Impact of Pain on Physical and Role Functioning in Adult Patients With Desmoid Tumors Treated With Nirogacestat

Presented by Ravin Ratan
Department of Sarcoma Medical Oncology, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

The Desmoid Tumor Research Foundation (DTRF) International Research Workshop, September 20, 2024. Houston, TX, USA.
This analysis was funded by SpringWorks Therapeutics, Inc.

Authors and Affiliations

Winette T.A. van der Graaf[1], Thierry Alcindor[2], Nam Quoc Bui[3], Rashmi Chugh[4], Mrinal M. Gounder[5], Bernd Kasper[6], Shivaani Kummar[7], Richard F. Riedel[8], Patrick Schöffski[9], Shengfan Zhou[10], Timothy Bell[10], Brad Tumminello[10], Yucheng Chu[11], Cristina Ivanescu[12], James C. Marcus[13], **Ravin Ratan**[14]

[1]Department of Medical Oncology, Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, The Netherlands; [2]Dana Farber Cancer Institute, Harvard Medical School, Harvard University, Boston, Massachusetts, USA; [3]Division of Oncology, Department of Medicine, Stanford University, Stanford, California, USA; [4]Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan, USA; [5]Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, Cornell University, New York, New York, USA; [6]University of Heidelberg, Mannheim University Medical Center, Mannheim Cancer Center, Sarcoma Unit, Mannheim, Germany; [7]Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon, USA; [8]Duke Cancer Institute, Duke University, Durham, North Carolina, USA; [9]Department of General Medical Oncology, University Hospitals Leuven, KU Leuven, Leuven, Belgium; [10]SpringWorks Therapeutics, Inc., Stamford, Connecticut, USA; [11]Sumptuous Data Sciences, Monmouth Junction, New Jersey, USA; [12]IQVIA, Patient Centered Solutions, Amsterdam, The Netherlands; [13]IQVIA, Patient Centered Solutions, Washington DC, USA; [14]Department of Sarcoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Financial and Competing Interests and Disclosures

The DeFi trial was sponsored by SpringWorks Therapeutics, Inc. Dr. Ravin Ratan reports the following:

- Consulting/advisory role for Inhibrx, Ipsen, and SpringWorks Therapeutics
- Honoraria from PeerView and touchIME, and travel, accommodations, and expenses from SpringWorks Therapeutics
- Research funding from Ayala Pharmaceuticals, C4 Therapeutics, Epizyme, and SpringWorks Therapeutics
- Stock and other ownership interests in Johnson & Johnson/Janssen and Medtronic

The DeFi Trial

DeFi was a phase 3 trial of nirogacestat vs placebo in adult patients with progressing DT

DeFi (NCT03785964) was an international, randomized, double-blind, placebo-controlled, phase 3 trial that compared the efficacy and safety of nirogacestat vs placebo in adult patients with progressing DT.[1]

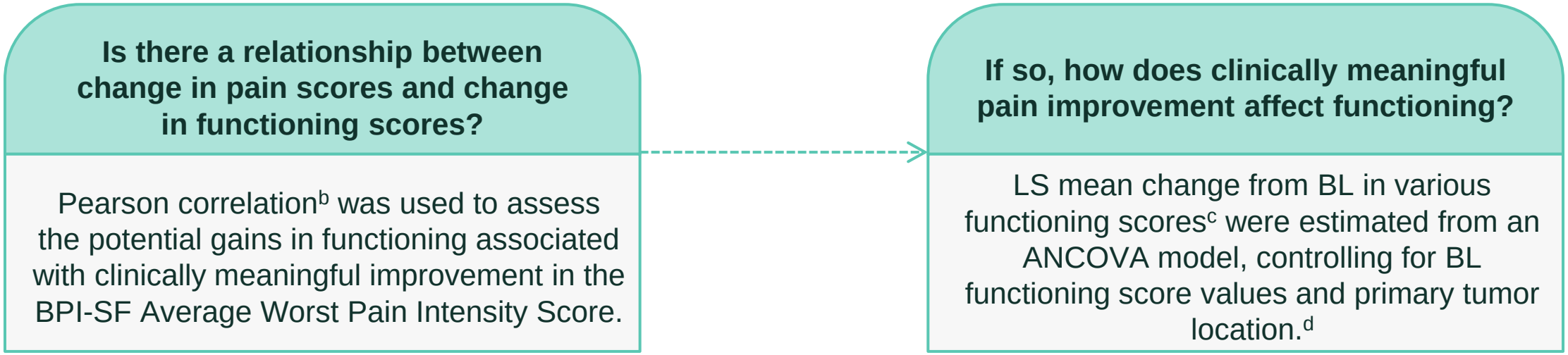
From May 2019 through August 2020, a total of 142 patients were randomized in DeFi — 70 to the nirogacestat group and 72 to the placebo group — across 37 sites in the United States, Canada, and Europe.[1]

1. Gounder M, et al. N Engl J Med. 2023;388:898–912..

DT, desmoid tumors

Methods

- Pain is a common symptom reported in patients with DT and may lead to limitations in function and mobility.[1,2]
- Therefore, pain reduction is a key treatment goal for patients with DT.[3]
- This analysis explored whether patients who demonstrated clinically meaningful improvement in BPI-SF Average Worst Pain Intensity Score[a] (0–10 scale) after treatment also experienced an associated improvement in functioning.
  - All analyses are based on data from Baseline (BL) to Cycle 10.



20/40 patients had BL BPI-SF Average Worst Pain Intensity Score ≥2 and non-missing data.
16/20 patients had a clinically meaningful pain reduction of ≥2 points from BL.

[a]The BPI-SF Average Worst Pain Intensity Score was calculated as the average of the daily BPI-SF Item 3 scores (worst pain in the past 24 hours) over the 7-day period prior to each visit. The score was derived only if 4 to 7 days had non-missing scores. [b]Correlations were assessed for PRO tool domains and LS mean changes were calculated for PRO tool individual items (e.g., questions). [c]PRO tools included BPI-SF Average Worst Pain Intensity Score, BPI-SF Pain Interference Index (BPI-SF PII), GODDESS© DTSS Total Symptom Score (TSS); GODDESS© DTIS Physical Functioning (PF), EORTC QLQ-C30 Role Functioning (RF) and EORTC-QLQ-30 Physical Functioning (PF). [d]LS mean changes at Cycle 10 from BL were estimated from an ANCOVA model, controlling for BL functioning scores and primary tumor location (intra-abdominal vs extra-abdominal).

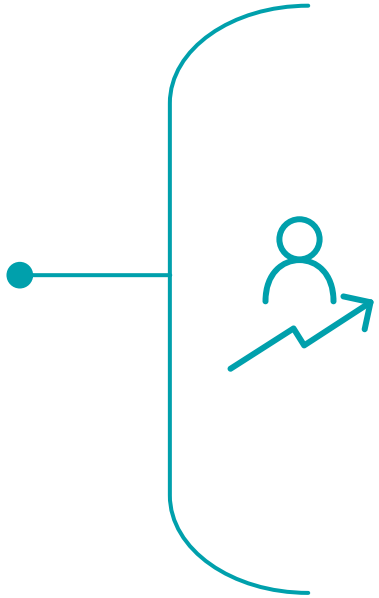
1. Husson O, et al. *Support Care Cancer*. 2019;27(3):965–980. 2. Bektas M, et al. *Adv Ther*. 2023;40(9):3697–3722. 3. Gounder MM, et al. *Cancer*. 2020;126(3):531–539.

BL, baseline; BPI-SF, Brief Pain Inventory Short Form; DT, desmoid tumors; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; GODDESS DTSS/DTIS; Gounder/Desmoid Tumor Research Foundation Desmoid Tumor Symptom Scale / Desmoid Tumor Impact Scale; LS, least-squares; PRO, patient-reported outcomes.

Results: Correlation Between Changes in Pain and Changes in Functioning

Mean changes from BL at Cycle 10[a] in BPI-SF Average Worst Pain Intensity Scores were correlated with mean changes in functioning domain scores for:

PRO Tool	*r-Value*	*Correlation Strength*[b]
BPI-SF PII[b] N = 40	0.79 *P*<0.0001	●●●●○
GODDESS© DTIS PF N = 37	0.46 *P*=0.004	●●●○○
EORTC QLQ-C30 RF N = 36	-0.41 *P*=0.013	●●●○○
EORTC QLQ-C30 PF N = 36	-0.19 *P*=0.255	●○○○○



Decreases in BPI-SF Average Worst Pain Intensity Score also corresponded with decreases in:

- Pain interference with tasks
- Difficulty performing physical activities
- Trouble performing roles

[a]Among the 14 patients not eligible for this analysis, 9 patients dropped out before Cycle 10, 3 had partial data at Cycle 10 (<4/7 days of data), and 2 had missing data. Among 9 dropouts, 3 had adverse events, 2 had radiographic progression, 2 had clinical progression, 1 represented a physician decision, and 1 withdrew. [b]Correlation strength: (1 Dot) Correlations < 0.20 are very weak; (2 Dots) Correlations from 0.20 to 0.39 are weak; (3 Dots) Correlations from 0.40 to 0.59 are moderate; (4 Dots) Correlations from 0.60 to 0.79 are strong; (5 Dots) Correlations >0.80 are very strong.[1] [b]BPI-SF PII was used as a proxy for functioning measurement in this analysis.

1. Papageorgiou SN. *J Orthod.* 2022;49(3):359-361.

BL, Baseline; BPI-SF PII, Brief Pain Inventory–Short Form Pain Interference Index; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; GODDESS©-DTIS, Gounder/Desmoid Tumor Research Foundation Desmoid Tumor Impact Scale; PF, physical functioning; PRO, patient-reported outcomes; *r*, rho; RF, role functioning.

Results: Functional Gains – BPI-SF Pain Interference Index (0–10 Scale)

LS mean change from BL to Cycle 10 (95% CI)[a]

Patients with a clinically meaningful reduction in pain of ≥2 points[b] on the BPI-SF Average Worst Pain Intensity Score at Cycle 10 had improvement in BPI-SF Pain Interference[c] Index items.

Item	LS mean changes (95% CI)[d]
Sleep	-4.19 (-5.64, -2.75)
Enjoyment of life	-3.15 (-4.26, -2.04)
Normal work	-3.04 (-4.28, -1.81)
Mood	-2.93 (-3.96, -1.90)
General activity	-2.90 (-4.03, -1.77)
Relations with other people	-2.70 (-3.61, -1.80)
Walking ability	-2.23 (-3.27, -1.20)

Most items improved about 3-points on the 0–10 scale, with sleep improving by more than 4 points.

[a]Negative changes from BL scores indicate improvement for the item scores. [b]"≥2" was the threshold to determine clinically meaningful improvement.[1,2] [c]BPI-SF Pain Interference Index was used as a proxy for functioning measurement in this analysis. [d]All results were statistically significant at an α of .05.

BL, Baseline; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; LS, least-squares.

1. Dworkin RH, et al. *J Pain*. 2008;9(2):105-121. 2. Farrar JT, et al. *Pain*. 2003;88(3):287-294.

Results: Functional Gains – GODDESS DTIS Physical Functioning (5-point Likert Scale)

LS mean change from BL to Cycle 10 (95% CI)[a]

Patients with a clinically meaningful reduction in pain of ≥2 points[b] on the BPI-SF Average Worst Pain Intensity Score at Cycle 10 had improvement in GODDESS© DTIS Physical Functioning items.

Item	LS mean changes (95% CI)[c]
Movement near the tumor[c] *(improved mobility)*	-1.69 (-2.62, -0.76)
Doing vigorous activities	-1.14 (-2.12, -0.16)
Doing moderate activities	-1.05 (-1.65, -0.46)
Accomplishing less than would like	-0.97 (-1.64, -0.31)
Reaching up	-0.82 (-1.14, -0.50)

Most items moved about 1 point on the 5-point Likert scale, with “Moving near the tumor” moving about 2 categories.

[a]Negative changes from BL scores indicate improvement for the item scores. [b]“≥2” was the threshold to determine clinically meaningful improvement.[1,2] [c]All results were statistically significant at an α of .05. [c]GODDESS®-DTIS item specifically reads: “moving near the tumor”.

BL, Baseline; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; GODDESS©-DTIS, Gounder/Desmoid Tumor Research Foundation Desmoid Tumor Impact Scale; LS, least-squares.

1. Dworkin RH, et al. *J Pain*. 2008;9(2):105-121. 2. Farrar JT, et al. *Pain*. 2003;88(3):287-294.

Results: Functional Gains – EORTC QLQ-C30 Physical Functioning (1–4 Scale)

LS mean change from BL to Cycle 10 (95% CI)[a]

Patients with a clinically meaningful reduction in pain of ≥2 points[b] on the BPI-SF Average Worst Pain Intensity Score at Cycle 10 had improvement in EORTC QLQ-C30 Physical Functioning items.

Item	LS mean changes (95% CI)[c]
Taking a long walk	-0.90 (-1.18, -0.62)
Doing strenuous activities	-0.63 (-1.16, -0.09)
Needing to stay in bed or chair during the day	-0.28 (-0.62, 0.06)
Taking a short walk	-0.27 (-0.51, -0.03)
Eating, dressing, washing, or using the toilet	-0.07 (NE, NE)

Taking a long walk improved by about 1 category on the 1–4 scale.

[a]Negative changes from BL scores indicate improvement for the item scores. [b]"≥2" was the threshold to determine clinically meaningful improvement.[1,2] [c]All results were statistically significant at an α of .05 except needing to stay in bed or chair during the day (not statistically significant) and eating, dressing, washing or using the toilet (not evaluable).
BL, Baseline; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; LS, least-squares; NE, nonestimable.

1. Dworkin RH, et al. *J Pain*. 2008;9(2):105-121. 2. Farrar JT, et al. *Pain*. 2003;88(3):287-294.

Results: Functional Gains – EORTC QLQ-C30 Role Functioning (1–4 Scale)

LS mean change from BL to Cycle 10 (95% CI)[a]

Patients with a clinically meaningful reduction in pain of ≥2 points[b] on the BPI-SF Average Worst Pain Intensity Score at Cycle 10 had improvement in EORTC QLQ-C30 Role Functioning items.

Item	LS mean changes (95% CI)[c]
Pursuing hobbies or other leisure time activities	-0.95 (-1.32, -0.58)
Doing work or other daily activities	-0.61 (-1.13, -0.10)

Both items improved by about 1 category on the 1–4 scale.

[a]Negative changes from BL scores indicate improvement for the item scores. [b]"≥2" was the threshold to determine clinically meaningful improvement.[1,2] [c]All results were statistically significant at an α of .05.
BL, Baseline; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; LS, least-squares.

1. Dworkin RH, et al. *J Pain*. 2008;9(2):105-121. 2. Farrar JT, et al. *Pain*. 2003;88(3):287-294.

Summary

Is there a relationship between pain and functioning?

Moderate to high correlations were found between most changes in pain and changes in functioning.

If so, how does clinically meaningful pain improvement affect functioning?

Patients with clinically meaningful reduction in pain experienced improvement in most dimensions associated with physical and role functioning.

Acknowledgements

The authors wish to acknowledge:

The DeFi trial patients and their families and caregivers

The staff members at the DeFi trial centers

The Desmoid Tumor Research Foundation (DTRF)

The Sarcoma Patient Advocacy Global Network (SPAGN)

Medical writing and editorial assistance for the development of this presentation were provided by IQVIA Medical Communications and funded by SpringWorks Therapeutics, Inc.