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

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INTRODUCTION
Demodectic tumors (aggressive fibromatoses) are rare, locally aggressive and invasive, soft-tissue tumors that can result in pain, functional impairment, and compromised quality of life.* The use of magnetic resonance imaging (MRI) to assess changes in tumor v0 at T2 signal intensity represents a novel imaging technique that could have prognostic or predictive value in patients with desmoid tumors:**

As exploratory DeFi endpoints, volumetric MRI (no contrast) and T2 hypointensity from baseline to any point in time post-treatment were evaluated at screening and every 6 cycles during the double-blind phase. CT or MR scans (investigator’s choice) were acquired to assess tumor status; consequently, volumetric MRI was not evaluable in all patients. – MRI T2 signal intensity was calculated as the ratio of hypointensity in total tumor volume to muscle background – All scans for tumor volume and T2 hypointensity were assessed by blind independent central review

RESULTS

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

Baseline patient characteristics were generally similar between groups and representative of the general patient population with desmoid tumors.

At baseline, medium 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.

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) 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]).

TUMOR VOLUME AND IMAGING

At baseline, similar proportions of patients in each arm had a T2 hypointensity ratio ≥50% in the largest target tumor (95% for nirogacestat and 98% for placebo for those with baseline T2 values).

TREATMENT WITH NIROGACESTAT LEAD TO SIGNIFICANT REDUCTION FROM BASELINE IN MRI-ASSESSED TUMOR VOLUME (FIGURE 1) AND T2 HYPOINTENSITY RATIO (FIGURE 2) OF THE LARGEST TARGET TUMOR VERSUS PLACEO

FIGURE 1. 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. Percent change in T2 hypointensity signal ratio at any time post-treatment in the largest target tumor by RECIST v1.1 best confirmed response

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 hypointensity results in desmoid tumors.

In exploratory DeFi endpoints, significant reduction in MRI-assessed tumor volume and T2 hypointensity 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 hypointensity may provide additional information in the evaluation of tumor and treatment responses in desmoid tumors.

Further exploration of the relationships among changes in tumor diameter (per RECIST version 1.1), T2 hypointensity, and patient-reported outcomes from DeFi are ongoing.

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