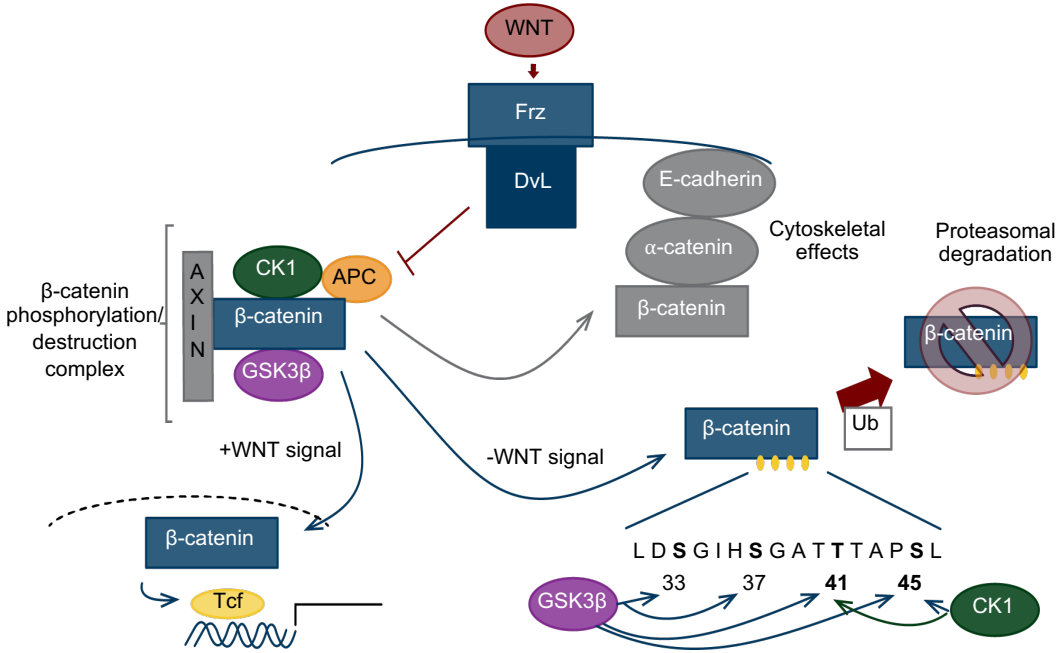
Rarity and histologic mimics contribute to misdiagnoses

Effective, safe, and regulatory-approved systemic therapies have been lacking

Recent clinical research advances are changing this

Desmoid Tumors Can Develop as a Result of *CTNNB1* Mutation or *APC* Loss[1]

- 85% of cases harbor a somatic mutation in the *CTNNB1* gene on **chromosome 3** (exon 3)
- APC mutation occurs in the context of a hereditary condition (familial adenomatous polyposis = Gardner's syndrome, an autosomal dominant disorder)
- Rarer *APC* (chromosome 5) deletion in *CTNNB1* wild type tumors may occur
- Both are mediators of the Wnt signaling pathway, which gives rise to an uncontrolled proliferation of fibroblasts

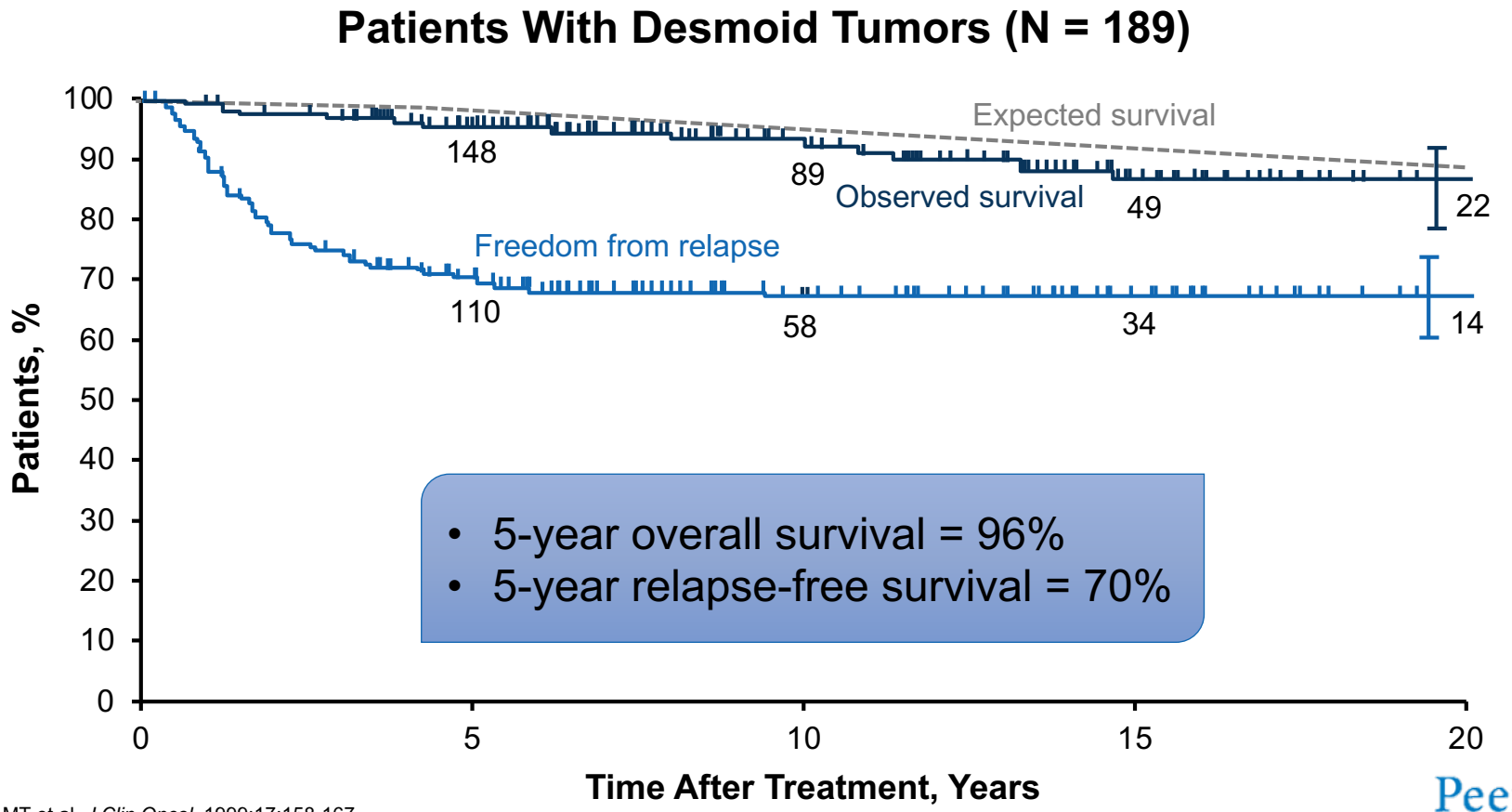


CK1, casein kinase 1; DvL, dishevelled; Frz, frizzled receptors; Tcf, T-cell factor; Ub, ubiquitin.

Either *CTNNB1* mutation or *APC* loss can lead to the development of desmoid fibromatosis

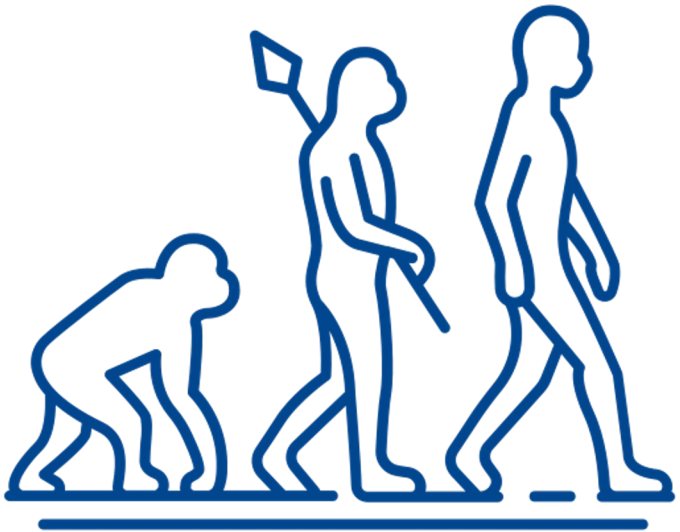
1. Mullen JT et al. *Oncologist.* 2013;18:1043-1049.

Desmoid Fibromatosis/Desmoid Tumor Has Historically Been Treated With Surgery, Which Is Associated With Considerable Risk of Recurrence[1]



1. Ballo MT et al. *J Clin Oncol*. 1999;17:158-167.

Evolution of the Treatment of Desmoid Tumors



Surgery is ***no longer*** the primary treatment for localized disease for typical desmoid tumors

1. Alman B et al. *Eur J Cancer*. 2020;127:96-107.

Global Desmoid Tumor Working Group Consensus Statement[1,a]

Diagnosis (core needle biopsy)

Frontline approach: active surveillance

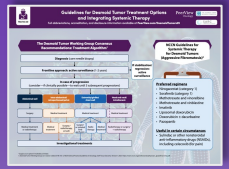
If stabilization/ regression: active surveillance

In case of progression
Consider, if clinically possible, to wait until confirmation of clinically relevant progression

Abdominal wall	Intra-abdominal/ retroperitoneal/pelvic	Extremity/girdles/ chest wall	Head and neck/ intrathoracic
Surgery	Medical treatment	Medical treatment	Medical treatment
Medical treatment or radiotherapy	Medical treatment; Surgery,[a] radiotherapy, or both	Surgery[a] or isolated limb perfusion; Radio-therapy; Medical treat-ment	Radiotherapy or surgery[a] + radiotherapy

Investigational treatments

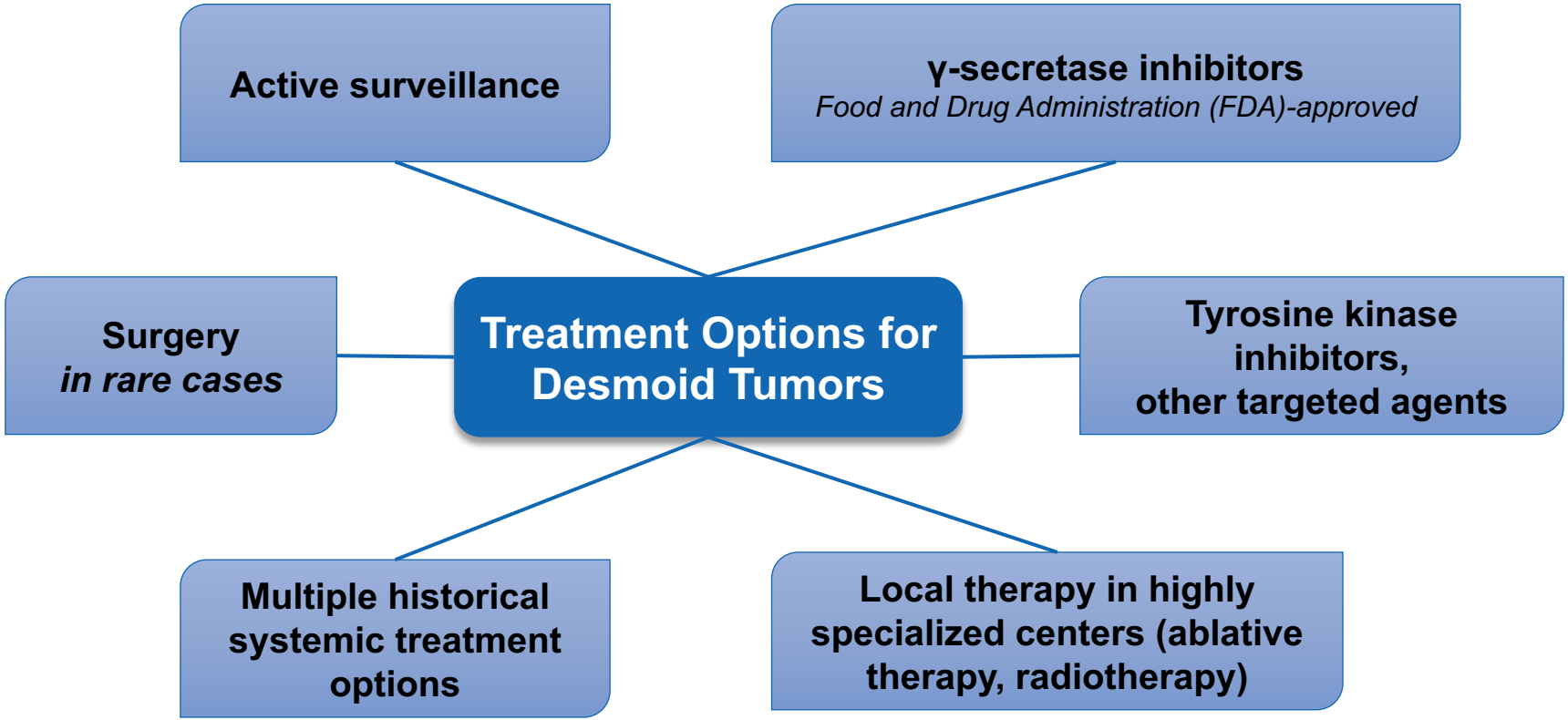
Download the Practice Aid



[a] Surgery is an option if morbidity is limited.

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

The Past, Present, and Future of Treatment Options for Desmoid Tumors[1,2]



1. Kasper B et al. *JAMA Oncol*. 2024;10:1121-1128. 2. Schöffski P et al. *Oncol Res Treat*. 2018;41:214-219.

An Excellent Resource for Patients: The Desmoid Tumor Research Foundation (DTRF)

DTRF's mission is to aggressively fund research to accelerate the development of improved therapies and, ultimately, find a cure for desmoid tumors. We collaborate with dedicated researchers and clinicians worldwide to improve the lives of patients through education, awareness, and support.

Resources for Researchers and Healthcare Providers

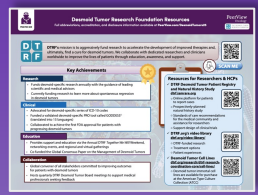
SCAN ME

- ✓ **DTRF Desmoid Tumor Patient Registry and Natural History Study*: dtrf.iamrare.org***
  - Online platform for patients to report cases
  - Prospectively-planned natural history study
  - Standards of care recommendations for the medical community and assistance for researchers
  - Support design of clinical trials

- ✓ **DTRF.org's video library: *dtrf.org/video-library***
  - DTRF-funded research
  - Treatment options
  - Patient experiences

- ✓ **Desmoid Tumor Cell Lines**
  - Desmoid tumor immortal cell lines are available for purchase at the American Type Culture Collection (ATCC)

Download the Practice Aid Resource

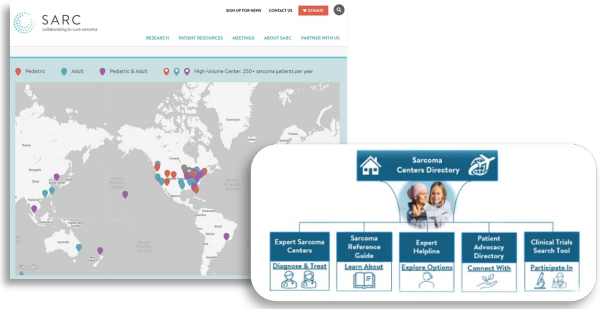


Sarcoma Alliance through Research and Collaboration (SARC): Programs and Resources for Patients and Clinicians

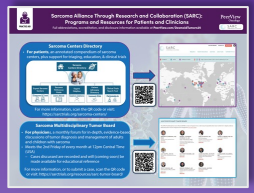
SARC

Sarcoma Centers Directory

For patients, an annotated compendium of sarcoma centers, plus support for triaging, education, and clinical trials.



Download the Practice Aid Resource

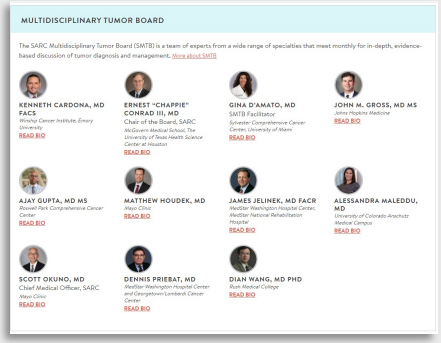


Sarcoma Multidisciplinary Tumor Board

For physicians, a monthly forum for in-depth, evidence-based discussions of tumor diagnosis and management of adults and children with sarcoma.

Meets the 2nd Friday of every month at 12 pm Central Time (USA). Cases discussed are recorded and will (coming soon) be made available for educational reference.

For more information, or to submit a case, go to: sarctrials.org/resources/sarc-tumor-board



Seminar & Tumor Board

Implementing Personalized Frameworks In Desmoid Tumors

Clinical Applications for Gamma-Secretase Inhibitors Across Patient Subgroups

Refining The Treatment Toolbox

The Latest Evidence From Randomized Trials

Prof. Dr. Patrick Schöffski, MD, MPH
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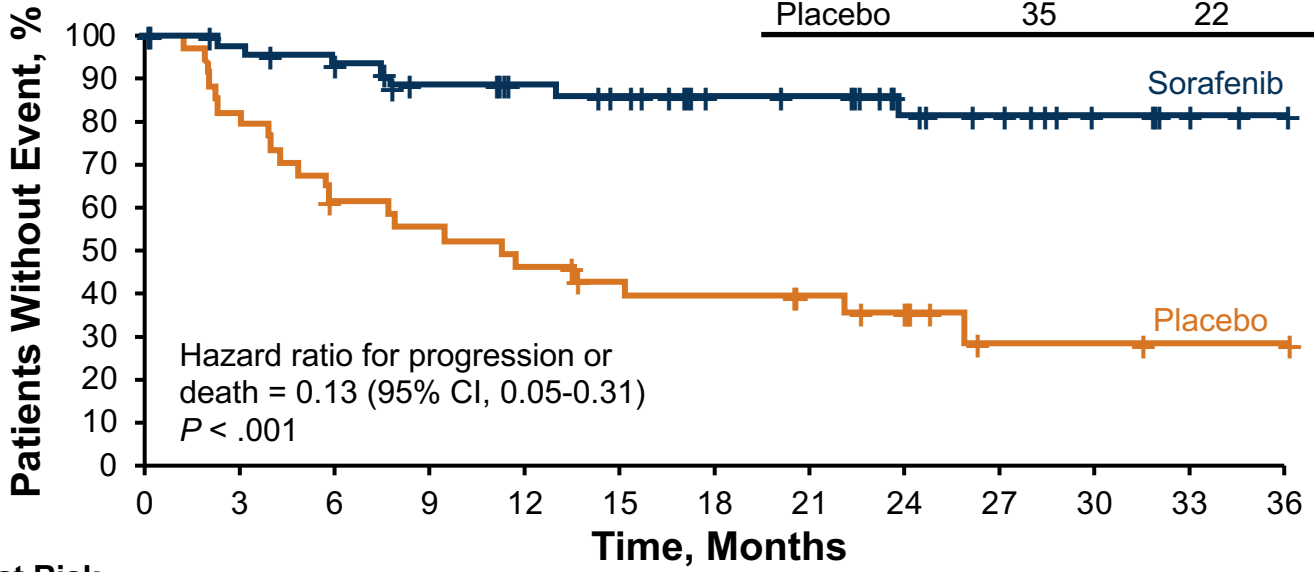
Sorafenib Significantly Prolongs Survival for Patients With Progressive, Refractory, or Symptomatic Desmoid Tumors[1]

Phase 3 Randomized Study

	No. of Patients	No. of Events	Median Progression-Free Survival, Months (95% CI)
Sorafenib	49	7	NE (NE-NE)
Placebo	35	22	11.3 (5.7-NE)



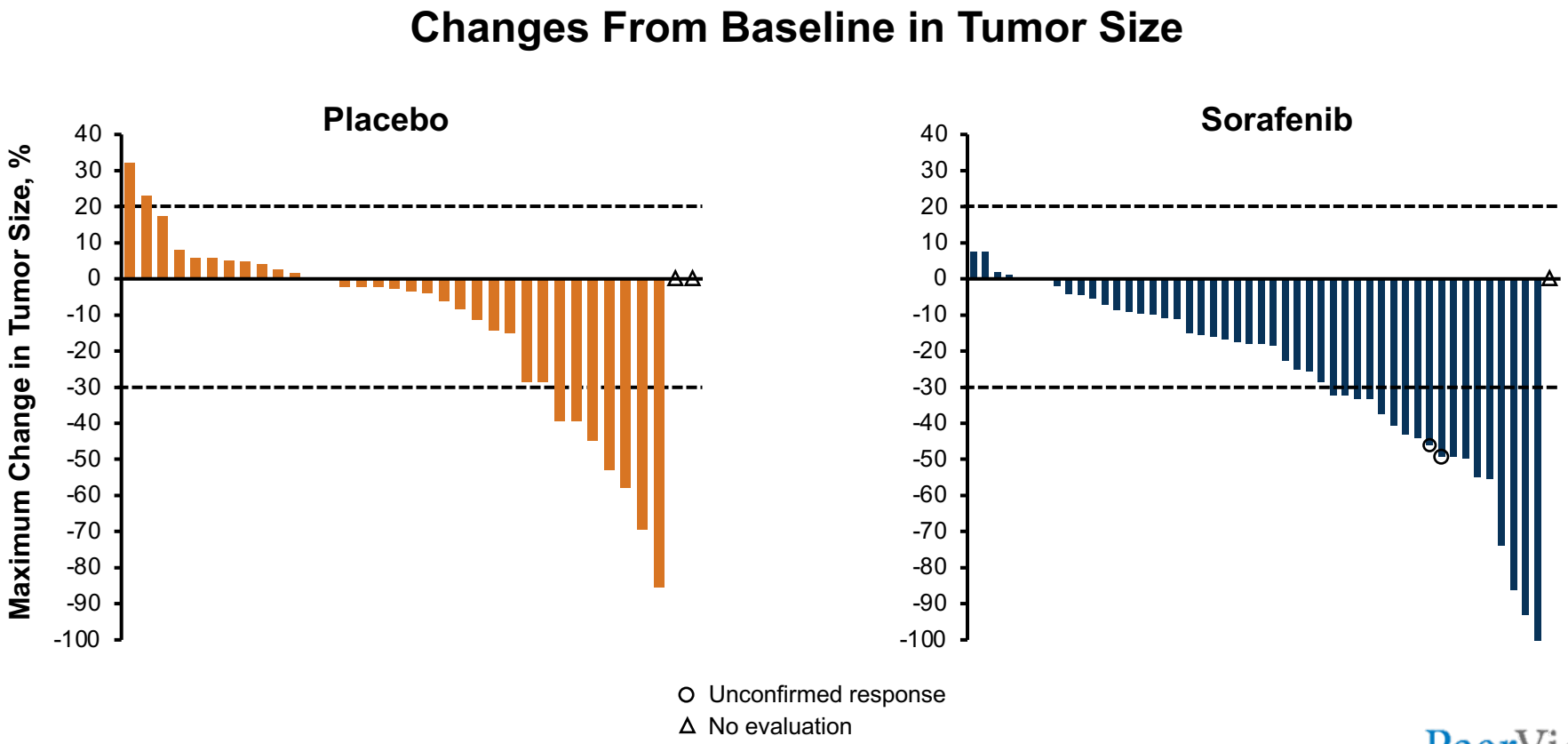
No. at Risk

Sorafenib	49	46	41	36	32	29	23	22	17	14	8	4	3
Placebo	35	28	20	18	15	12	11	10	7	3	3	2	2

CI, confidence interval; NE, not evaluable.

1. Gounder MM et al. *N Engl J Med*. 2018;379:2417-2428.

Sorafenib Induces Durable Responses in Progressive, Refractory, or Symptomatic Desmoid Tumors[1]



1. Gounder MM et al. *N Engl J Med*. 2018;379:2417-2428.

Gamma Secretase Inhibition in Desmoid Tumors: Summary of Approval Status[1-5]

Nirogacestat

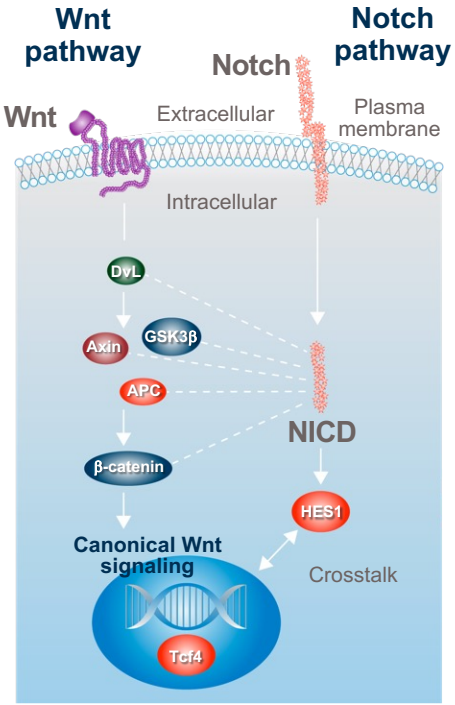
Oral, selective, small-molecule gamma-secretase inhibitor that has shown evidence of antitumor activity in desmoid tumors with a manageable adverse event profile

- Received FDA approval in 2023 for patients with progressing desmoid tumors who require systemic treatment
- European Medicines Agency is evaluating marketing authorization and approval process is ongoing

Varegacestat (AL102)

Investigational, oral, potent inhibitor of gamma secretase

- Received Orphan Drug Designation by the FDA for the treatment of progressing desmoid tumors
- Not yet approved in the US or European Union



DvL, dishevelled; HES1, hes family BHLH transcription factor 1; NICD, Notch intracellular domain; Tcf4, T-cell factor 4.

1. Kasper B et al. ESMO 2022. Abstract LBA2 2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nirogacestat-desmoid-tumors. 3. Gounder MM et al. ESMO 2022. Abstract 1488MO. 4. https://www.globenewswire.com/news-release/2023/11/06/2774068/0/en/Ayala-Pharmaceuticals-Announces-AL102-Receives-Orphan-Drug-Designation-for-Desmoid-Tumors.html. 5. Andersson ER et al. Development. 2011;138:3593-3612.

DeFi: Phase 3 Study of Nirogacestat vs Placebo in Adult Patients With Desmoid Tumors[1,2]

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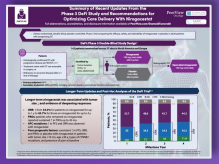
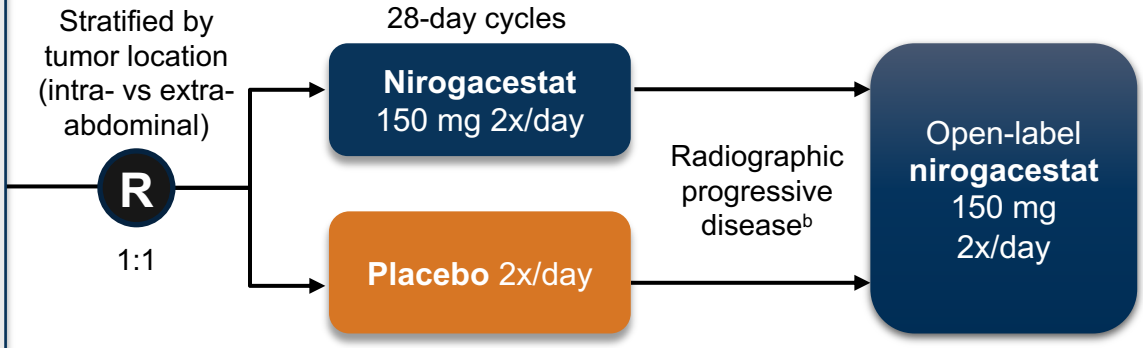


- Global, randomized, double-blind, placebo-controlled, phase 3 trial comparing the efficacy, safety, and tolerability of nirogacestat vs placebo in adult patients with progressing desmoid tumors
- 142 patients randomized across 37 sites in North America and Europe

Key Inclusion Criteria

- Adult patients
- Histologically confirmed desmoid tumors with progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST v1.1)[a]
  - Treatment-naïve with Desmoid tumors not amenable to surgery, *or*
  - Refractory or recurrent disease (after ≥1 line of therapy)



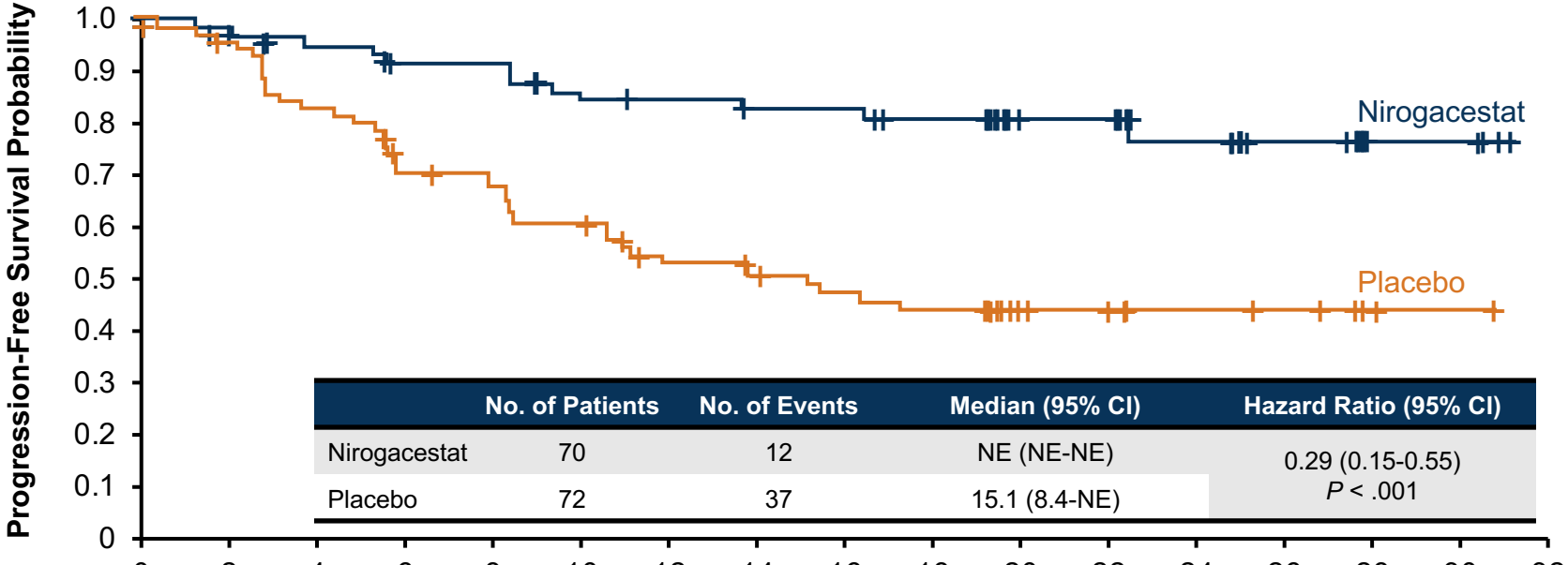
- **Primary endpoint:** Progression-free survival[c]
- **Secondary endpoints:** Overall response rate and patient-reported outcomes, including symptom burden, physical/role function, and overall quality of life[d]

Primary Analysis Data Cutoff: April 7, 2022

[a] Progressive disease defined by histologically confirmed desmoid tumors that has progressed ≥20% within the past 12 months by RECIST v1.1. Target tumors identified at screening by the investigator. [b] Radiographic disease progression or once the required number of events have been observed and the primary progression-free survival analysis has been completed.
[c] 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. [d] As assessed by change from baseline for Brief Pain Inventory-Short Form, GODDESS Desmoid Tumor Symptom Score, GODDESS Desmoid Tumor Impact Scale, and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 at cycle 10.

1. Gounder MM et al. *N Engl J Med*. 2023;388:898-912. 2. https://clinicaltrials.gov/ct2/show/NCT03785964.

DeFi: Nirogacestat Significantly Reduces the Risk of Disease Progression[1]



	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* < .001

No. of Risk

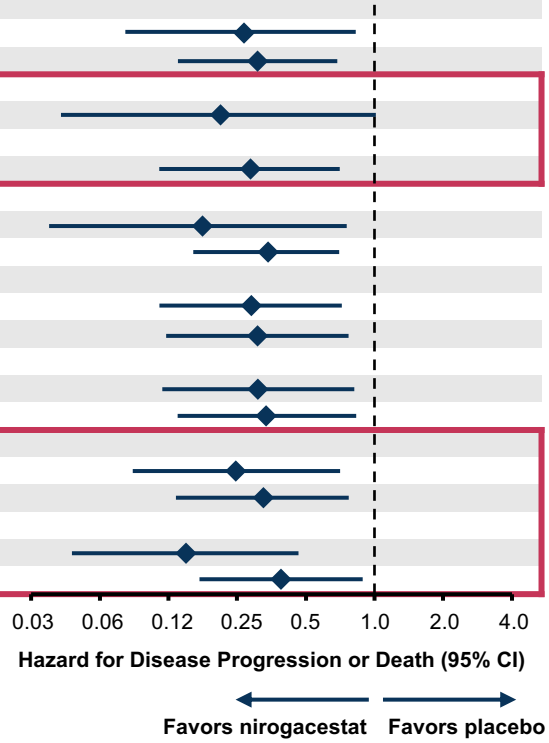
Nirogacestat	70	63	56	52	52	47	46	44	44	41	26	26	17	12	4	4	0
Placebo	72	67	58	47	45	40	32	29	27	25	10	8	6	5	1	1	0

CI, confidence interval; NE, not evaluable.
Median follow-up time was 19.2 months for nirogacestat and 10.9 months for placebo.

1. Gounder MM et al. *N Engl J Med*. 2023;388:898-912.

DeFi: Progression-Free Survival Benefit With Nirogacestat Is Observed Across Prespecified Subgroups[1]

	Hazard Ratio	Nirogacestat, Events/Patients	Placebo, Events/Patients
Sex			
Men	0.26	4/25	11/25
Women	0.30	8/45	26/47
***APC* mutation**			
Yes	0.20	2/11	8/11
***CTNNB1* mutation**			
Yes	0.28	6/43	21/42
Target tumor location			
Intra-abdominal	0.17	2/17	11/18
Extra-abdominal	0.34	10/53	26/54
Focality			
Single	0.29	6/43	19/41
Multifocal	0.30	6/27	18/31
Prior surgery			
Yes	0.31	5/31	23/44
No	0.33	7/39	14/28
Prior chemotherapy			
Yes	0.24	5/24	17/27
No	0.32	7/46	20/45
Prior tyrosine kinase inhibitor treatment			
Yes	0.15	4/23	16/24
No	0.38	8/47	21/48

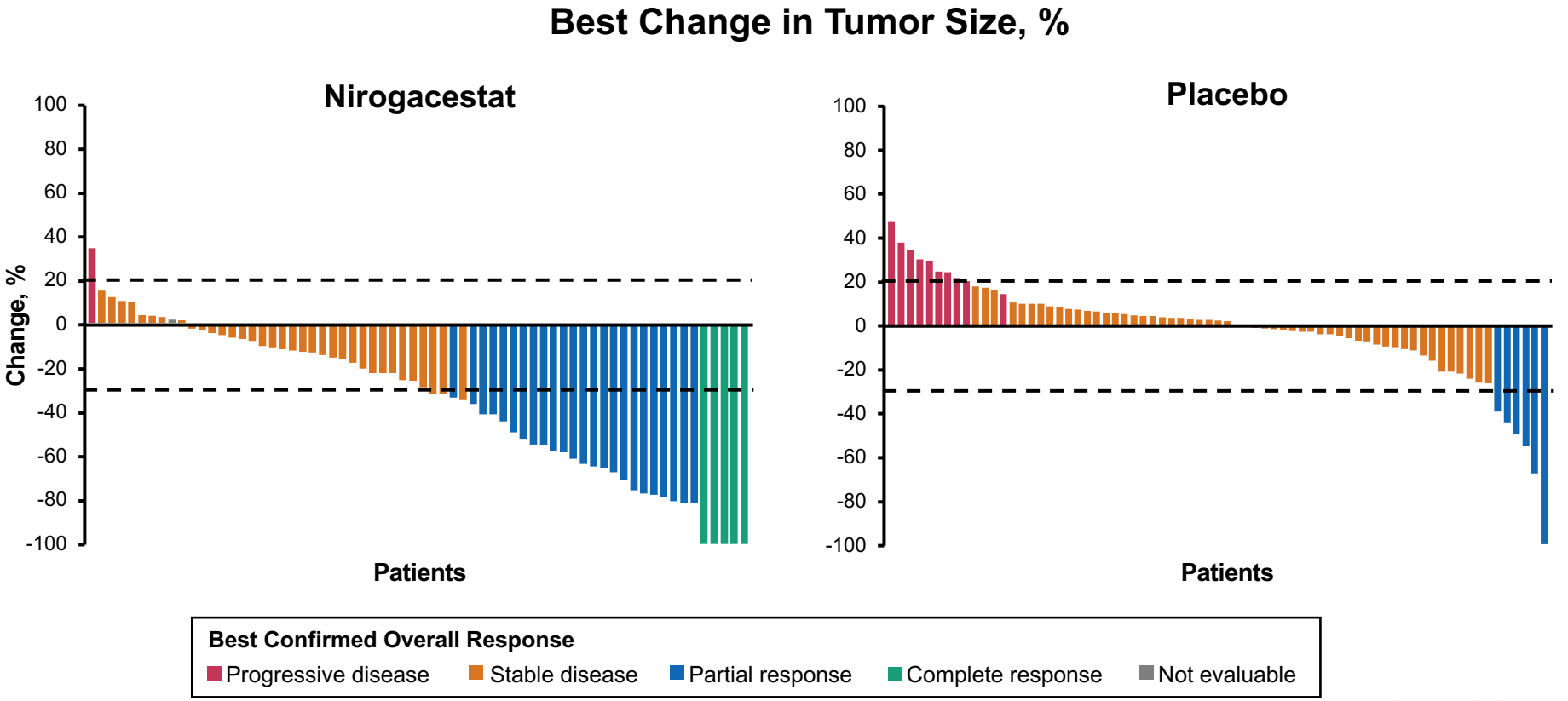


Nirogacestat is effective in both sporadic and hereditary desmoid tumors

CI, confidence interval.

1. Gounder MM et al. *N Engl J Med*. 2023;388:898-912.

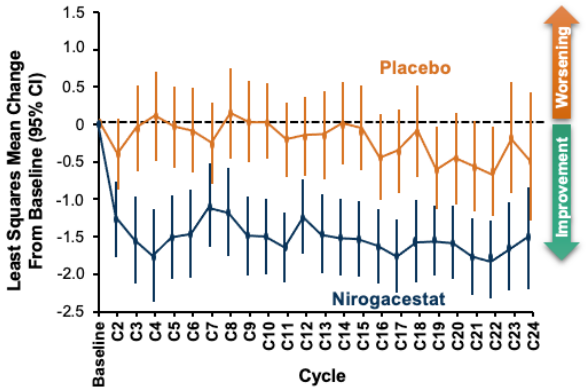
DeFi: Significant Improvement of Objective Response Is Associated With Nirogacestat Versus Placebo[1]



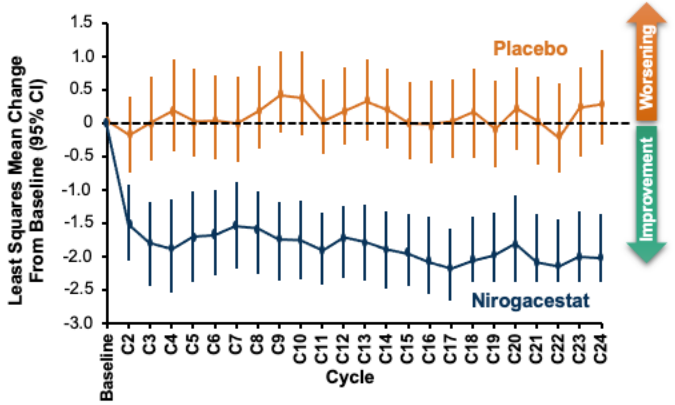
1. Gounder MM et al. *N Engl J Med*. 2023;388:898-912.

Nirogacestat Significantly Reduces Pain, Desmoid Tumor–Specific Symptom Severity, and Physical Functioning/Quality of Life[1]

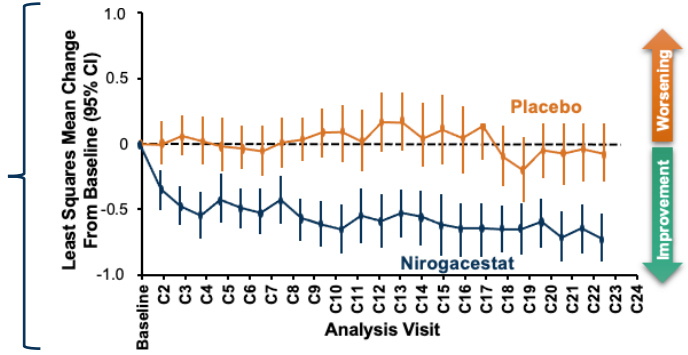
Brief Pain Inventory-Short Form: Worst Pain Intensity[a]



GODDESS Desmoid Tumor Symptom Score: Total Symptom Score[b]



GODDESS Desmoid Tumor Impact Scale: Physical Functioning Impact Score[c]



Nirogacestat also significantly improved European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 physical functioning ($P < .001$), role functioning ($P < .001$), and global health status/quality of life ($P = .007$) at Cycle 10 compared with placebo

CI, confidence interval.

[a] Mean (standard deviation) baseline scores: nirogacestat, 3.2 (3.26); placebo, 3.3 (3.31). Differences at cycle 10 were statistically significant and clinically meaningful. Least squares mean change from baseline represents the 7-day average of "worst pain in last 24 hours". [b] Mean (standard deviation) baseline scores: nirogacestat, 3.4 (2.34); placebo, 3.5 (2.57). Differences at cycle 10 were statistically significant and clinically meaningful. Desmoid Tumor Symptom Score total includes pain, fatigue, swelling, muscle weakness, and difficulty moving. [c] Mean (standard deviation) baseline scores: nirogacestat, 2.8 (1.14); placebo, 2.7 (1.24). Differences at cycle 10 were statistically significant and clinically meaningful. Desmoid Tumor Impact Scale physical functioning includes moving, reaching, vigorous activity, moderate activity, and accomplishing less.

1. van der Graaf et al. ASCO 2023. Abstract 11564.

Nirogacestat Has a Manageable Safety Profile for Progressing DTs[1]

Safety Population, n (%)	Nirogacestat (n = 69)		Placebo (n = 72)	
Duration of study drug exposure, median, mo (range)	20.6 (0.3-33.6)		11.4 (0.2-32.5)	
Dose intensity, mg/d, median (range)	288.3 (169-300)		300.0 (239-300)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any Treatment-emergent Adverse Event (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]	

[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 transaminase (ALT) increase (n = 3 [2%]), aspartate aminotransferase (AST) increase (n = 2 [1%]), and metabolism/nutritional disorders (n = 2 [1%]).

1. Kasper B et al. ESMO 2022. Abstract LBA2.

Ongoing Trials and Future Directions

Gamma-Secretase Inhibitors in Desmoid Tumor Care

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University of Colorado Cancer Center
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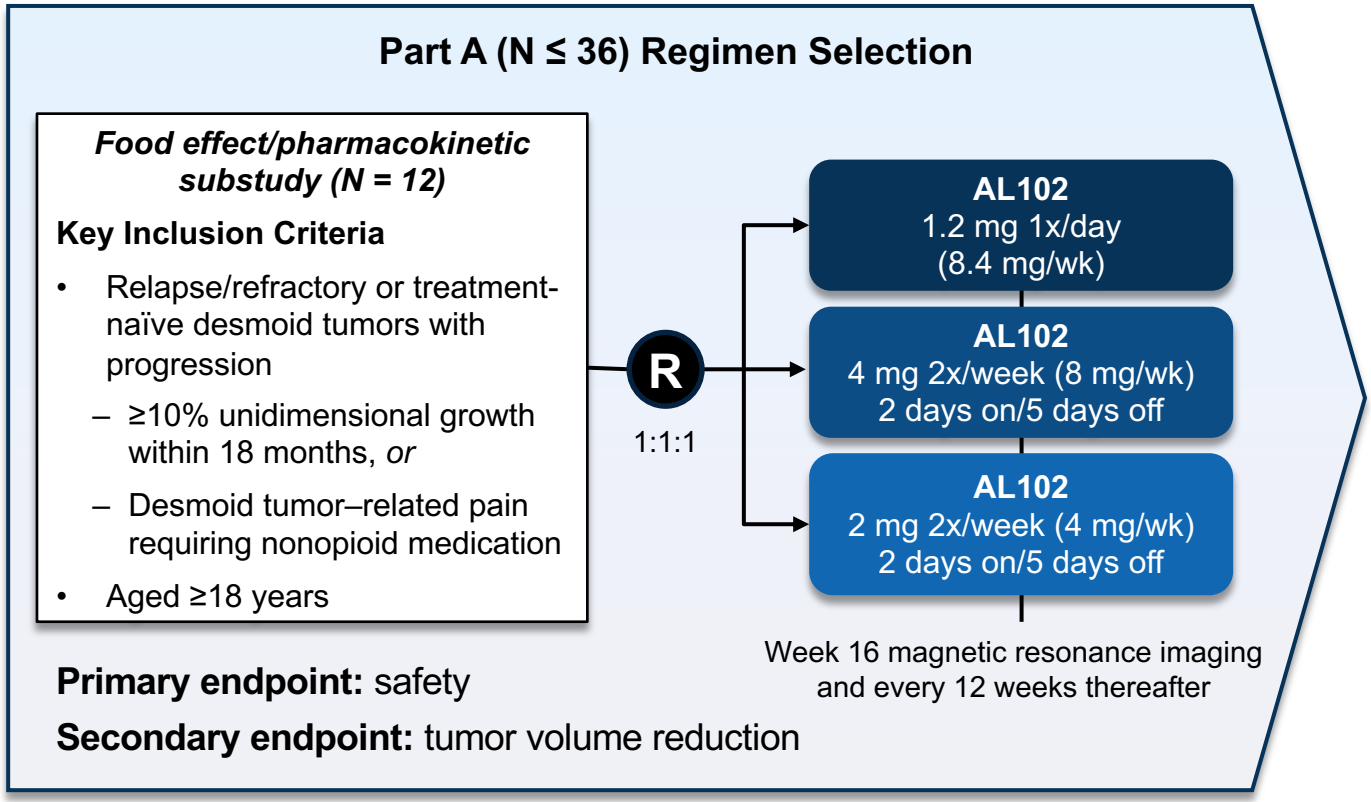
RINGSIDE: Phase 2/3 Trial of AL102 in Adults With Desmoid Tumors[1]



Part B (N = 156)
Double-blind, placebo controlled, and open-label extension at radiographic progression

AL102 selected regimen vs **placebo**

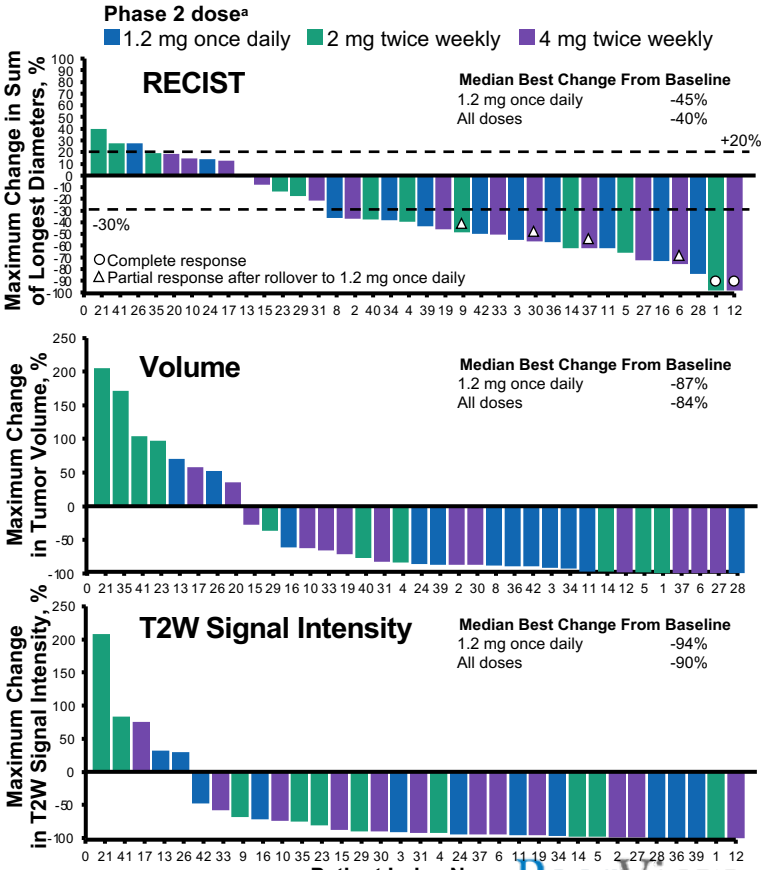
1. Gounder MM et al. ESMO 2022. Abstract 1488MO.

RINGSIDE: Updated Results and Open-Label Extension of AL102 for Treatment of Desmoid Tumors[1]

Best Response Per RECIST	1.2 mg Once Daily		All Patients All Doses	
	Evaluable (n = 12)	ITT (n = 14)	Evaluable (n = 36)	ITT (n = 42)
ORR (CR + OR), n (%)	**9 (75)**	**9 (64.3)**	**23 (63.9)**	**23 (54.8)**
Best overall response, n (%)				
Complete response	0	0	2 (5.6)	2 (4.8)
Partial response	9 (75)	9 (64.3)	21 (58.3)	21 (50)
Stable disease	3 (25)	3 (21.4)	12 (33.3)	12 (28.6)
Progressive disease	0	0	1 (2.8)	1 (2.4)
Time to objective response, median (range), months	6.8 (3.8-15.0)		9.4 (4.0-22.8)	

CR, complete response; ITT, intent-to-treat; OR, overall response; ORR, overall response rate.

- AL102 was generally well tolerated in all dose arms; safety is consistent with the gamma-secretase inhibitor class of drugs
- More rapid and persistent tumor responses in volume reduction, T2-weighted (T2W) signal intensity and RECIST with AL102 1.2 mg once daily than with intermittent doses
- Most patients achieved an overall response rate of 75% in the 1.2 mg once daily arm and 63.9% in all patients
- Early and deep volume (-52%) and T2W (-58%) reductions within 16 weeks of starting 1.2 mg once daily may correlate with symptomatic improvements



[a] All patients received 1.2 mg once daily in the open-label extension.

1. Kasper B et al. ESMO 2024. Abstract 1766P.

Phase 2 Trial Assessing Nirogacestat in Children and Adolescents With Progressive Unresectable Desmoid Tumors

Key Inclusion Criteria

- Patients aged >12 months and <18 years
- Histologically confirmed desmoid tumors with measurable disease per RECIST v1.1
- Refractory or recurrent disease (after ≥1 line of therapy)

28-day cycles

Nirogacestat 90 mg/m^2 2x/day on days 1-28

Patients undergo echocardiogram and computed tomography (CT) or magnetic resonance imaging (MRI) and may also undergo x-ray imaging and blood sample collection on study

Primary endpoints: progression-free survival, safety, pharmacokinetic parameters

Secondary endpoint: overall response rate

Fully accrued

1. clinicaltrials.gov/study/NCT04195399

Future Directions: Unanswered Questions …

Duration of treatment?

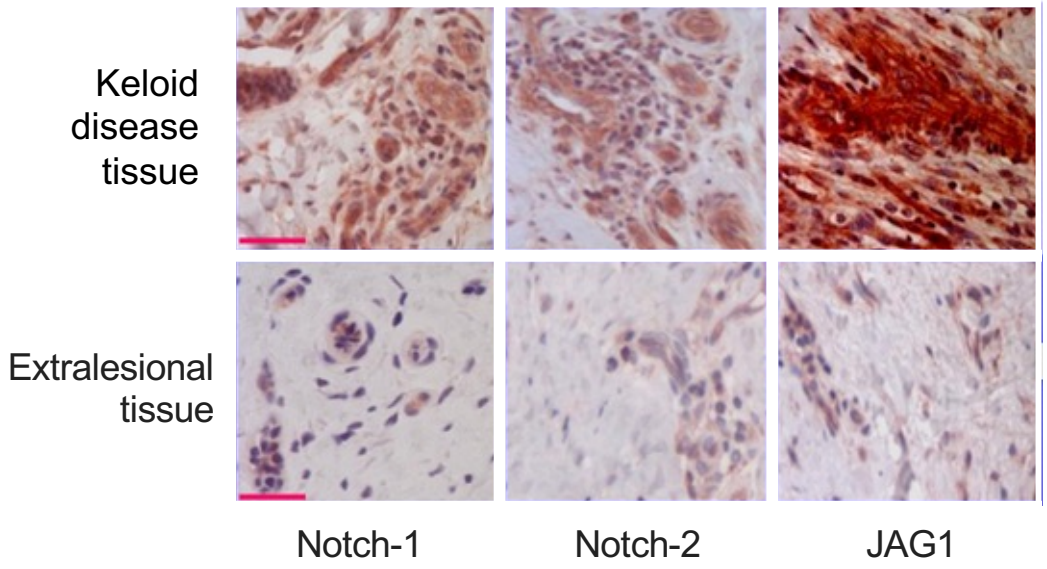
- How long is needed to ensure durable disease control after response?
- Do you need active disease to get response?
- Responses after drug interruption?
- Mechanisms of response/resistance?

Long-term impact of ovarian disruption?

- Considerations in younger patients?
- Treatment for patients who want to become pregnant?

Future Directions: What's on the Horizon for Desmoid Tumors?

- Is there a role to explore nirogacestat in other processes depending on Notch signaling?
  - Patients with intractable keloids?



1. Syed F and Bayat A. Wound Repair Regen. 2012;20:688-706.

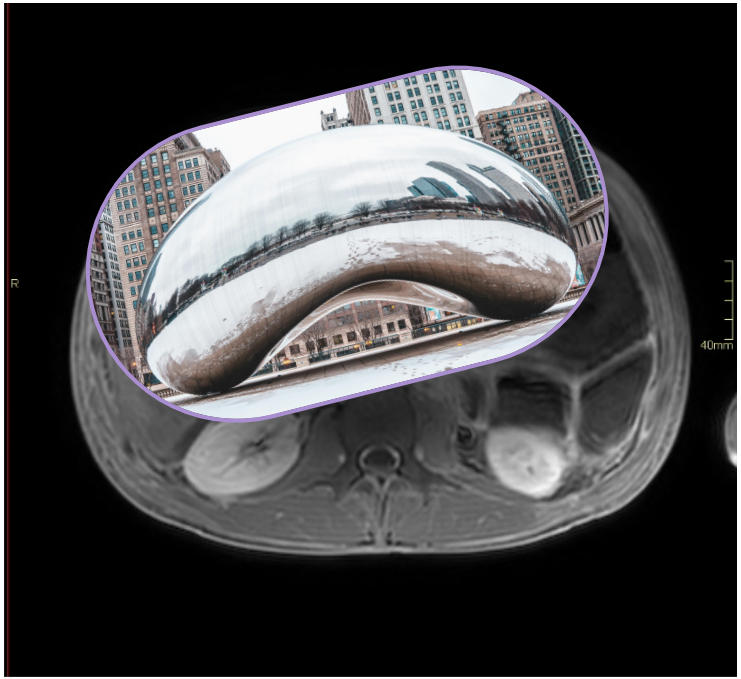
Patient Cases and Panel Discussion

Case 1: Male Patient With Familial Adenomatous Polyposis (FAP)–Related Desmoid Fibromatosis

- Male patient working in the central pharmacy of our university hospital, involved in distribution of medication in house
- Diagnosis of FAP at the age of 17 years
- Total colectomy 6 years later
- Diagnosis of desmoid fibromatosis at the age of 28 years
- APC exon 13 mutation (c.1660 C>T, p.R554X) in patient and other family members

Discussion

- What would be your next steps for this patient?
- How do you approach surveillance?
- When would you consider medical intervention? How would FAP influence your decision?



21-9-2019 *T1 fat suppression*

T1-weighted images after intravenous contrast administration.
MRI images courtesy of Dr. Maarten Steyvers, University Hospitals Leuven.

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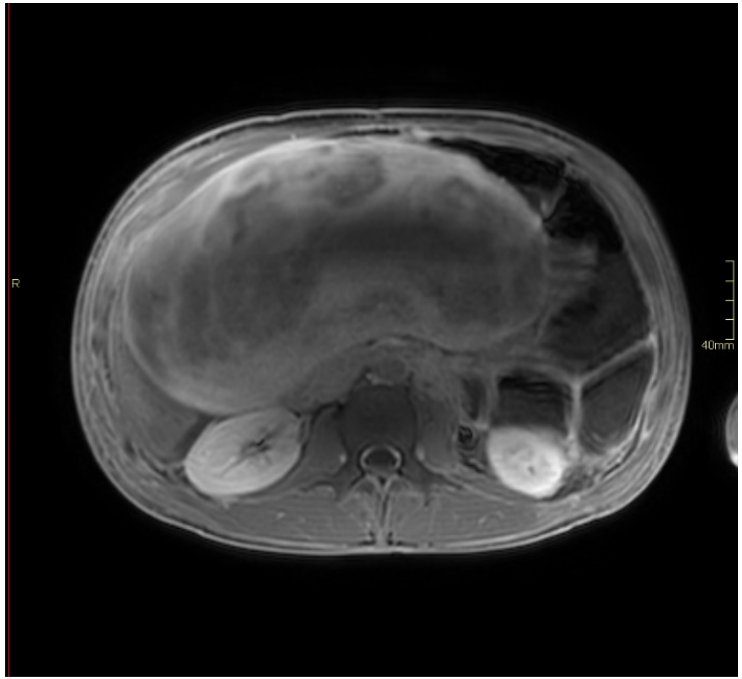

21-9-2019 *T1 fat suppression*

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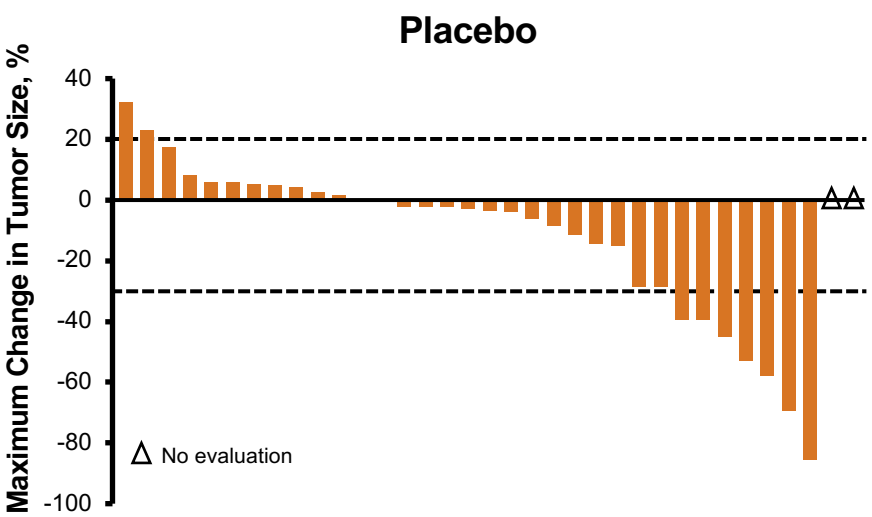
MRI images courtesy of Dr. Maarten Steyvers, University Hospitals Leuven.

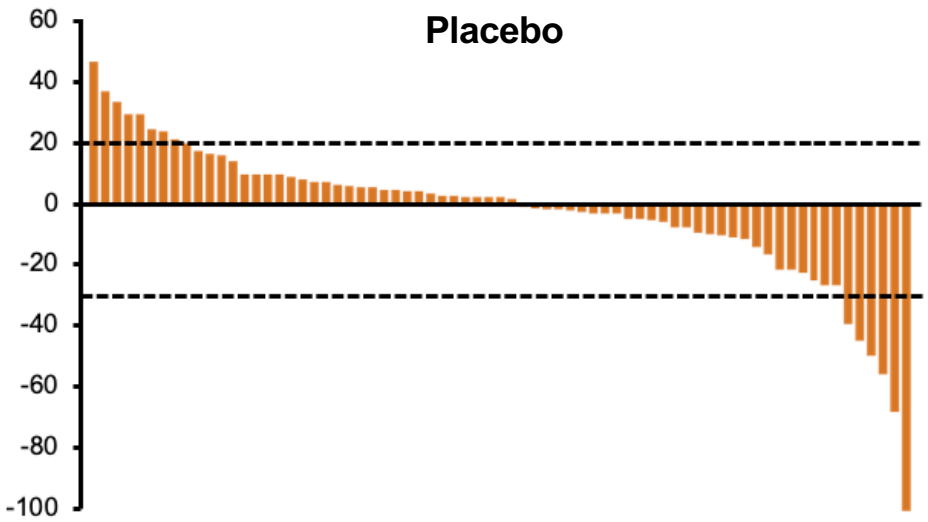
Spontaneous Regression of Desmoid Tumors[1,2]

Sorafenib vs Placebo
Overall Response Rate 18%



- Unresectable or with unacceptable surgical morbidity: 76%
- Progression ≥10% in previous 6 months: 43%
- Symptomatic disease with Brief Pain Inventory ≥3

Nirogacestat vs Placebo
Overall Response Rate 8%



- Patients with RECIST progressive disease in prior 12 months

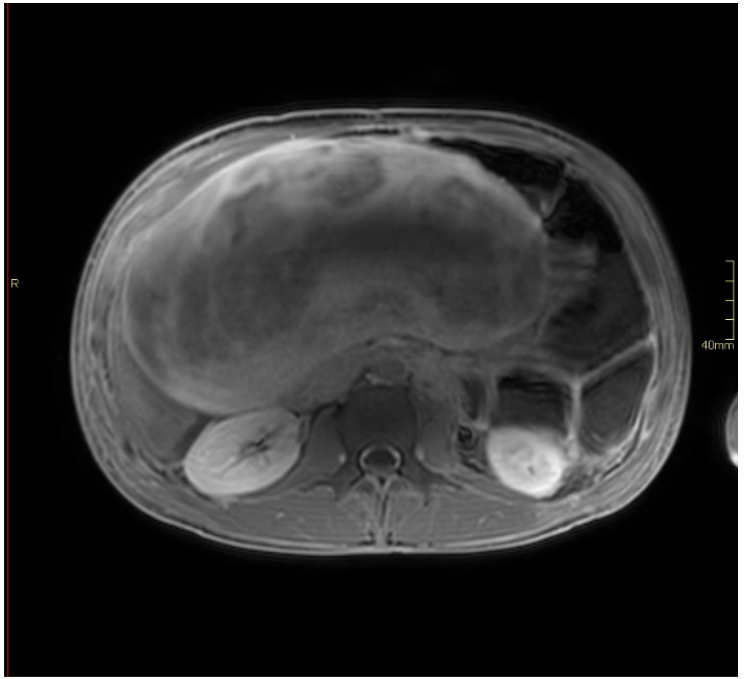
1. Kasper B et al. ESMO 2022. Abstract LBA2. 2. Gounder MM et al. *N Engl J Med*. 2018;379:2417-2428.

Case 1 Continued: Male Patient With FAP-Related Desmoid Fibromatosis

- The patient undergoes active surveillance, but experiences small bowel obstruction due to adhesions and progressive desmoid tumor
- Initiated on 150 mg nirogacestat twice daily
- One month later he experiences skin toxicity, diarrhea, and apthous stomatitis

Discussion

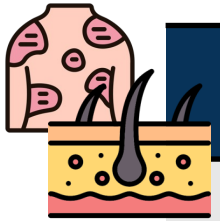
- How would you proceed?
- How would you address the skin toxicity? gastrointestinal symptoms?
- Is dose-reducing an option? If so, how do you determine dosing?



21-9-2019 *T1 fat suppression*

T1-weighted images after intravenous contrast administration.
MRI images courtesy of Dr. Maarten Steyvers, University Hospitals Leuven.

Recommendations for Managing Skin Rash and Gastrointestinal Toxicity Associated With Gamma-Secretase Inhibitor Therapy[1]



Managing Skin Rash and Hidradenitis Suppurativa

Gamma-secretase mutations directly implicated in pathogenesis of hidradenitis suppurativa

- Refer to dermatology
- Clindamycin, doxycycline, minocycline, cefadroxil, clindamycin, and/or surgical procedure
- **Hold** drug and consider **dose** reduction based on toxicity grade

Managing Gastrointestinal Toxicity

Gamma-secretase mutations directly implicated in pathogenesis by increasing intestinal goblet cells

- Try antidiarrheals (loperamide and diphenoxylate/atropine)
- Check serum phosphorus and replete if low
- **Hold** drug and **dose** reduce depending on severity of symptoms

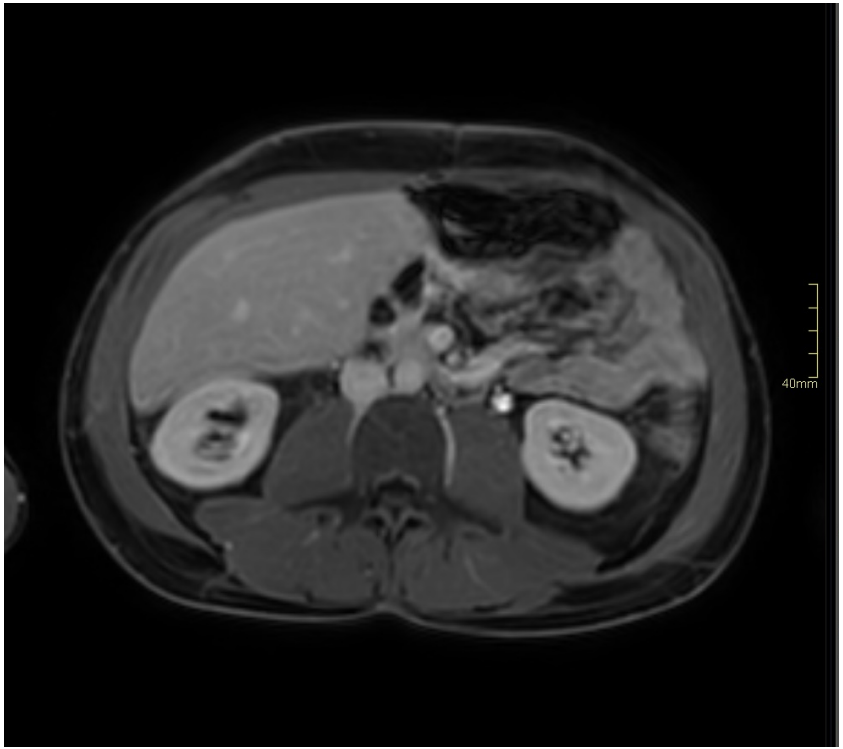
Download the Practice Aid

1. Ali Alikhan. *JAMA Dermatol*. 2016;152:736.

PeerView

Case 1 Continued: Male Patient With FAP-Related Desmoid Fibromatosis

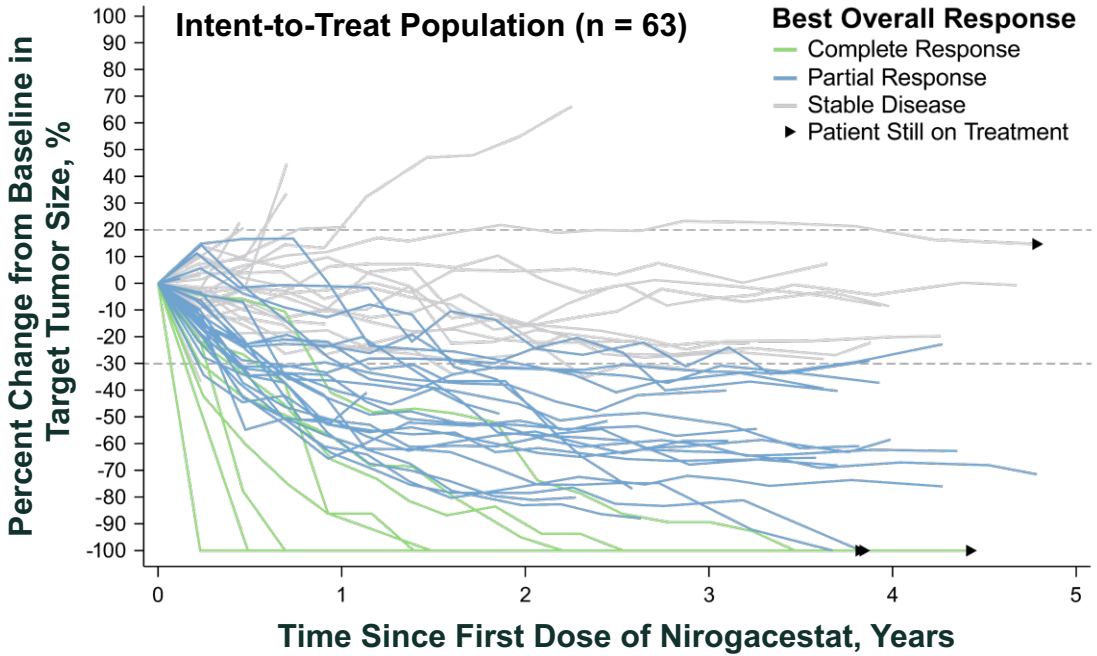
- Nirogacestat is reduced to 100 mg twice daily, and two months later has stable disease
- After 6 months, the patient achieves partial response (RECIST)
- 3 years later, dose is reduced to 50 mg twice daily due to fatigue and diarrhea
- Patient is continuing nirogacestat at the reduced dose and achieved a complete response



21-1-2025 *T1 fat suppression + gadolinium*

T1-weighted images after intravenous contrast administration.
MRI images courtesy of Dr. Maarten Steyvers, University Hospitals Leuven.

Longer-Term Nirogacestat Is Associated With Durable Tumor Size Reductions and Evidence of Deepening Responses[1]

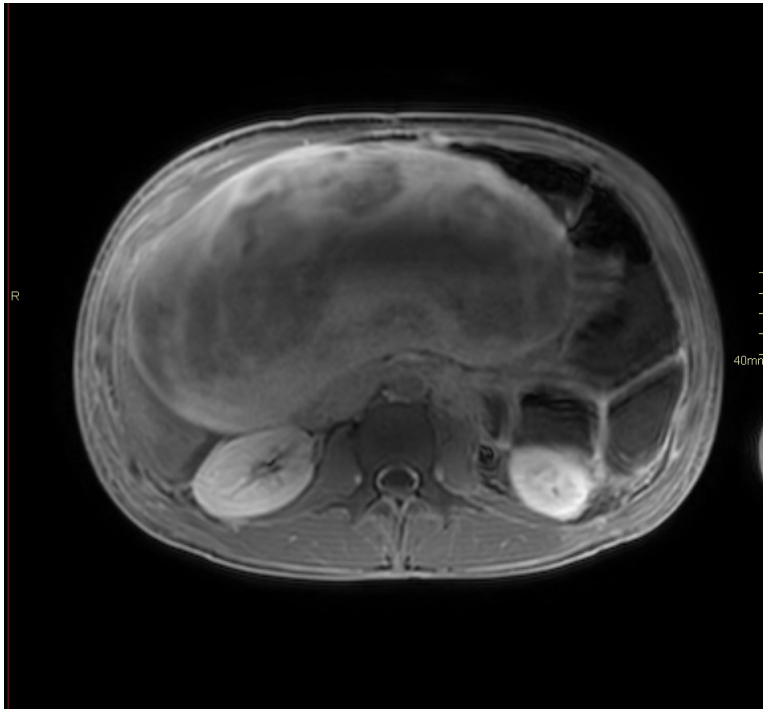


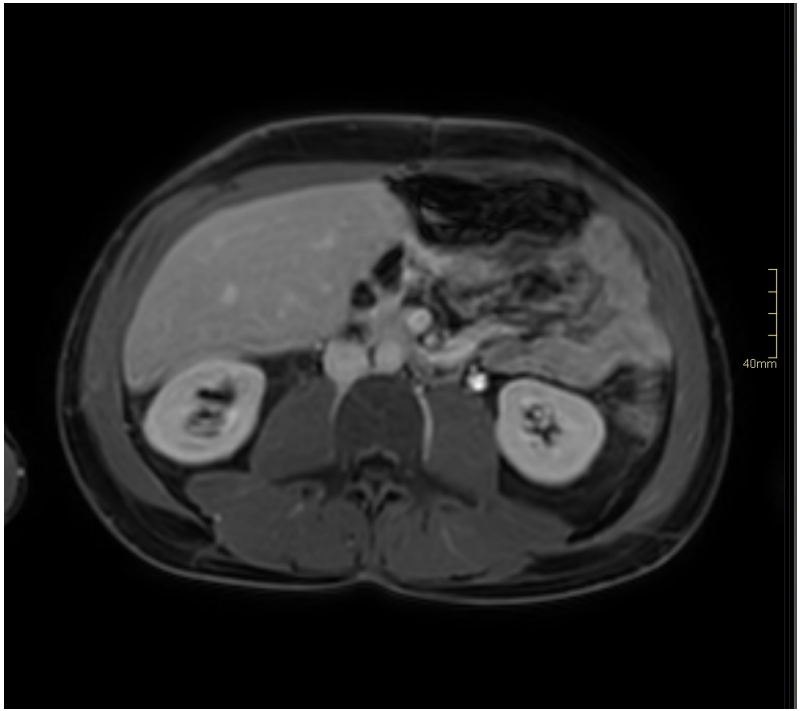
Median best % change from baseline target tumor size per RECIST v1.1 improved at each annual milestone

	Median % (min, max)
At least 1 year of treatment (n = 46)	-32.3 (-100, 6)
At least 2 years of treatment (n = 40)	-42.5 (-100, 2)
At least 3 years of treatment (n = 33)	-51.3 (-100, 2)
At least 4 years of treatment (n = 15)	-75.8 (-100, 2)

1. Ratan R et al. CTOS 2024. Paper 103.

Case 1 Conclusion: Before and After Treatment With Nirogacestat





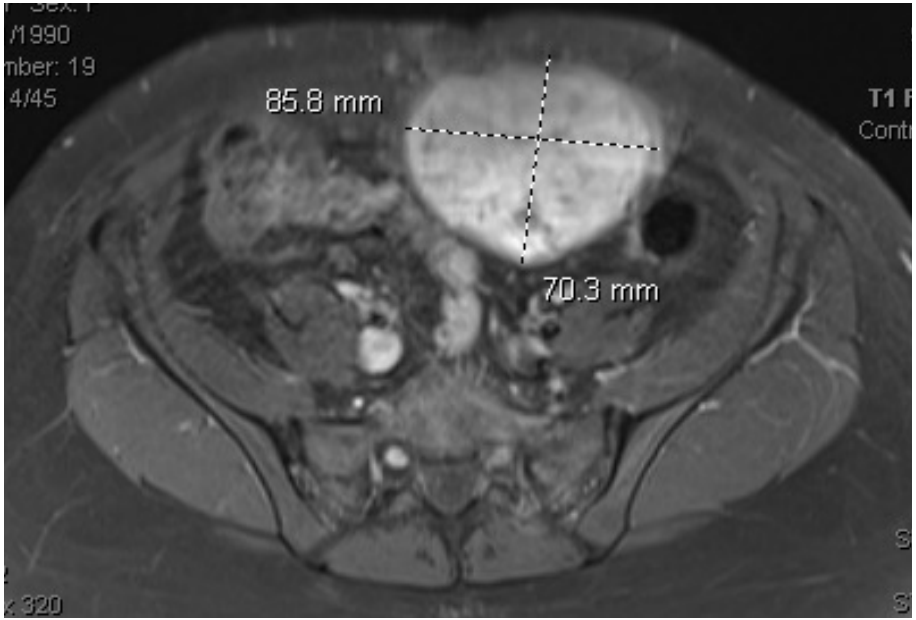
21-9-2019 *T1 fat suppression*

21-1-2025 *T1 fat suppression + gadolinium*

This case is treated by Patrick Schöffski.
T1-weighted images after intravenous contrast administration
MRI images courtesy of Dr. Maarten Steyvers, University Hospitals Leuven.

Case 2: 34-Year-Old Woman With a Large, Aggressive Tumor

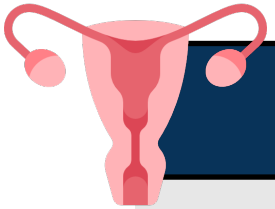
- 34 yo Hispanic female who is status post three pregnancies in 2018, 2020, and then emergent Caesarian section 2021
- Summer 2024, began noticing left lower quadrant pain with growth of palpable mass
- Biopsy-confirmed desmoid fibromatosis, CTNNB1 T41A mutation
- Presents to sarcoma clinic 11/2024 for treatment recommendations
- Multidisciplinary discussion advised against surgical resection despite abdominal wall location
- She is interested in treatment with nirogacestat but also plans for one more pregnancy



Baseline MRI pelvis w/wo contrast

Reproductive Considerations: Primary Ovarian Insufficiency[1]

Download the Practice Aid



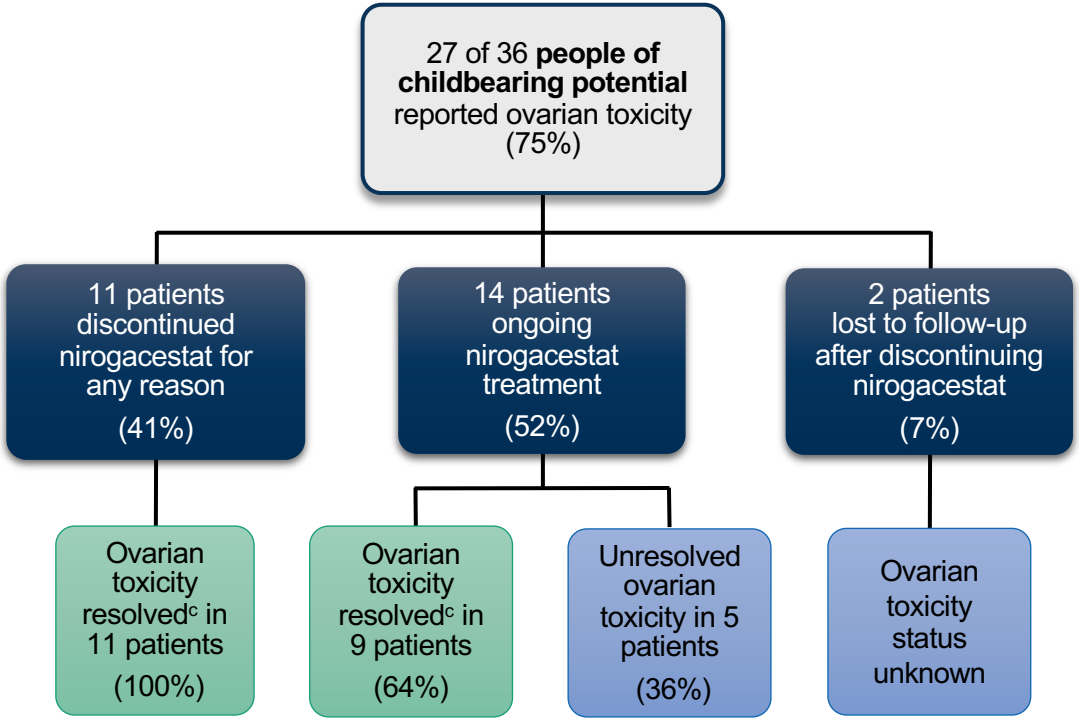
Ovarian Toxicity (75%) Observed With Nirogacestat

- Changes in female reproductive hormone levels (anti-Mullerian hormone, follicle-stimulating hormone, luteinizing hormone, estradiol) and clinical manifestations (drug-related amenorrhea)
- Majority of patients (78%) had resolution of symptoms and hormonal levels after drug cessation or even while on drug
- Discuss fertility preservation in patients of childbearing potential

1. Loggers ET et al. *Cancer*. 2024;130:2812-2821.

Frequency and Resolution of Ovarian Toxicity Observed With Nirogacestat[1]

- Ovarian toxicity is a composite adverse event associated with changes in female reproductive hormone levels and clinical manifestations[2,3]
- Protocol-mandated serum hormone collection at baseline and cycles 1, 2, 4, and every 3 thereafter
- Among patients of childbearing potential, ovarian toxicity[a] was observed in 75% receiving nirogacestat and 0% receiving placebo[b]
  - Median time to first onset of ovarian dysfunction: 8.9 wk
  - Median duration of ovarian dysfunction events: 21.3 wk



[a] Ovarian dysfunction among patients of childbearing potential was defined by investigators who reported the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms of amenorrhea, premature menopause, menopause, and ovarian failure.
[b] As of July 20, 2022.[c] Resolution of ovarian dysfunction events was defined by the investigator.

1. Kasper B et al. ESMO 2022. Abstract LBA2. 2. Thurston RC, Joffe H. *Obstet Gynecol Clin North Am*. 2011;38:489-501.
3. Mauri D et al. *Front Endocrinol (Lausanne)*. 2020;11:572388.

Case 2 Discussion: Considerations for Females of Reproductive Potential

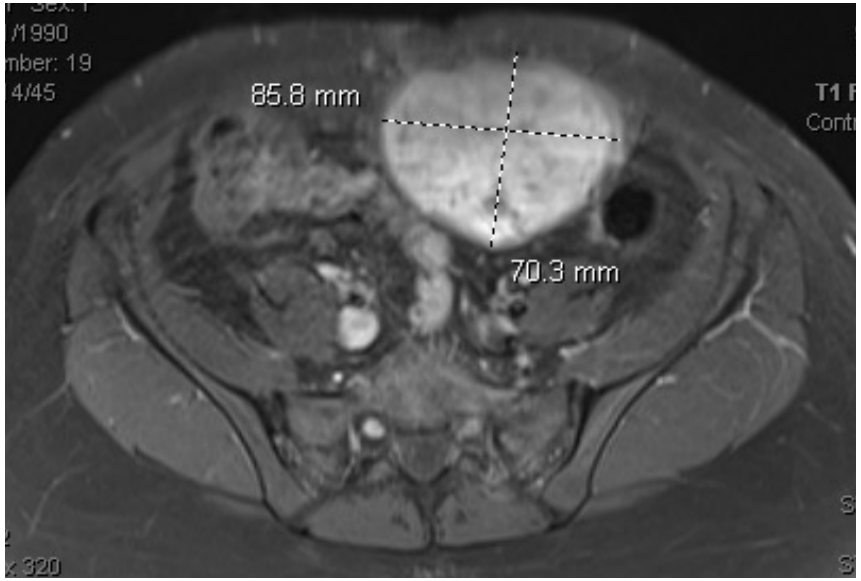
Discussion

- How would you approach counseling for a patient worried about primary ovarian insufficiency?
- How long would you have the patient on nirogacestat? Is it safe to discontinue?
- Is it safe to become pregnant? What if the patient wanted to become pregnant before initiating the drug?

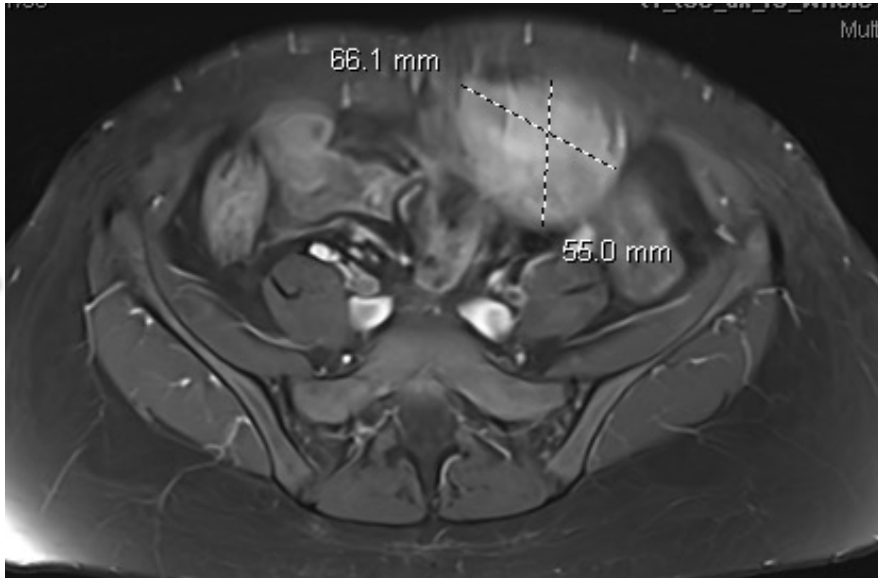
Unanswered Questions

- Role of fertility preservation prior to treatment?
- How long for effects to resolve after treatment before safe to attempt pregnancy?
- Differences in return of normal ovarian function depending on age (ie age 30 vs age 40 approaching perimenopause)
- Push for continued data collection to advise patients

Case 2 Conclusion: Patient Response Following Three Months of Treatment



Baseline MRI pelvis w/wo contrast



March 2025: 3 months on treatment

- Early promising response after only 3 months of treatment; loss of menses after first month on treatment, noting hot flashes/mood swings
- She's hoping to be off treatment within one year due to these symptoms!

Summary and Take-Home Messages

- As desmoid tumors are a rare disease, work with sarcoma centers to integrate a multidisciplinary plan
- Active surveillance is a reasonable approach in a subset of patients
- Discuss surgery in a multidisciplinary team
- Chemotherapy, tyrosine kinase inhibitors, and gamma-secretase inhibitors are therapeutic options in the first-line or subsequent lines of therapy
  - Nirogacestat is currently the only FDA-approved treatment for desmoid tumors

Abbreviations

- CI: confidence interval
- CK1: casein kinase 1
- CR: complete response
- CT: computed tomography
- DVL: dishevelled
- FAP: familial adenomatous polyposis
- FDA: Food and Drug Administration
- Frz: frizzled receptors
- GI: gastrointestinal
- HES1: hes family BHLH transcription factor 1
- ITT: intent-to-treat
- MRI: magnetic resonance imaging
- NE: not evaluable
- NICD: Notch intracellular domain
- OR: overall response
- ORR: overall response rate
- RECIST: Response Evaluation Criteria in Solid Tumors
- T2W: T2-weighted
- TCF: T-cell factor
- Tcf4: T-cell factor 4
- TEAE: treatment-emergent adverse event
- Ub: ubiquitin