Effect of Dose Reduction on the Safety and Efficacy of Nirogacestat in Patients With Desmoid Tumors: Post Hoc Analyses of the DeFi Trial

#3741P

Bernd Kasper,[1] Bruno Vincenzi,[2] Gregory M Cote,[3] Gina D'Amato,[4] Noah Federman,[5] Lee Hartner,[6] Peter Reichardt,[7] Silvia Stacchiotti,[8] Chetna Bhattacharyya,[9]* Yucheng Chu,[10] Rachel Cohen,[9]* Melissa O'Gorman,[9] Ravin Ratan[11]

[1]University of Heidelberg; Mannheim University Medical Center, Mannheim, Germany; [2]Policlinico Universitario Campus Bio-Medico and University Campus Bio-Medico, Rome, Italy; [3]Mass General Brigham Cancer Institute, Boston, MA, USA; [4]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [5]David Geffen School of Medicine, University of California, Los Angeles; [6]University of Pennsylvania, Abramson Cancer Center, Pennsylvania Hospital, Philadelphia, PA, USA; [7]Helios Klinikum Berlin-Buch, Berlin, Germany; [8]Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [9]SpringWorks Therapeutics, a healthcare company of Merck KGaA, Darmstadt, Germany; [10]Sumptuous Data Sciences, Monmouth Junction, NJ; [11]University of Texas, MD Anderson Cancer Center, Department of Sarcoma Medical Oncology, Division of Cancer Medicine, Houston, TX, USA

*At the time of analysis

GET POSTER PDF

Copies of this poster and supplemental information obtained through QR codes are for personal use only and may not be reproduced without written permission of the authors.

CONCLUSIONS

- **In this post hoc analysis of the phase 3 DeFi trial of nirogacestat in patients with progressing desmoid tumors (DTs), dose reduction from 150 mg twice daily (BID) to 100 mg BID due to treatment-emergent adverse events (TEAEs) was associated with improved tolerability without apparent loss of clinical benefit, and patient-reported outcome (PRO) benefits appeared to be maintained**
- **These findings support dose reduction as a strategy to manage TEAEs and facilitate continued nirogacestat treatment in patients with progressing DT**
- **Active TEAE management with early and proactive dose modification when indicated, can help tailor treatment based on individual tolerability, supporting long-term treatment goals while maintaining clinical benefit**

PLAIN LANGUAGE SUMMARY

- **Nirogacestat is a recommended and approved treatment for adults who have progressing DT and require systemic treatment**
- **In the phase 3 DeFi clinical trial, patients experienced a decrease in the size of their tumor and improved their symptoms with 150 mg of nirogacestat twice daily; however, because of side effects, some patients needed to lower their dose to 100 mg twice daily to continue treatment**
- **This study shows that patients on the 150 mg twice daily starting dose with higher than expected concentrations of nirogacestat in their blood were more likely to require dose changes due to side effects. At the reduced dose, patients had fewer side effects while still experiencing a decrease in tumor size and improved symptoms**
- **Clinicians should monitor and manage side effects early, including reducing the dose when needed. This can help tailor treatment to each patient's needs, allowing them to stay on treatment and maintain the benefits of treatment**

INTRODUCTION

- DT are rare, locally aggressive, and invasive soft-tissue tumors associated with debilitating symptom burden[1,2]
- Nirogacestat, an oral, targeted gamma secretase inhibitor, is the only treatment approved by the US Food and Drug Administration, European Commission, and certain other major global health agencies for adults with progressing DT who require systemic treatment[3-5]
  - The indicated dosage of nirogacestat is 150 mg BID
  - Nirogacestat is a Category 1 preferred systemic treatment by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and primary treatment option by the Desmoid Tumor Working Group for the active treatment of DT[6,7]
- In the global, multicenter, double-blind (DB) phase 3 DeFi trial (NCT03785964) of nirogacestat in adults with progressing DT, nirogacestat 150 mg BID significantly improved tumor response and PRO versus placebo[8]
- In DeFi, dose reductions to 100 mg BID nirogacestat were implemented in some patients to manage TEAEs and allow continued treatment

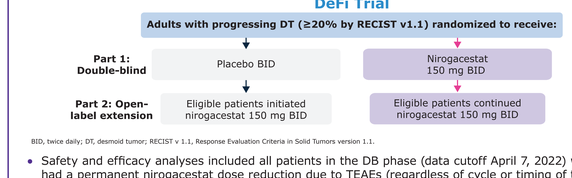
OBJECTIVE

- This post hoc analysis of DeFi evaluated the safety, efficacy, and pharmacokinetics (PK) of nirogacestat in patients who modified their dose, including dose reductions from 150 mg BID to 100 mg BID, compared to patients who did not modify their dose

METHODS

- In DeFi, patients were randomized 1:1 to nirogacestat 150 mg BID (N=70) or placebo (N=72) in 28-day cycles; upon trial completion, eligible patients could continue to an optional open-label extension (OLE) phase (**Figure 1**); full DeFi trial details are previously reported in Gounder et al.[8]
- Nirogacestat dose reduction to 100 mg BID was permitted for AE management of grade ≥3 diarrhea, nausea, vomiting, skin toxicities, hypophosphatemia, and hematologic or nonhematologic toxic effects, in collaboration with the medical monitor, and was required in cases of significant toxicity
  - For grade ≥2 ovarian toxicity, dose reduction to 100 mg BID was optional
  - After dose reduction, the DeFi protocol did not allow for dose increases back to 150 mg BID

Figure 1. Study design



BID, twice daily; DT, desmoid tumor; RECIST v 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

- Safety and efficacy analyses included all patients in the DB phase (data cutoff April 7, 2022) who had a permanent nirogacestat dose reduction due to TEAEs (regardless of cycle or timing of the reduction) and patients who did not dose reduce
- The percentage of patients with objective response (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) was determined with a 95% CI using the exact method based on binomial distribution
- Safety and efficacy analyses were descriptive except for PRO analysis, which was assessed using mixed model repeated measure in nirogacestat-treated patients with and without dose reduction versus placebo
- Separate safety/efficacy analyses for patient groups with dose reduction versus without were supported by PK analysis results showing higher nirogacestat exposure in those requiring dose modification
- PK analyses included patients in the DB and OLE phases (data cutoff October 17, 2024) who had a dose modification (dose reduction or dose hold), compared to patients who did not modify dose
  - Minimum plasma concentration (C_{min}), maximum plasma concentration (C_{max}), and area under the concentration-time curve over the dosing interval (AUC_{tau}) were estimated using empirical Bayes estimates derived from the final population pharmacokinetic (PopPK) model
  - Logistic regression was used to assess the statistical significance between dose modification versus exposure for C_{min}, AUC_{tau}, and C_{max}
  - Associations between patient characteristics and nirogacestat exposure levels were assessed using covariate effect analyses based on the PopPK model

RESULTS

Demographics

- Of 142 total patients in the DB phase of DeFi, 69 patients received ≥1 dose of nirogacestat (safety population); among these, 29 (42%) patients permanently reduced their nirogacestat dose from 150 to 100 mg BID due to TEAEs
- Of 69 nirogacestat-treated patients, patient demographics and disease characteristics were generally similar between patients who dose reduced and patients who did not dose reduce (**Supplemental Table 1**, via the QR code)
  - Dose reductions were more frequent in patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1 or 2 (53%; 10/19) than with ECOG PS of 0 (38%; 19/50)

Safety

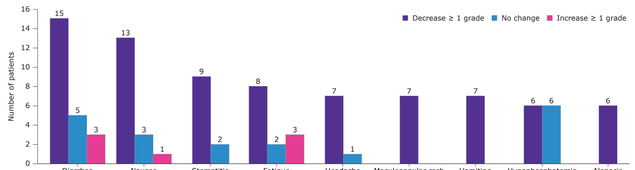
- The median duration of nirogacestat exposure was similar between patients who reduced their dose compared to those who did not reduce (21.03 vs 20.17 months)
- TEAEs leading to dose reduction were reported in 42% (29/69) of patients
  - The most common TEAEs resulting in dose reduction were diarrhea (9%; 6/69), ovarian toxicity (6%; 2 of 36 females of reproductive potential), stomatitis (4%; 3/69), maculopapular rash (4%; 3/69), hypophosphatemia (4%; 3/69), folliculitis (3%; 2/69), and hidradenitis (3%; 2/69)
- The median time on nirogacestat before reducing the dose was 3 completed cycles (range: <1 to 24 cycles)
- In general, the number of patients experiencing the most common TEAEs decreased after dose reduction (**Table 1**)
  - Ovarian toxicity was a notable exception, where the number of patients reporting ovarian toxicity events before dose reduction was similar to after dose reduction
- Most patients reported a reduction in severity by ≥1 grade for the most common TEAEs occurring in >20% of patients (**Figure 2**)
- The rate of nirogacestat treatment discontinuation due to TEAEs was lower in patients who reduced their dose compared with those who did not (17% vs 28%)
- Of the 29 patients who reduced their nirogacestat dose due to a TEAE, only 2 (7%) patients later discontinued due to that same TEAE (hypophosphatemia and diarrhea)

Table 1. Most common TEAEs occurring in >20% of patients before or after dose reduction

	Before dose reduction (n=29)		After dose reduction (n=29)	
	Patients, n (%)	Number of events	Patients, n (%)	Number of events
Diarrhea	23 (79)	50	14 (48)	30
Nausea	17 (59)	24	8 (28)	12
Ovarian toxicity[a]	9 (53[b])	12	7 (41[b])	11
Fatigue	13 (45)	17	7 (24)	14
Hypophosphatemia	12 (41)	17	8 (28)	18
Stomatitis	11 (38)	21	5 (17)	13
Headache	8 (28)	10	1 (3)	3
Maculopapular rash	7 (24)	13	5 (17)	9
Vomiting	7 (24)	10	2 (7)	4
Alopecia	6 (21)	7	4 (14)	6
Weight increased	2 (7)	2	6 (21)	11
COVID-19	0	0	6 (21)	6

[a]Ovarian toxicity was identified by investigators in females of reproductive potential based on abnormal reproductive hormone values or perimenopausal symptoms or both. The verbatim terms for ovarian toxicity events were coded to the MedDRA preferred terms of ovarian failure, premature menopause, amenorrhea, and oligomenorrhea.
[b]Incidence calculated in females of reproductive potential in the dose reduced subgroup of safety population (N=17).
TEAEs, treatment-emergent adverse events.

Figure 2. Relative shift in grade from before to after dose reduction of selected common TEAEs occurring in >20% of patients



Note: Common TEAEs occurring in >20% of patients also included ovarian toxicity, COVID-19, and weight increase, but were not included in this analysis due to lack of established grading criteria per CTCAE v5.0 (ovarian toxicity and COVID-19) and irrelevance (weight increased).
CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Efficacy

- The Kaplan-Meier median progression-free survival was not reached in either patients with or without dose reduction
- The likelihood of being event-free at 1 year was numerically higher with dose reduction (92.3% [95% CI, 72.6 to 98.0]) than without (78.5% [95% CI, 59.9 to 89.2])
  - The likelihood of being event-free at 2 years was similar between patients with a dose reduction (74.7% [95% CI, 45.8 to 89.7]) and those without (78.5% [95% CI, 59.9 to 89.2])
- Objective response rate was numerically higher in patients who dose reduced compared to those who did not (48% vs 38%; **Table 2**)
- Median (range) time to objective response was similar in patients who dose reduced and those who did not, with 5.55 (2.6, 13.8) and 6.01 (2.8, 19.4) months, respectively

Patient-reported outcomes

- Both patients with and without dose reduction had significant improvements in PRO assessments with nirogacestat compared to placebo at cycle 10 ($P<.01$, for all except EORTC QLQ-C30 global health status/quality of life with $P<.05$; **Figure 3**)
- There were no significant differences overall through cycle 24 in PRO improvement or time to PRO improvement when comparing nirogacestat-treated patients with and without a dose reduction (**Figure 3**)

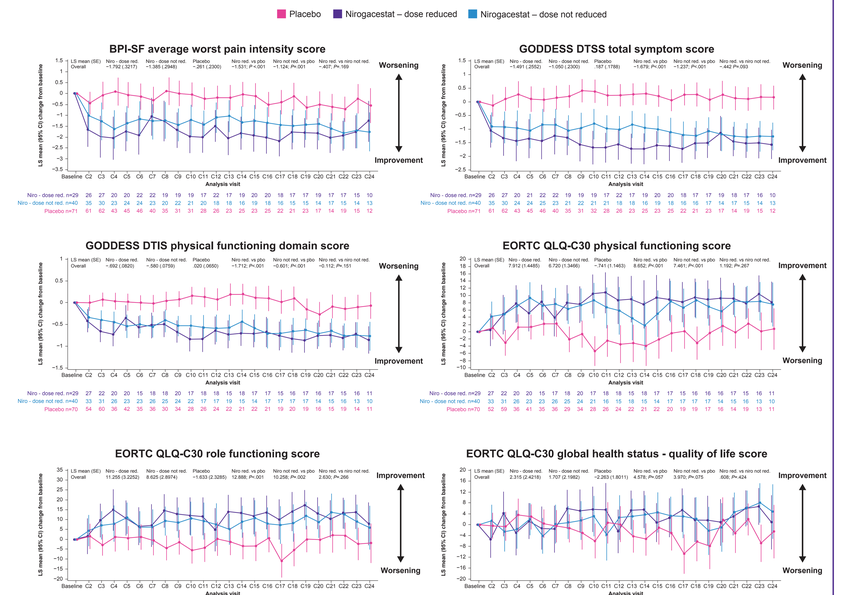
Pharmacokinetics

- Higher nirogacestat exposure, as seen with C_{min} and AUC_{tau}, was a statistically significant predictor of patients requiring a dose modification in the DB or OLE phase of DeFi ($P<.05$)
- Patients with dose modification had higher initial nirogacestat C_{min} and AUC_{tau} before modifying compared to those without dose modification (**Figure 4**)
  - After dose modification, nirogacestat C_{min} and AUC_{tau} values tended to decrease to levels similar to those observed in patients who did not modify dose
- Age, sex, race, and concomitant medications were not associated with any clinically meaningful differences in nirogacestat exposure

Table 2. Objective response rate and best overall response by dose reduction status

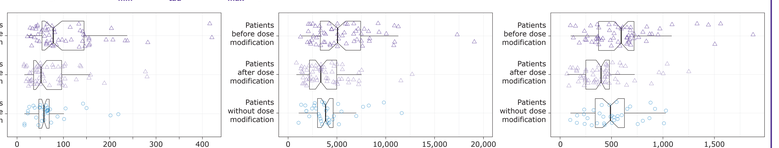
	Dose reduced (n=29)	Dose not reduced (n=40)
Objective response rate; n (%)	14 (48)	15 (38)
95% CI	29, 68	23, 54
Two-sided *P*-value	0.369	
Best overall response – confirmed; n (%)		
Complete response	3 (10)	2 (5)
Partial response	11 (38)	13 (33)
Stable disease	14 (48)	21 (53)
Progressive disease	0	1 (3)
Not evaluable	1 (3)	3 (8)
Time to objective response; median (range), months	5.55 (2.6, 13.8)	6.01 (2.8, 19.4)

Figure 3. Patient-reported outcomes by dose reduction status



Only patients with a baseline score and ≥1 post baseline score were included in the analysis. Scheduled visits with <10 patients in either group or unscheduled visits were not included.
Mean (+SD) scores at baseline were as follows: BPI-SF average worst pain intensity score, 3.5±3.0 in the nirogacestat dose not reduced group and 2.9±3.5 in the nirogacestat dose reduced group; GODDESS DTSS total symptom score, 3.3±2.0 and 3.4±2.6, respectively; GODDESS DTIS physical functioning domain score, 2.8±1.0 and 2.7±1.2, respectively; EORTC QLQ-C30 physical functioning score, 77.7±21.3 and 77.3±23.4, respectively; EORTC QLQ-C30 role functioning score, 65.5±30.8 and 65.0±34.1, respectively; and EORTC QLQ-C30 global health status–quality of life score, 62.4±24.9 and 58.3±24.5, respectively.
BPI-SF, Brief Pain Inventory–Short Form; C, cycle; DTSS, Desmoid Tumor Symptom Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, global health status; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; LS, least squares; niro, nirogacestat; pbo, placebo; red, reduced.

Figure 4. Nirogacestat C_{min}, AUC_{tau}, and C_{max} by dose modification status



Boxes indicate interquartile range; dark line represents median.

REFERENCES

1. Bektas M, et al. *Adv Ther*. 2023;40(9):3697-3722.
2. Kasper B, et al. *Oncologist*. 2017;22(7):755-763.
3. FDA. FDA approves nirogacestat for desmoid tumors. 2023. Accessed July 2, 2026. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nirogacestat-desmoid-tumors
4. European Commission. Union Register of medicinal products for human use - Ogsiveo. 2025. Accessed July 2, 2026. https://ec.europa.eu/health/documents/community-register/html/h1932.htm
5. Medicines and Healthcare Products Regulatory Agency. Nirogacestat hydrobromide approved to treat desmoid tumours. 2025. Accessed July 2, 2026. https://www.gov.uk/government/news/nirogacestat-hydrobromide-approved-to-treat-desmoid-tumours
6. NCCN Clinical Practice Guidelines in Oncology. Soft Tissue Sarcoma. Version 1.2026. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
7. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.1.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed September 9, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
8. Gounder M, et al. *N Engl J Med*. 2023;388(10):898-912.

DISCLOSURES

BK has acted in a consulting or advisory role for Ayala Pharmaceuticals, Bayer, GlaxoSmithKline, SpringWorks Therapeutics, and Boehringer Ingelheim; received honoraria from Bayer, GlaxoSmithKline, Pharmamar-zeltia; and received research funding from Ayala Pharmaceuticals, Cogent Medicine, Pharmamar, SpringWorks Therapeutics, and Immunome. **BV** has acted in a consulting or advisory role for Abbott, GlaxoSmithKline, and Lilly; served on a speakers bureau for PharmaMar; and received research funding from Bayer, Eisai, Immunomedics, Merck Sharp & Dohme, Novartis, PharmaMar, Servier, and SpringWorks Therapeutics. **GC** has acted in a consulting or advisory role for Bayer, Deciphera, Epizyme, Jazz Pharmaceuticals, Merck Sharp & Dohme, Novartis, Pfizer, Sarcoma Alliance for Research through Collaboration Foundation, Life Raft Group, and The ENE Foundation; has received honoraria from Gilead Therapeutics and BioMed; and has received institutional research funding from PharmaMar, MacroGenics, Merck KGaA/EMD Serono Research and Development Institute, Jazz Pharmaceuticals, Immunomedics, Pfizer, Plexxikon, Daiichi Sankyo, Epizyme, SpringWorks Therapeutics, and Deciphera. **GD** has acted in a consulting or advisory role for Bayer and SpringWorks Therapeutics; served on a speakers bureau for Bayer, Fennec Pharma, and SpringWorks Therapeutics; and received research funding from the California Institute for Regenerative Medicine and the National Institute for Health/National Center for Advancing Translational Sciences. **LH** has nothing to disclose. **PR** has received honoraria from Deciphera, PharmaMar, Boehringer Ingelheim, Thermosome, Kabi, Merck, Cogent, and Immunome; **SS** has acted in a consulting or advisory role for Bayer, Boehringer, Deciphera, Daiichi Sankyo, Gentili, Glaxo Smith Kline, Ibsena, Ipsen, Merck, Nerviano, NKC Organnanalysis AS, Orion, Pandelis, Pierrecare, Pierrewave, Pharma Essentia, Sarcoma Patients EuroNet, Sanofi, Seagen, Servier, Springworks, Tesaro, Zanofi, and Zeno; has received honoraria from Bayer, Boehringer, Deciphera, Daiichi Sankyo, Merck Serono, Merck Sharp & Dohme LLC, Novartis, PharmaMar, Servier, and SpringWorks Therapeutics; **CB, YC, RC, and MOG** declare former or current employment and stock ownership for Springworks Therapeutics; **RR** has acted in a consulting or advisory role for Inhibrx and SpringWorks Therapeutics; has received honoraria from touchIME and Peerview; has received research funding from SpringWorks Therapeutics, Ayala Pharmaceuticals, and CA Therapeutics; and declares employment and stock ownership with Johnson & Johnson/Janssen and Medtronic.

ACKNOWLEDGMENTS

This trial was funded by SpringWorks Therapeutics, a healthcare company of Merck (ROR ID: https://ror.org/04vpcfb52). Medical writing support was provided by Alana Chin, PhD, from Citrus Health Group, Inc (Chicago, IL, USA), and was funded by SpringWorks Therapeutics, a healthcare company of Merck.

Presented at the 2026 European Society for Medical Oncology (ESMO) Congress | October 23–27, 2026 | Madrid, Spain

Effect of Dose Reduction on the Safety and Efficacy of Nirogacestat in Patients With Desmoid Tumors: Post Hoc Analyses of the DeFi Trial

#3741P

Bernd Kasper,[1] Bruno Vincenzi,[2] Gregory M Cote,[3] Gina D'Amato,[4] Noah Federman,[5] Lee Hartner,[6] Peter Reichardt,[7] Silvia Stacchiotti,[8] Chetna Bhattacharyya,[9]* Yucheng Chu,[10] Rachel Cohen,[9]* Melissa O'Gorman,[9] Ravin Ratan[11]

[1]University of Heidelberg; Mannheim University Medical Center, Mannheim, Germany; [2]Policlinico Universitario Campus Bio-Medico and University Campus Bio-Medico, Rome, Italy; [3]Mass General Brigham Cancer Institute, Boston, MA, USA; [4]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [5]David Geffen School of Medicine, University of California, Los Angeles; [6]University of Pennsylvania, Abramson Cancer Center, Pennsylvania Hospital, Philadelphia, PA, USA; [7]Helios Klinikum Berlin-Buch, Berlin, Germany; [8]Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [9]SpringWorks Therapeutics, a healthcare company of Merck KGaA, Darmstadt, Germany; [10]Sumptuous Data Sciences, Monmouth Junction, NJ; [11]University of Texas, MD Anderson Cancer Center, Department of Sarcoma Medical Oncology, Division of Cancer Medicine, Houston, TX, USA

*At the time of analysis

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Demographics and baseline disease characteristics for patients with and without dose reduction

	Dose reduced (n=29)	Dose not reduced (n=40)
Median age, years (range)	29.0 (18, 72)	34.0 (18, 73)
Baseline BMI, median, kg/m^2	23.6	24.3
Female, n (%)	20 (69)	24 (60)
Childbearing potential[a], n (%)	17 (85)	19 (79)
Family history of FAP, n (%)	6 (21)	5 (13)
Any *APC* mutation, n (%)	7 (24)	6 (15)
Any germline *APC* mutation, n (%)	6 (21)	3 (8)
Any *CTNNB1* mutation, n (%)	15 (52)	27 (68)
Race[b], n (%)		
White	26 (90)	37 (93)
Black	2 (7)	2 (5)
Asian	1 (3)	0
Other	0	1 (3)
Ethnic group[b], n (%)		
Non-Hispanic or Latino	28 (97)	38 (95)
Hispanic or Latino	0	1 (3)
Not reported	1 (3)	1 (3)
Target-tumor location[c], n (%)		
Intra-abdominal	7 (24)	10 (25)
Extra-abdominal	22 (76)	30 (75)
Focal category, n (%)		
Single	17 (59)	25 (63)
Multifocal	12 (41)	15 (38)
Baseline ECOG PS, n (%)		
0	19 (66)	31 (78)
1	9 (31)	9 (23)
2	1 (3)	0
DT treatment status, n (%)		
Treatment-naïve	6 (21)	12 (30)
Refractory or recurrent	23 (79)	28 (70)
Median prior lines of treatment (range)	2 (0, 13)	2 (0, 14)
Median target-tumor size according to RECIST v1.1 (IQR), mm	93.4 (68.9, 132.1)	91.0 (60.1, 135.2)

[a]Women of childbearing potential were defined in the trial protocol as women between menarche and confirmed menopause (ie, 12 months since last menstruation) with intact ovarian function. The determination of whether trial patients met this definition was based on the investigator's judgment.
[b]Race and ethnic group were self-reported.
[c]Patients could have a tumor that presented in more than one location. Therefore, population counts cannot be summed across the locations. If the participant had multiple target tumors in both intra- and extra-abdominal locations, the tumor was classified as intra-abdominal.
BMI, body mass index; DT, desmoid tumor; ECOG PS; Eastern Cooperative Oncology Group Performance Status; FAP, familial adenomatous polyposis; IQR, interquartile range; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.