Clinical Activity of the γ -Secretase Inhibitor PF-03084014 in Adults With Desmoid Tumors (Aggressive Fibromatosis)

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ABSTRACT

Purpose

Desmoid tumors (aggressive fibromatosis) arise from connective tissue cells or fibroblasts. In general, they are slow growing and do not metastasize; however, locally aggressive desmoid tumors can cause severe morbidity and loss of function. Disease recurrence after surgery and/or radiation and diagnosis of multifocal desmoid tumors highlight the need to develop effective systemic treatments for this disease. In this study, we evaluate objective response rate after therapy with the γ -secretase inhibitor PF-03084014 in patients with recurrent, refractory, progressive desmoid tumors.

Patients and Methods

Seventeen patients with desmoid tumors received PF-03084014 150 mg orally twice a day in 3-week cycles. Response to treatment was evaluated at cycle 1 and every six cycles, that is, 18 weeks, by RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1. Patient-reported outcomes were measured at baseline and at every restaging visit by using the MD Anderson Symptoms Inventory. Archival tumor and blood samples were genotyped for somatic and germline mutations in *APC* and *CTNNB1*.

Results

Of 17 patients accrued to the study, 15 had mutations in *APC* or *CTNNB1* genes. Sixteen patients (94%) were evaluable for response; five (29%) experienced a confirmed partial response and have been on study for more than 2 years. Another five patients with prolonged stable disease as their best response remain on study. Patient-reported outcomes confirmed clinician reporting that the investigational agent was well tolerated and, in subgroup analyses, participants who demonstrated partial response also experienced clinically meaningful and statistically significant improvements in symptom burden.

Conclusion

PF-03084014 was well tolerated and demonstrated promising clinical benefit in patients with refractory, progressive desmoid tumors who receive long-term treatment.

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INTRODUCTION

Desmoid tumors (aggressive fibromatosis) are slow-growing, locally invasive soft-tissue tumors with highly heterogeneous phenotypes—the disease can be asymptomatic or associated with severe loss of organ function and significant morbidity. The postsurgical recurrence rate is high, and for those tumors that are not amenable to resection, watchful waiting may be indicated because the disease may stabilize on its own¹⁻³; however, some tumors cause pain or functional

limitations that require treatment. Although the molecular pathogenesis of desmoid tumors is not fully understood, dysregulation of the Wnt/ β -catenin pathway and consequent transcription of prosurvival and proliferative genes likely play a critical role.⁴ Desmoid tumors and aggressive fibromatosis may arise sporadically as a result of somatic mutations in the *CTNNB1* (β -catenin) proto-oncogene or via germline mutations in the regulator of β -catenin *APC* (adenomatous polyposis coli) gene.⁵⁻⁷ The prevalence of specific *CTNNB1* mutations (T41A, S45E, and S45P) in sporadic desmoid tumors may be as high as

86%,^{6,8,9} whereas germline mutations in *APC* lead to accumulation of β -catenin and cause familial adenomatous polyposis (FAP) or Gardner syndrome, a phenotypical variant of FAP.^{10,11} These conditions are associated with a significant increase in the risk of developing desmoid tumors—the incidence rate is 10% to 30% for individuals with FAP.^{12,13} Antecedent trauma, including prior surgical resection, has also been implicated as a risk factor in patients with FAP, which is consistent with the mesenchymal etiology of these tumors.^{14,15}

Incidence of desmoids in the general population is estimated at 2.4 to 4.3 cases per million per year.¹⁶ Treatment with targeted antitumor agents, notably kinase inhibitors, has resulted in modest response rates (5% to 25%).¹⁷⁻¹⁹ The Notch pathway constitutes another target of interest for targeted therapy, as cross-talk with Wnt signaling was recently demonstrated,^{20,21} and aberrant Notch signaling has been linked to poor prognosis in both hematologic malignancies²²⁻²⁴ and solid tumors.²⁵⁻²⁷ Notch signaling involves the cleavage of the Notch intracellular domain by γ -secretase, followed by translocation of the Notch intracellular domain to the nucleus, where it modulates gene transcription²⁸; therefore, γ -secretase inhibitors have been tested for targeted inhibition of Notch in preclinical cancer models.²⁹ Of note, in a phase I clinical trial of the small-molecule γ -secretase inhibitor PF-03084014 in patients with advanced solid tumors, five of seven evaluable patients with desmoid tumors experienced partial responses, whereas two patients had some evidence of tumor shrinkage with prolonged disease stabilization.^{30,31} Pharmacodynamic assessment demonstrated a drug-induced decrease in Notch effector HES4 in blood samples of all patients. On the basis of these promising observations, we conducted a phase II trial of PF-03084014 to further evaluate the efficacy of this agent in patients with unresectable desmoid tumors. PF-03084014 was administered at the recommended phase II oral dose of 150 mg twice per day, continuously, in 21-day cycles. Archival tumor biopsy tissues and blood samples collected at baseline were genotyped for somatic and germline mutations in *APC* and *CTNNB1*. Considering the typical morphologic asymmetry of these lesions and the different radiologic criteria proposed for their evaluation,³² we carried out both computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) tumor segmentation in this trial.

PATIENTS AND METHODS

Patient Eligibility

Patients age ≥ 18 years with histologically confirmed desmoid tumors not amenable to surgical resection or definitive radiation therapy, and who experienced actively progressing disease following at least one line of standard therapy, were eligible for enrollment. An Eastern Cooperative Oncology Group performance status of ≤ 2 and adequate liver, kidney, and marrow function defined as an absolute neutrophil count $\geq 1,500/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, hemoglobin ≥ 9 g/dL, total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase $\leq 2.5 \times$ ULN, and creatinine $< 1.5 \times$ ULN were required. Prior treatment with γ -secretase inhibitors or anti-Notch antibody therapy was not permitted. Previous anticancer therapy, radiation, or surgery must have been completed at least 2 weeks before enrollment with resolution of toxicities to baseline and/or eligibility levels, and evidence of disease progression with the previous treatment regimen by staging scans was required. Exclusion criteria included inability to swallow pills, uncontrolled

intercurrent illness, pregnancy or breastfeeding, congenital long QT syndrome or a QTc interval of > 470 milliseconds, and GI conditions that might predispose to drug intolerance or poor drug absorption. This trial was conducted under a National Cancer Institute (NCI)–sponsored investigative new drug program with institutional review board approval. Informed consent was obtained from each participant, and protocol design and conduct followed all applicable regulations, guidance, and local policies. The trial opened in November 2014 and completed patient accrual in May 2015.

Trial Design

This was an open-label, single-center, phase II trial of PF-03084014 in patients with desmoid tumors (aggressive fibromatosis). Pfizer (Groton, CT) supplied PF-03084014 to the NCI and the NCI Division of Cancer Treatment and Diagnosis under a clinical trial agreement. PF-03084014 was administered orally at 150 mg twice a day throughout a 21-day cycle. There were no restrictions on food consumption, and patients maintained study diaries that documented the time of drug ingestion and any associated adverse effects. Adverse events were graded according to NCI Common Toxicity Criteria version 4.0. Grade 3 nonhematologic toxicities had to resolve to grade ≤ 2 or baseline—except alopecia or easily corrected electrolyte abnormalities—or the patient was to be taken off study. Grade 3 hematologic toxicities had to resolve to grade ≤ 2 —except lymphopenia or leucopenia in the absence of neutropenia—before starting the next cycle. PF-03084014 was dose reduced for grade ≥ 2 nausea, vomiting, or diarrhea if not controlled by supportive measures. No more than two dose reductions per patient were allowed. If toxicities did not resolve to retreatment criteria within 3 weeks, the patient was taken off study.

Table 1. Patient Characteristics (N = 17 patients)

Characteristic	No.*
Median age (range), years	34 (19-69)
Gender	
Male	3 (18)
Female	14 (82)
Primary tumor site	
Thorax	1 (6)
Abdomen	4 (24)
Extremity	6 (35)
Spine and spinal girdles	6 (35)
ECOG performance status	
0	1 (6)
1	16 (94)
Median prior therapies, No. (range)	4 (1-9)
Cytotoxic chemotherapy†	12 (71)
NSAID (sulindac, celecoxib)	11 (65)
TKI (imatinib, sorafenib)	10 (59)
Mutation type	
<i>CTNNB1</i> T41A somatic	9 (53)
<i>CTNNB1</i> S45F somatic	3 (18)
<i>APC</i> somatic	1 (6)
<i>APC</i> germline	2 (12)
None	2 (12)
Reported prior genetic diagnosis	
Gardner syndrome	2
FAP	0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FAP, familial adenomatous polyposis; NSAID, nonsteroidal anti-inflammatory drug; TKI, tyrosine kinase inhibitor.

*Values in parentheses indicate percentages unless otherwise noted.

†Prior cytotoxic chemotherapy included cyclophosphamide, dacarbazine, doxorubicin, hydroxyurea, methotrexate, temozolomide, vinblastine, and vinorelbine.

Fig 1. Patient response and mutation status. Best response of partial response is shown with a blue arrow. Mutations in *APC* and *CTNNB1* genes are shown. Ten patients remain on study (gold arrow).

Efficacy and Patient-Reported Outcome Evaluations

Radiographic evaluation was performed at baseline and every six cycles $\pm$ one cycle—that is, 3 weeks—to assess tumor response on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.³³ An optional contrast-enhanced MRI was performed before the start of study treatment, after cycle 1, and at restaging on a contrast-enhanced T1-weighted MRI by using a semiautomated generic software embedded into the NCI clinical center radiology reporting system, PACS (Carestream Health, Rochester, NY).

Participants were also asked to complete the psychometrically validated MD Anderson Symptom Inventory (MDASI)^{34,35} questionnaire at baseline and at restaging visits to evaluate severity over the previous 24 hours of 13 treatment-related symptoms on a 0 to 10 numerical scale. Mean subscale scores for symptom severity and interference were calculated and examined graphically. We also conducted a patient-reported outcome (PRO) responder analysis,³⁶ for which a PRO response was defined as an improvement in mean symptom severity of ≥ 1.2 points³⁷ when comparing pretreatment score with severity at the final available PRO assessment. We also examined response on a per symptom basis and defined more than minimal improvement as improvement from

a symptom rating of moderate (5 to 6) or severe (7 to 10) to a symptom rating of mild (1 to 4) or none (0), between baseline and the last PRO assessment (~ 20 months of therapy).³⁴

Genotyping

Five-milliliter blood samples were collected in EDTA-containing vacutainer tubes at baseline for germline sequencing of *APC* and *CTNNB1*, then aliquoted and frozen in 2-mL screw-top cryovials at -20°C . Genomic DNA was later extracted for clinically targeted sequencing (see Results section). A 4- μm hematoxylin and eosin–stained section was examined for tumor content by a pathologist at the NCI Clinical Tumor Profiling Laboratory, and a matching formalin-fixed paraffin-embedded tissue block or 10 unstained slides were extracted for DNA using the Qiagen formalin-fixed paraffin-embedded tissue all-prep procedure and genotyped for somatic mutations in *APC* and *CTNNB1* genes.

Statistical Analysis

The study was conducted as a single-stage, single-arm phase II trial. To rule out an unacceptably low 10% objective response rate (objective response rate = partial response [PR] plus complete response) in favor of a 35% objective response rate, the accrual ceiling was set at 17 patients for 90% statistical power with a type I error rate of 10%. At least four objective responses were to occur to qualify PF03084014 as a promising therapeutic option for treatment of desmoid tumors. Symptom measurements were summarized by mean $\pm$ standard deviation for continuous measurements, and by frequency distributions for categorical measurements. Mutations in *APC* and *CTNNB1* genes were summarized with frequency distributions. Wilcoxon signed-rank test was used to assess the significance of changes in symptom severity.

RESULTS

Demographics and Clinical Outcome

Seventeen patients were enrolled in this trial. Median age was 34 years (range, 19 to 69 years), with a male:female ratio of 3:14. All patients had been previously treated, with a median of four prior lines of therapy (range, 1 to 9; Table 1). Several patients had

Table 2. Clinical Outcomes (N = 17)

Clinical Outcome	No.
Median follow-up time, months (range)	> 25 (3-30)
Median cycles, No. (range)	36 (4-43)
Remain on study (≥ 2 years), No. (%)	10 (59)
On study ≥ 1 year, No. (%)	12 (71)
Off study, No. (%)	7 (41)
Patient choice	6 (35)
Adverse event	1 (6)
Response rate, No. (%)	
Complete response	0 (0)
Partial response	5 (29)
Stable disease	11 (65)
Disease progression	0 (0)
Not evaluated	1 (6)

Fig 2. Antitumor activity of PF-03084014. (A) Objective response measured by RECIST 1.1 criteria. Five patients achieved a partial response to PF-03084014. Dotted lines represent cutoffs for partial response (-30% change from baseline) and for progressive disease ($+20\%$ change from baseline). Patient #01 is not shown because of a missing baseline computed tomography measurement, and patient #14 was not evaluable per protocol. Patients who consented to magnetic resonance imaging (MRI) are denoted with an asterisk (*). (B) Representative pre- and post-treatment MRI scans for patient #16 who presented with a left axillary mass that had recurred after surgical resection before enrollment in the current study. Contrast-enhanced axial T1-weighted MRI of the chest shows a 3.4×2.02 cm soft-tissue lesion in the left axilla at baseline MRI (red arrow), which decreased in size after cycle 12 (ie, 9 months of treatment [2.17×1.36 cm; red arrow]). For this patient, drug-induced tumor regression was accompanied by meaningful improvement in symptoms, such as pain, and increased range of motion. (C) Relative change in tumor volume over time measured by contrast-enhanced MRI and labeled with patient numbers.

previously received cytotoxic chemotherapy (12; 70.5%); molecularly targeted treatments, including kinase inhibitors (10 patients, 59%); and nonsteroidal anti-inflammatory drugs (11; 65%). Sixteen patients were evaluable for response to treatment. Seven patients stopped treatment by choice, including one who discontinued therapy because of an adverse event (recurrent urticarial maculopapular rash). Median follow-up time was > 25 months (range, 3 to 30 months), as 12 patients remained on study for more than 1 year (17 cycles of therapy), and 10 patients (59%) continued on therapy for more than 2 years (Fig 1).

Genomic Sequencing

In 15 (88%) of 17 patients, a somatic or germline mutation in *CTNNB1* or *APC* was identified (Fig 1). The majority of patients

($n = 9$; 53%) had the somatic missense mutation *CTNNB1* T41A, and an additional three patients (17%) were noted to have a missense *CTNNB1* S45F mutation variant. Two patients had been diagnosed previously with Gardner syndrome (Table 1). From our sequencing work, this diagnosis was confirmed in only one of those two patients—an *APC* germline mutation was also identified in a different patient not previously diagnosed with Gardner syndrome (data not shown). One patient carried a somatic *APC* mutation.

Efficacy

Five patients (29%) achieved a confirmed PR by RECIST 1.1 criteria after a median of 32 cycles (96 weeks) of treatment with PF-03084014 (Table 2). Four of these five patients had previously received imatinib and/or sorafenib without reported response (data

Table 3. Common Adverse Events—Occurring in $\geq 20\%$ of the Study Population—by Patient (N = 17)

Adverse Event	Grade		
	1	2	3
Blood and lymphatic system disorders			
Anemia	6 (35)	—	—
GI disorders			
Diarrhea	10 (59)	3 (18)	—
Dry mouth	7 (41)	—	—
Mucositis oral	3 (18)	1 (6)	—
Nausea	9 (53)	—	—
General disorders			
Fatigue	7 (41)	—	—
Investigations			
ALT increased	5 (29)	1 (6)	—
AST increased	10 (59)	—	—
Lymphocyte count decreased	8 (47)	1 (6)	—
Platelet count decreased	4 (24)	—	—
White blood cell decreased	3 (18)	1 (6)	—
Hypocalcemia	5 (29)	—	—
Hypokalemia	4 (24)	—	—
Hyponatremia	4 (24)	—	—
Hypophosphatemia	—	5 (29)	8 (47)
Reproductive system and breast disorders			
Irregular menstruation	4 (24)	—	—
Skin and subcutaneous tissue disorders			
Rash (maculopapular)	5 (29)	4 (24)	—
Vascular disorders			
Hot flashes	5 (29)	—	—

NOTE. Data are given as No. (%). Worst grade that is at least possibly related to study drugs is shown for each patient.

not shown). Clinical benefit was observed regardless of mutational status of *CTNNB1* or *APC* genes. Eleven patients had a best response of stable disease, and no instances of progressive disease were observed (Fig 2A). To further assess changes in tumor volume after treatment, 11 of 17 patients had a same-cycle MRI in addition to prespecified CT scans. Representative images of tumors pre- and post-treatment are shown in Fig 2B. All but one evaluated patient had a measurable regression of tumor volume (Fig 2C). In 16 of 17 patients, the decrease in tumor volume was more prominent within the first 300 days of the initiation of treatment cycles.

Toxicity

All patients experienced grade 1 and 2 adverse events, notably, diarrhea (76%) and skin disorders (71%). Four patients met

criteria for dose reduction—two patients received a reduced dose of 100 mg twice per day as a result of persistent grade 2 nausea and diarrhea, but neither patient required corticosteroid therapy as symptoms fully resolved after dose reduction. One patient developed urticaria, which did not respond to dose reduction, and was taken off study because of an allergic reaction. One patient developed grade 2 maculopapular rash, which resolved with dose reduction, and this patient continued on study for > 2 years without recurrent or additional toxicity. The only grade 3 toxicity that was attributable to the study drug was reversible hypophosphatemia, which was reported in eight patients (47%; Table 3)—this is a known class effect of γ -secretase inhibitors that may be related to GI loss and can be easily reversed with oral phosphate replacement and without secondary symptoms of hypocalcemia or hypomagnesaemia.

PROs

All participants were evaluable for PRO by using MDASI, and results of the PRO analysis are listed in Table 4. Partial responders had a 1.65-point improvement in mean symptom severity ($P = .008$). The five patients with stable disease as their best response had a 0.8-point improvement in mean symptom severity ($P = 0.08$). Of seven patients whose treatment was discontinued or who withdrew from the study, mean change in symptom severity was negligible. Two of the five confirmed PRs experienced a PRO response (≥ 1.2 -point improvement in mean symptom severity compared with baseline) after 20 months on treatment; however, four of five PRs experienced more than minimal improvement in the severity of at least one symptom, and none experienced worsening of any symptom. As shown in Fig 3A, symptoms that demonstrated improvement were pain (three of five), numbness/tingling (two of five), fatigue (one of five), sleep disturbance (one of five), and distress (two of five). The trajectories of mean symptom interference in general activity, mood, work, and walking are shown in Fig 3B.

DISCUSSION

β -Catenin (encoded by *CTNNB1*) is an integral component of the Wnt/ β -catenin/T-cell transcription factor signaling cascade frequently dysregulated in cancer.³⁸⁻⁴⁰ In normal cells, a multiprotein complex of APC, axin, casein kinase 1 α , and glycogen synthase

Table 4. MD Anderson Symptom Inventory

Best Disease Response	Mean Change in Symptom Severity	PRO Responder*	Responder per Symptom (more than minimal improvement in at least one symptom)	Worsening per Symptom (more than minimal worsening in one or more symptoms)
Partial response (baseline to 20 months; n = 5)	1.65-point improvement†	2 of 5	4 of 5	0 of 5
Stable disease (baseline to 20 months; n = 5)	0.80-point improvement (n.s.)	1 of 5	2 of 5	1 of 5
No response/dropout (baseline to last available PRO score; n = 7)	0.04-point improvement (n.s.)	2 of 7	3 of 7	3 of 7

Abbreviations: n.s., not statistically significant; PRO, patient-reported outcome.

*A PRO responder was defined as a participant who reported ≥ 1.2 -point improvement in mean symptom severity from baseline.

† $P < .01$.

Fig 3. Longitudinal symptom severity and interference by therapeutic response. (A) Individual symptoms demonstrating clinically meaningful improvement in partial responders (PRs) were pain (three of five), numbness/tingling (two of five), fatigue (one of five), sleep disturbance (one of five), and distress (two of five). Thumbnails show longitudinal evolution of mean severity of these symptoms in PRs (solid gold line) and in patients with sustained stable disease (SD, dashed blue line). Patients with a best response of SD also experienced modest improvements in these symptoms. Neither group experienced clinically meaningful worsening in any individual symptom. (B) Thumbnails show longitudinal changes in mean symptom interference with respect to activities of daily living, mood, work, and walking for PRs (solid gold line) and patients with SD (dashed blue line).

kinase β regulates degradation of β -catenin.^{41,42} Mutations in either *CTNNB1* or *APC* may cause an accumulation of β -catenin that is subsequently translocated to the nucleus, which results in activation of T-cell transcription factor 4 and aberrant gene expression.^{40,43} At least three different point mutations have been identified in exon 3 of *CTNNB1* (T41A, S45E, and S45P)^{1,10,41,44}; presence of β -catenin mutations is associated with a lower 5-year recurrence-free survival rate.^{5,45} In this study, patients were genotyped for germline and somatic mutations in *APC* and *CTNNB1* genes, and the majority (15 of 17) had positive mutation status in either of these genes (Table 1 and Fig 1). As a result of the low number of patients accrued and the absence of disease progression, we did not detect any robust associations between clinical response and mutations in the *CTNNB1* or *APC* genes.

Targeting γ -secretase inhibition to prevent Notch cleavage is of clinical relevance because of the role of Notch in cellular differentiation at different maturation stages of bone marrow and peripheral immune cells,⁴⁶⁻⁴⁸ as well as GI cell differentiation.⁴⁷ Activation of Notch pathway components in tumor samples from patients with aggressive fibromatosis has been demonstrated previously.⁴⁹ For instance, Messersmith et al,^{30,31} who demonstrated good tolerability of PF-03084014 consistent with our results, also reported drug-induced downregulation of Notch-related target protein HES4 in all evaluable study participants, which suggested that this agent disrupted Notch signaling. Goblet cell hyperplasia after chronic γ -secretase inhibition is a noted class effect in animal models^{47,48,50}; many clinical studies with γ -secretase inhibitors have reported Notch-associated adverse events, including diarrhea, changes in lymphocyte phenotypes, and skin/subcutaneous disorders.^{31,51-54} However, in this trial, PF-03084014 was well tolerated—diarrhea was the only major symptomatic adverse event (grade 2 as the maximum severity), but did not negatively impact overall symptom severity and associated interferences, as reported by the MDASI (Fig 3). This, together with the fact that no patient required adjuvant corticosteroid therapy, supports the conclusion that this agent is well tolerated, even with long-term administration. We observed a trend for participants with a subsequent PR to experience improvements in symptom severity as early as cycles 2 or 3 (as shown in Fig 3), although objective responses, as defined by a decrease in tumor size $\geq 30\%$, occurred at cycle 12 or later. Although we cannot exclude the possibility of reporting bias in this single-arm,⁵⁵ unblinded trial, if these observations are confirmed in subsequent studies, our results could be used to counsel patients who are beginning this treatment about its anticipated toxicities and the timeline for demonstrating disease response. In addition, with its durable response and favorable effect on PROs, PF-03084014 seems to be a good potential alternative to surgical resection, which may negatively affect quality of life by inducing such symptoms as pain and fatigue.⁵⁶ Our results also suggest that tumor size is not the defining parameter for morbidity, because patients with large tumors—arbitrarily defined as a target lesion ≥ 6 cm—did not demonstrate high baseline MDASI scores (data not shown).

Of the five patients who experienced a PR, three did not achieve PR until at least 22 months on treatment by RECIST 1.1 criteria (Fig 2A and Table 2). Although, spontaneous tumor

regression cannot be ruled out, a different imaging method may have been able to detect signs of clinical response to the study drug more promptly. As a result of the noted heterogeneity of desmoid tumors, it is difficult to delineate accurate tumor burden by CT. MRI provides excellent soft-tissue contrast, thereby allowing better estimates of volumetric tumor burden; therefore, MRI-derived longitudinal volumetric evaluation may be a more sensitive technique for detecting treatment responses in patients with soft-tissue sarcomas, as noted by Sheth et al and others.^{57,58} However, there are currently no validated criteria with which assess volumetric tumor response to therapy in either solid tumors or sarcomas, though recent publications have explored this approach.^{59,60} Given our findings, a longitudinal volumetric analysis of tumor size in patients with desmoid tumors may allow identification of patients who achieve an objective response at an earlier time and may be a more accurate assessment of tumor response to treatment (Fig 2C). In addition, we used a generic semiautomated tumor volume delineation software that can reveal volumetric results more quickly than conventional planimetric—slice-by-slice manual tumor boundary delineation—methods, saving time and allowing researchers to perform more objective and unbiased longitudinal tumor size analyses. Further assessment of tumor volumetrics via CT and MRI scans is in progress.

Our results suggest that γ -secretase is a promising target for the treatment of aggressive fibromatosis and desmoid tumors. The fact that three of five of our patients experienced objective responses that occurred almost 2 years after the start of treatment suggests that the actual mechanism of tumor regression produced by PF-03084014 may not fit standard models of cell death that are applicable to more common forms of malignancy; however, tolerability of this agent makes it suitable for long-term therapy. Further investigation of this agent is needed to confirm its mode of action via pharmacodynamic studies and to identify any long-term toxicity and benefits over the natural history of this rare and difficult-to-treat disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Clinical Activity of the γ -Secretase Inhibitor PF-03084014 in Adults With Desmoid Tumors (Aggressive Fibromatosis)

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