Tumor Volume and T2 Hyperintensity Changes from DeFi: A Phase 3, Randomized, Controlled Trial of Nirogacestat in Patients With Desmoid Tumors

ABSTRACT #11514
POSTER BOARD #448

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INTRODUCTION

- Desmoid tumors (aggressive fibromatosis) are rare, locally aggressive and invasive, soft-tissue tumors that can result in pain, functional impairment, and compromised quality of life[1–9]
- The use of magnetic resonance imaging (MRI) to assess changes in tumor volume or T2 signal intensity represents a novel imaging technique that could have prognostic or predictive value in patients with desmoid tumors[10,11]
  - For example, hyperintense areas on T2-weighted images are associated with active fibroblastic proliferation, and ≥90% hyperintensity has been suggested to be associated with progressive disease, whereas iso- or hypo-intense areas can be associated with inactive disease[10,11]
  - Because T2 signal intensity reflects water content within the tissue, a high signal intensity can be considered a surrogate for cellular (biologically active) activity within the tumor (as compared with fibrous, extracellular components)[10]
- Nirogacestat is an investigational, oral, small-molecule, selective gamma-secretase inhibitor evaluated in DeFi (NCT03785964), the largest double-blind, randomized, controlled trial completed to date in adult patients with desmoid tumors
  - In DeFi, nirogacestat demonstrated statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS; hazard ratio: 0.29 [95% CI, 0.15–0.55]; two-sided *P*<0.001) and in all key secondary efficacy endpoints (objective response rate [ORR; 41% vs 8%; *P*<0.001]; pain, disease-specific symptom burden, physical functioning, role functioning, and overall quality of life [*P*<0.01 for all])
  - Nirogacestat demonstrated a manageable safety profile that was generally consistent with gamma-secretase inhibition

OBJECTIVE

- To conduct exploratory analyses of changes in MRI-assessed desmoid tumor volume and T2 signal intensity in the phase 3 DeFi study

METHODS

- DeFi was a phase 3, global, double-blind, randomized, placebo-controlled study of the efficacy and safety of nirogacestat in patients aged 18 years or older with histologically confirmed, progressing, desmoid tumors, per RECIST version 1.1 criteria
  - Eligible patients either had not received previous treatment for progressing desmoid tumors that were not amenable to surgery, or had refractory or recurrent desmoid tumors after at least one line of therapy
  - Patients received oral nirogacestat (150 mg) or placebo twice daily, taken continuously in 28-day cycles until discontinuation, disease progression, trial completion, or death
  - MRI or computed tomography (CT) scans were obtained at screening, cycle 4, and every 3 cycles thereafter
  - Both imaging-based (RECIST version 1.1) and clinical progression were confirmed by blinded, independent, central review
- As exploratory DeFi endpoints, volumetric MRI (no contrast required) and T2 hyperintensity of each patient's largest target tumor were evaluated at screening and every 6 cycles during the double-blind phase. CT or MRI scans (investigator's choice) were acquired to assess tumor changes; consequently, volumetric MRI was not evaluable in all patients
  - MRI T2 signal intensity was calculated as the ratio of hyperintensity in total tumor volume to muscle background
  - All scans for tumor volume and T2 hyperintensity were assessed by blinded independent central review

RESULTS

BASELINE CHARACTERISTICS

- From May 2019 through August 2020, a total of 142 patients were randomized (70 to the nirogacestat group and 72 to the placebo group) across 37 sites in the United States, Canada, and Europe[8]
- Baseline patient characteristics were generally similar between groups and representative of the general patient population with desmoid tumors[8]
  - At baseline, median tumor volume of the largest target tumor was 152.0 mL (IQR, 55.8 to 508.0 mL) for nirogacestat and 162.4 mL (IQR, 47.0 to 576.7 mL) for placebo
  - At baseline, similar proportions of patients in each arm had a T2 hyperintensity ratio ≥90% in the largest target tumor (95% for nirogacestat and 98% for placebo for those with baseline T2 values)

TUMOR VOLUME AND IMAGING

- Treatment with nirogacestat led to significant reduction from baseline in MRI-assessed tumor volume **(Figure 1)** and T2 hyperintensity ratio **(Figure 2)** of the largest target tumor versus placebo
- **Figures 1** and **2** show waterfall plots of the best percent change at any time point from baseline in the largest target tumor per patient
  - For tumor volume, median best percent change from baseline at any time post-treatment was –58.9% (IQR, –84.7 to –8.9) for nirogacestat versus +13.8% (IQR, –26.1 to +58.6) for placebo (*P*<0.001)
  - For T2 hyperintensity ratio, median best percent change from baseline at any time post-treatment was –55.1% (IQR, –73.5 to –20.4) for nirogacestat versus –21.4% (IQR, –42.9 to +3.4) for placebo (*P*<0.001)
- Best changes in tumor volume and RECIST response generally trended in the same direction for most patients although, as expected, larger changes tended to be observed in tumor volume compared with RECIST, and only the largest tumor was assessed for tumor volume
- Descriptive analyses suggest deeper and more sustained decreases over time were observed with nirogacestat than with placebo in the largest target tumor's volume and T2 hyperintensity signal ratio (see Supplementary Materials accessible using the QR code)

Figure 1. Best percent change in MRI-assessed tumor volume at any time post-treatment in the largest target tumor by RECIST v1.1 best confirmed response

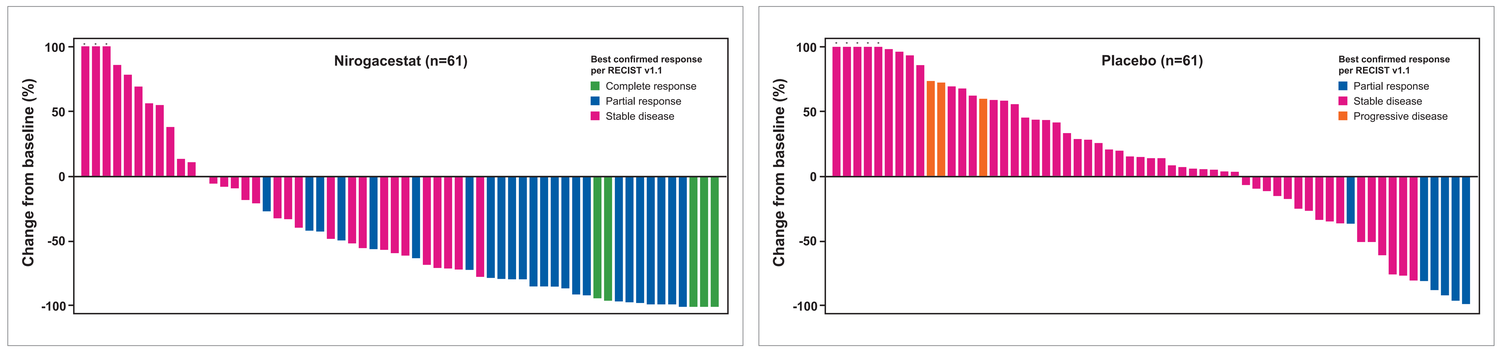

Figure 2. Best percent change in T2 hyperintensity signal ratio at any time post-treatment in the largest target tumor by RECIST v1.1 best confirmed response

*Value exceeds 100%.
Colors indicate the best confirmed overall response according to RECIST v1.1 in all target tumors per blinded independent central review.

Figure 3. Representative MRI images of RECIST v1.1 complete response with nirogacestat

Figure 4. Representative MRI images of RECIST v1.1 partial response with nirogacestat

CONCLUSIONS

- The phase 3 DeFi study is the largest dataset to date to prospectively evaluate and report volumetric MRI and T2 hyperintensity results in desmoid tumors
- In exploratory DeFi endpoints, significant reduction in MRI-assessed tumor volume and T2 hyperintensity of the largest target tumor was observed with nirogacestat compared with placebo
- These exploratory, imaging-based results from DeFi are consistent with the significant improvement in PFS and ORR achieved with nirogacestat compared with placebo in patients with desmoid tumors
- These data suggest that volumetric MRI and T2 hyperintensity may provide additional information in the evaluation of tumor and treatment responses in desmoid tumors
- Further exploration of the relationships among changes in longest tumor diameter (per RECIST version 1.1), tumor volume, T2 hyperintensity, and patient-reported outcomes from DeFi are ongoing

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