Descriptive Evaluation of Patients With Desmoid Tumor and Co-Occurring Somatic Mutations of *CTNNB1* and *APC* in the Phase 3 DeFi Trial

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INTRODUCTION

- Desmoid tumors (DT) are rare, locally invasive, nonmetastatic, soft-tissue tumors driven by Wnt/β-catenin signaling pathway alterations[1,2]
  - Most DT (80%–90%) occur sporadically and are characterized by somatic mutations in the *CTNNB1* gene that encodes for β-catenin[1,3]
    - The most common *CTNNB1* mutations are T41A (~55%), S45F (~35%), and S45P (~10%)[1]
  - Approximately 10%–20% of DT are associated with mutations in the *APC* gene, which encodes for the adenomatous polyposis coli tumor suppressor protein that regulates cellular β-catenin levels[1,3]
- Nirogacestat is an oral, targeted gamma secretase inhibitor that blocks proteolytic activation of the Notch receptor; when dysregulated, Notch can activate pathways that contribute to tumor growth[4]
- Nirogacestat is the only US Food and Drug Administration–approved treatment for adults with progressing DT who require systemic treatment[4,5]
- In the pivotal, randomized, phase 3 DeFi trial, nirogacestat (n=70) demonstrated statistically significant and clinically meaningful improvement vs placebo (n=72) in[6]:
  - Progression-free survival (PFS; hazard ratio, 0.29 [95% CI, 0.15–0.55]; *P*<.001)
  - Objective response rate (ORR; 41% vs 8%; *P*<.001)
  - Patient-reported outcomes of pain, DT-specific symptom burden, physical and role functioning, and overall quality of life (*P*≤.01, all)
- In prespecified subgroup analyses of PFS and ORR, improvements with nirogacestat compared with placebo were observed in patients with somatic *CTNNB1* mutations[6,7] and in those with somatic *APC* mutations[6,8]
- To our knowledge, there are no reports of patients with DT who harbor co-occurring somatic *CTNNB1* and *APC* aberrations

OBJECTIVE

- To describe the characteristics and outcomes of patients with co-occurring somatic *CTNNB1* and *APC* mutations in the DeFi trial

METHODS

- DeFi (NCT03785964) was a global, multicenter, randomized, double-blind, phase 3 trial that evaluated the efficacy, safety, and tolerability of nirogacestat in adults (aged ≥18 years) with progressing DT
- Patients were randomized 1:1 to receive oral nirogacestat 150 mg (n=70) or placebo (n=72) twice daily in continuous 28-day cycles
- Descriptive post hoc analysis was conducted to assess the effects of nirogacestat in patients who were identified as harboring co-occurring somatic mutations in *CTNNB1* and *APC*
- Matching blood and tumor biopsy samples were collected prior to the first dose of study treatment
  - Tissue samples were histologically examined for the presence of tumor
  - Somatic mutations were identified by next-generation sequencing (NGS)
  - Co-occurring somatic mutations in tumor cells were confirmed through NGS and Clinical Laboratory Improvement Amendments (CLIA) gene panel, which included Sanger sequencing
  - If somatic mutations in *CTNNB1* and *APC* genes were identified, the blood samples were analyzed for the presence of germline mutations in these 2 genes
- Tumor response was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 through blinded independent central review and was confirmed
- The data cutoff date for this analysis was April 7, 2022

RESULTS

PATIENTS

- Of the 142 patients randomized in the DeFi trial, 3 patients (nirogacestat, n=2; placebo, n=1) had co-occurring somatic mutations of *CTNNB1* and *APC*
  - No germline mutations were detected in these 3 patients
- Baseline characteristics and study drug exposure are provided in **Table 1**

Table 1. Baseline characteristics and exposure

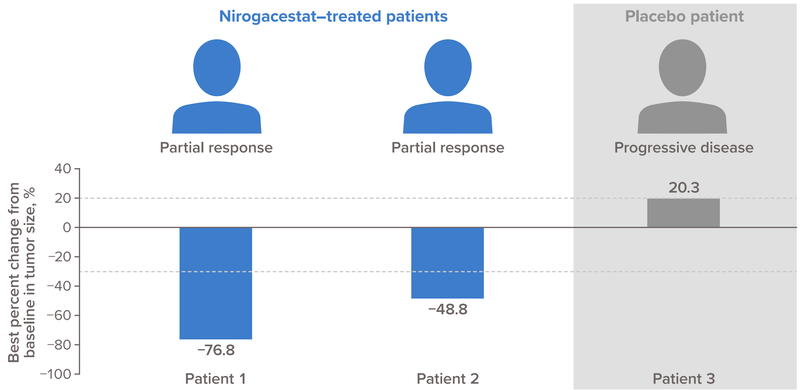
	Nirogacestat		Placebo
	Patient 1	Patient 2	Patient 3
Baseline characteristics			
CTNNB1 mutation type	S45F	S45P	S45F
APC mutation type	p.P2320L	p.S1198*[,a]	p.P2513A
Time since diagnosis to randomization, months	27.24	11.30	12.42
Family history of FAP	No	No	No
DT treatment status	Refractory	Refractory	Treatment naïve
Focal category	Single	Single	Single
Tumor location	Upper extremity	Abdominal wall	Upper extremity
Baseline tumor size, mm	59.6	69.1	81.8
ECOG PS	1	0	1
Prior systemic therapy	Methotrexate, vinblastine	Sorafenib, imatinib	No
Prior radiation	No	No	No
Prior surgery	No	Yes	No
Exposure			
Treatment end (relative to start date), days[b]	1022	706	110

[a]In genetic mutation data, an asterisk is the standard way to denote the stop codon: the end of a protein sequence within a mutation, meaning the protein will be truncated at that point due to the altered DNA.
[b]If patient treatment was ongoing at time of data cutoff, treatment end date was determined from either the date of cutoff (if patient did not have an interruption recorded immediately prior to cutoff) or the date before the start of interruption (if patient had an interruption immediately prior to the cutoff).
DT, desmoid tumor; ECOG PS, Eastern Cooperative Oncology Group performance status; FAP, familial adenomatous polyposis.

EFFICACY

- The 1 patient randomized to placebo experienced progressive disease in 2.6 months, with a +20.3% change from baseline in tumor size (**Figure 1**)
- Both patients randomized to nirogacestat achieved a best overall response (BOR) of partial response (**Figure 1**)
  - Best percent changes from baseline in tumor size were −76.8% and −48.8% (**Figure 1**)
- Time to objective response for the 2 nirogacestat-treated patients was 6.0 and 13.8 months

Figure 1. BOR by patient



Dashed lines on graph indicate at least a 30% decrease or 20% increase in the sum of diameters of target lesions as indicated by the RECIST response, taking as reference the baseline sum diameters.
BOR, best overall response; RECIST, Response Evaluation Criteria in Solid Tumors.

SAFETY

- Adverse events reported in the 3 patients with co-occurring somatic mutations of *CTNNB1* and *APC* are detailed in **Table 2**
  - Of the 16 adverse events in patients 1 and 2, the following were observed in ≥15% of nirogacestat-treated patients of the overall DeFi population: diarrhea, nausea, fatigue, ovarian toxicity, maculopapular rash, stomatitis, COVID-19, weight increased, and decreased appetite[6]
- All adverse events were Grade 1 or 2 except for an event of weight increased in patient 1, which was Grade 3

Table 2. Adverse events

Nirogacestat		Placebo
Patient 1	Patient 2	Patient 3
• COVID-19 • Decreased appetite • Depression • Diarrhea • Hypertension • Ovarian toxicity[a,b] • Tumor pain • Weight increased	• Constipation • Dizziness • Fatigue • Maculopapular rash • Irregular menstruation • Nausea • Sinusitis • Stomatitis	• Aspartate aminotransferase increased • Diarrhea • Noncardiac chest pain • Tooth infection • Transaminases increased
Dose modification due to adverse events		
Dose reduced for ovarian toxicity (Grade 2)[c]	Dose interrupted for maculopapular rash (Grade 1)[c]	N/A

[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 these events were coded to the MedDRA (version 24.0) preferred terms of ovarian failure, premature menopause, amenorrhea, and menopause.[5]
[b]Ovarian toxicity was reported to resolve.
[c]Adverse event deemed related to study treatment (by the investigator).
MedDRA, Medical Dictionary for Regulatory Activities; N/A, not applicable.

CONCLUSIONS

- In the pivotal phase 3 DeFi trial, 3 patients were identified with co-occurring somatic mutations of *CTNNB1* and *APC*, including 2 treated with nirogacestat
- Although the small number of patients limited a formal analysis, descriptive results suggest that patients with this mutational profile benefit from nirogacestat treatment in a manner that is generally consistent with the overall DeFi population

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