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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Long-Term Follow-Up of Desmoid Fibromatosis Treated with PF-03084014, an Oral Gamma Secretase Inhibitor

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ABSTRACT

Background. Desmoid fibromatosis is a fibroblastic neoplasm driven by aberrations within the WNT pathway, exhibiting mutations in β-catenin or APC. We review the long-term follow-up of patients in a phase I study treated with an oral gamma secretase inhibitor, PF-03084014.

Methods. PF-03084014 was administered orally at doses ranging from 20 to 330 mg twice daily. Tumor assessments were performed using computed tomography/magnetic resonance imaging (CT/MRI) within 4 weeks of study entry, and every other cycle through cycle 9. After cycle 9, patients were evaluated as clinically indicated.

Results. Seven patients with desmoid fibromatosis were treated between December 2009 and December 2016 at the University of Colorado. Five patients (71.4%, 95% confidence interval [CI] 29.0–96.3%) achieved a partial response (PR), with a mean time to achieving response of 11.9 months (95% CI 2.5–21.4 months). All patients who achieved a PR continue to maintain responses between 47.9 and 73+ months. Four patients stopped treatment yet remain free of progression between 11 and 53+ months. One patient had PFS of 42+ months, with a 17% decrease in the target lesion. A biopsy performed at the end of the study showed decreased tumoral cellularity compared with previous biopsies. Effective treatment doses ranged from 80 to 330 mg administered orally twice daily.

Conclusions. PF-03084014 was effective in treating desmoid tumors, with an objective response rate of 71.4% (95% CI 29.0–96.3%) in this small cohort of patients. PF-03084014 exhibits promising activity, even at relatively low doses (80 mg twice daily), with high tolerability leading to prolonged disease control even after therapy discontinuation.

Desmoid tumors are benign, locally invasive tumors of musculo-aponeurotic origin that arise within the abdominal or chest wall, intra-abdominally, or in the extremities (37–50% abdominal).[1–3] Despite their benign nature, desmoid tumors can behave aggressively, causing considerable morbidity, with high rates of local recurrence despite wide excisions (9–27%).[4–8] Age younger than 37 years, size >7 cm, R2 resection, and location on extremities, trunk, head and neck, or buttocks were associated with significantly worse progression-free survival (PFS).[9] Desmoid tumors arising in the abdominal wall experienced the highest rates of long-term local recurrence-free survival of 90% at 5 years.[10] There is a well-established association between desmoid fibromatosis and Gardner syndrome; patients with germline mutations in APC exhibit an approximately 850-fold increased risk of developing desmoid tumors.[3] The large majority of desmoids develop spontaneously and are most frequently driven by somatic mutations in *CTNNB1* (β-catenin).[11] The Notch pathway was also found to be activated in desmoid

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cell lines, along with higher expression of HES1 in desmoid tissue, compared with dermal scar tissue.[12,13]

Historically, the mainstay of treatment of desmoid tumors has been wide local surgical resection, although this has led to substantial morbidity in many patients. Increasingly, more conservative approaches with surveillance alone have been shown to be safe and effective for select patients, although many will recur or progress.[6,8,14] Many systemic therapies exhibit antitumor activity, including tamoxifen/sulindac, imatinib, sorafenib, vinblastine/methotrexate, liposomal doxorubicin, and, more recently, a gamma secretase inhibitor (GSI).[15–22]

Inhibition of gamma secretase has been an active area of study since it showed clinical activity in patients with desmoid tumors.[16,21–26] Gamma secretase is an integral membrane protein that cleaves multiple different transmembrane protein complexes, including Notch, E-cadherin, amyloid precursor protein, and others. The mechanism of action for GSIs in desmoid tumors is still not clear, but some cooperativity between WNT pathway activation and active NOTCH signaling may exist. PF-03084014 is a noncompetitive, reversible, targeted agent that selectively inhibits gamma secretase. Herein, we present the long-term follow-up of desmoid patients included in the phase I, dose-escalation study for PF-03084014 at the University of Colorado Comprehensive Cancer Center that was previously reported in 2015.[21]

METHODS

Study Design and Patient Selection

We retrospectively analyzed the medical records of desmoid fibromatosis patients enrolled in a multicenter, open-label, phase I study of PF-03084014 at the University of Colorado Comprehensive Cancer Center between December 2009 and December 2016.[21] Patients were enrolled between December 2009 and March 2012. Radiological assessments were made according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0, WHO bidimensional response criteria, computed tomography (CT) density, and magnetic resonance imaging (MRI) enhancement ratio (MER) in both T1 post-contrast and T2 pre-contrast fat-saturated images. The phase I study was supported by Pfizer Inc. and registered at ClinicalTrials.gov (ID: NCT00878189).

Treatment

PF-03084014 was administered orally at doses ranging from 20 to 330 mg twice daily, continuously, per 21-day cycle. Two expansion cohorts were treated at doses of 220 mg twice daily and 150 mg twice daily to estimate the maximum tolerated dose and select the recommended phase II dose (RP2D). Seven patients with desmoid tumors received PF-03084014 at different starting dose levels, including 80 mg (n = 2), 100 mg (n = 1), 150 mg (n = 2), 220 mg (n = 1), and 330 mg (n = 1) administered orally twice daily. Study drug administration was continued until disease progression, unacceptable toxicity, patient preference, a treatment delay of >2 weeks, or more than two dose reductions without clinical benefit.

Assessments

Patient safety data have been reported previously.[21] Tumors were assessed via CT or MRI scans within 4 weeks of study entry, at the beginning of cycle 3, and every two cycles through 9 cycles, then as clinically indicated. For this article, with informed consent and Institutional Review Board approval, we collected long-term follow-up data and tumor measurements. The initial protocol utilized RECIST 1.0 to determine clinical progression. Since there is no documentation of PFS for therapies rendered prior to this study, we have inferred that the initiation of a new therapy signifies that the patient has had recurrence or progression of disease, thus utilizing the term clinical benefit (CB) as a surrogate outcome for PFS or time to progression (TTP). This value is calculated as the difference between the start of therapy from the next therapy start date.

Additional post hoc analysis was performed using WHO response criteria, changes in CT tumor density, and changes in MER. For CT scans, tumor density was measured using a freehand region of interest (ROI) drawn around the largest axial cross-sectional area of the tumor in Hounsfield units (HUs). MRI enhancement was calculated by drawing a freehand ROI around the largest, most reproducible cross-sectional area of the tumor to obtain the tumor enhancement. An ROI was drawn on the same image slice of an adjacent muscle group, and this same muscle group was used for every subsequent scan to maintain consistency. The quotient of tumor enhancement divided by muscle enhancement represents the MER. This ratio was taken using T1 post-contrast and/or T2 pre-contrast fat-saturated images, as available. Tumor density and MER measurements were performed utilizing Philips Intellispace PACS Enterprise Version 4.4.516.42. Statistical methods included the paired t-test and unpaired t-test assuming unequal variances with a two-sided type 1 error rate of 0.05.

RESULTS

Treatment and Safety

Seven patients with desmoid tumor were treated with PF-03084014 for 14.7–84.2 months, with a mean duration of treatment of 49.5 months (95% confidence interval [CI] 28.4–70.6). Baseline characteristics are summarized in electronic supplementary Table 1. Based on the published phase I trial data of 64 treated patients with multiple tumor types, the side effect profile was tolerable, with adverse events that were reversible with dose reduction and/or termination of drug.[21] The most common side effects included diarrhea (55%), nausea (38%), fatigue (30%), hypophosphatemia (27%), vomiting (23%), and rash (20%). Only one desmoid patient required dose reductions from 330 mg twice daily to 130 mg twice daily for grade 3 arthralgias and remained on study for 163 additional weeks.

Efficacy

Five of seven patients (71.4%, 95% CI 29.0–96.3%) achieved RECIST partial responses (PRs), with a mean time to response (TTR) of 11.9 months (95% CI 2.5–21.4 months) and median TTR of 9.9 months (95% CI 2.9–30.4 months). Every desmoid patient at this institution experienced dramatic, sustained symptomatic relief (decreased tumor pain and/or increased mobility), usually within weeks of starting on therapy, often preceding radiographic changes by months. Median PFS has not been reached (electronic supplementary Fig. 1). All patients who achieved a PR continue to maintain durations of response (DOR) between 47.9 and 73.6+ months, with median DOR not reached (range 1.7+ to 69.2+ months). As of 30 December 2016, four patients stopped treatment and continue off therapy, free of progression between 11 and 53+ months. Two patients remain on treatment in an extension protocol (NCT02955446), both maintaining PRs with CB of 84+ months and DOR of 54+ and 74+ months. Figure 1 shows the spider plot with change in target tumor burden using RECIST 1.0 criteria. Only one of seven patients (14.3%) has progressed clinically since starting PF-03084014. The only patient with clinical progression received PF-03084014 (220 mg twice daily) for 15.2 months (■) and exhibited significant clinical improvement during therapy. PF-03084014 exhibits long-term efficacy, even at lower doses of 80 mg twice daily (Fig. 1, ▲).

Patient 7 achieved PFS of more than 42 months on therapy, with a maximum 17% decrease in tumor size, after which she withdrew consent in the absence of progression. Figure 2a–c shows early and sustained decreases in levels of T2 MRI enhancement despite a marginal diminution in size. Pre- and post-treatment biopsies show a dramatic pathologic response. The pre-treatment specimen (Fig. 2d) exhibits a higher degree of cellularity, with more plump, active-appearing tumor cells, many with open chromatin and distinct nucleoli. The extracellular matrix is less densely collagenous. In the post-treatment specimen (Fig. 2e), the tumor appears less cellular, with a more densely collagenous background, while the cells appear more quiescent, with small, attenuated nuclei. This patient remains off therapy with no evidence of clinical or radiographic progression for over 15.9 months. The only patient with progression has Gardner's syndrome (germline APC mutation); however, patients 2 and 4 also have Gardner's syndrome (Fig. 1, orange lines) and had excellent and prolonged responses to therapy. Despite being taken off study due to a protocol violation at week 63, patient 4 achieved a dramatic PR and remains free of progression off therapy for 53+ months.

Figure 3a illustrates the chronologic efficacy of each prior therapy in these patients. Patients were treated with between one and six lines of therapy from their time of diagnosis. Figure 3b shows the CB in weeks for each regimen. Mean CB was 63.8+ months (95% CI 46.4–81.2, $n = 7$) for the GSI compared with 12.8 months (95% CI 3.3–22.3, $n = 14$) for all other interventions, including surgical resections ($p < 0.001$). Most notable is the prolonged duration of PFS in those patients who are no longer being actively treated with the GSI (yellow bars). The horizontal arrows indicate that the patient is still free of progression and has not yet started any other therapy. Patients who stopped therapy prior to progression received drug between 42.1 and 53.9 months and remain free of progression off therapy. Three patients withdrew from the study due to patient choice.

Optimal Endpoints in Desmoid Tumor Trials

There is consensus among desmoid experts that RECIST may not be the most effective criteria for evaluating efficacy in desmoid tumor trials. It is becoming increasingly recognized that other imaging characteristics may act as a useful surrogate for response.[27,28] Figure 4 shows how RECIST as an endpoint, using only the single longest diameter, may not fully capture the tumor response. Patient 4 (pictured) was treated for 63 weeks and was removed from the study due to a violation. The depth of response at week 63 is captured more evidently using bidimensional WHO criteria (−80%) versus RECIST (−31%).

To further explore different imaging modalities, we analyzed the response curves using spider plots for each patient, measuring their response with RECIST criteria, WHO criteria, MER using T1-weighted post-contrast images and T2-weighted pre-contrast fat-saturated images,

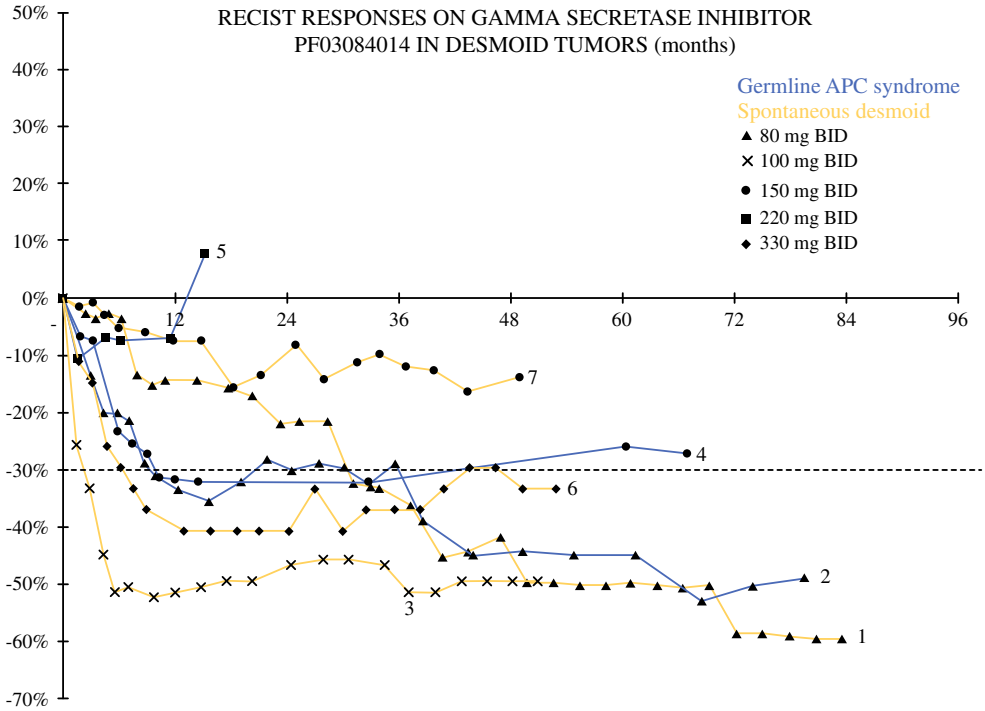


FIG. 1 RECIST spider plots. Spider plot using RECIST criteria measurements. Yellow lines represent patients with spontaneous desmoid tumors, while blue lines represent patients with Gardner's syndrome. The shape of each point coincides with the initial dose during the study: triangle = 80 mg twice daily, × = 100 mg twice daily, circle = 150 mg twice daily, square = 220 mg twice daily, diamond = 330 mg twice daily. Numbers on the graph indicate the patient number. RECIST Response Evaluation Criteria in Solid Tumors, BID twice daily

or CT in HUs (Fig. 5). The mean TTR for both RECIST and WHO criteria were similar, i.e. 11.9 months (95% CI −1.7 to 25.1) versus 13.5 months (95% CI −3.1 to 30.1), respectively ($n = 5$, $p = 0.54$). Using an arbitrary cut-off of 30% reduction in the MER as a response point, dramatic early changes in MER correlated closely with eventual RECIST and WHO response outcomes. The decrease in MER also correlates with pathologic response, even in the absence of RECIST or WHO response, as shown in patient 7 (Figs. 2, 5). The mean TTR was 3.5 months (95% CI 1.1–5.9) for T1-weighted imaging and 1.6 months (95% CI 1.0–2.2) for T2-weighted MRI imaging ($p = 0.07$, $n = 3$). The lack of sufficient patient numbers limit their statistical significance, although the trend on the spider plots favors T2-weighted imaging. With only three patients undergoing MR surveillance having responses, TTR of T2 MER, while not significantly shorter than RECIST (1.6 months vs. 11.9 months, $p = 0.099$), does appear clinically to be an early marker of response. Unexpectedly, on CT evaluation, an increase in density measured by HUs appears to correlate with response to therapy. Mechanistically, this may be related to the decreased cellularity and increased fibrosis in the tumors as they respond. CT changes during fibrosis have been noted in pancreatic neuroendocrine tumors, with more fibrotic-appearing tumors having increased HUs in the unenhanced and portal venous phases.[29] Increased HUs have also been used to detect levels of liver fibrosis using CT scans.[30] Again, using an arbitrary increase of 20% in HUs to suggest early response, the mean TTR for CT density was 3.7 months (95% CI −1.8 to 9.2, $n = 3$), which was not significantly different when compared with the mean TTR of 11.9 months for RECIST criteria (95% CI −1.7 to 25.1, $n = 5$, $p = 0.16$). Changes of tumor density using CT HUs, and enhancement changes using MER, are not prospectively validated approaches, but changes in MER have been shown to correlate closely with desmoid response.[27,28]

DISCUSSION

This retrospective analysis from a dose-escalation trial of PF-03084014 displays excellent clinical efficacy in desmoid tumors, with a RECIST response rate of 71.4%. PF-03084014 is active in a broad dose range, with doses as low as 80 mg twice daily (RP2D is 150 mg twice daily) exhibiting long-term efficacy and a tolerable side

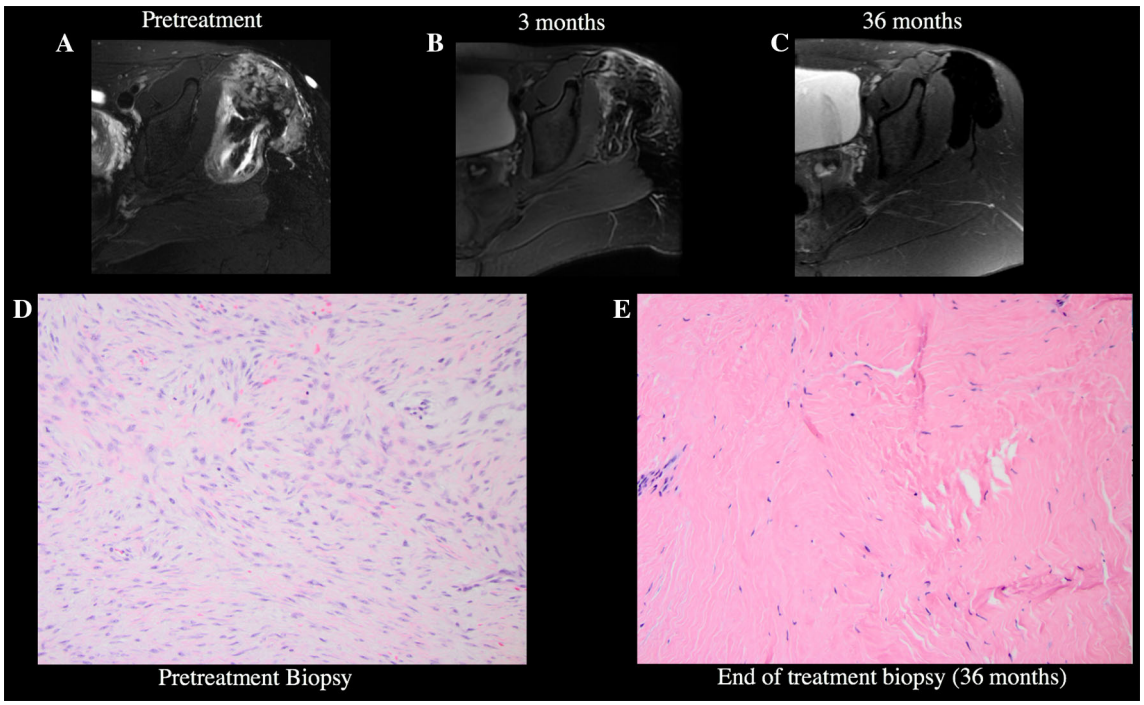
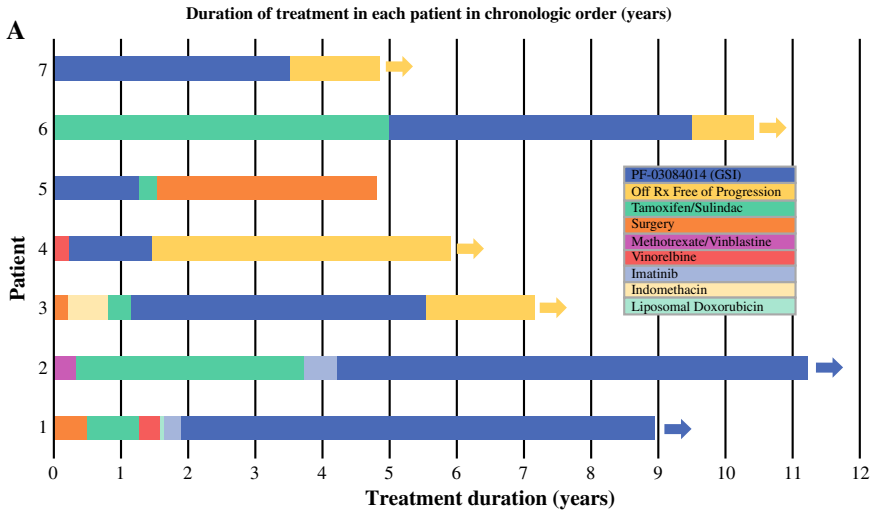


FIG. 2 Response on MR enhancement and pathology. Patient 7 changes in MR enhancement of left hip mass at (**a**) pretreatment, (**b**) 3 months after the start of PF-03084014, and (**c**) at 36 months. Biopsy of the desmoid tumor (**d**) prior to initiating therapy with PF-3084014 and (**e**) just prior to coming off study due to patient preference. *MR* magnetic resonance

effect profile, and with many patients garnering significant benefits to tumor-related pain and morbidity. Recently, Kummar et. al. published their results of a phase II, single-institution study of PF-03084014 administered at 150 mg twice daily in desmoid tumors.[22] PF-03084014 demonstrated excellent disease control, with 0 of 17 patients progressing and a 29% PR rate. Examination of their data indicates that 7 of 17 patients stopped treatment within 18 months without progression, 6 of whom (85%) withdrew from the study due to patient choice. Many of these patients had a reduction in their tumor size and may have stopped therapy prior to achieving a PR. Early withdrawals and differences in the length of follow-up on this current study may help explain the notable disparity in response rates in our data compared with the data from Dr. Kummar.

There are considerable limitations to the findings in this clinical trial, stemming from being a phase I, dose-escalation study with no confirmation of radiographic progression required prior to entry. Additionally, the clinical symptom benefits were not objectively characterized with a patient-reported outcomes assessment. However, despite lack of prior progression being documented in all patients, the overall response rate remains encouraging. Of note, the mean CB was 63.8+ months, while the mean duration of therapy was 49.5 months. The indolent nature of desmoid tumors may play a part in this disparity, but the CB achieved by the drug beyond stoppage of therapy may inform clinical trial design to assess whether continuous therapy is truly necessary beyond documented response or beyond a certain time point. The variable behavior of desmoid tumors, especially their predilection for occasionally resolving spontaneously, makes the robust study of these rare tumors more difficult and will optimally require a randomized study design. While these tumors cause high levels of morbidity, their low mortality rate renders overall survival benefit relatively meaningless. Additionally, the slow response via size-related criteria increase the challenge of collecting efficacy data in a timely fashion. Further study of these tumors should include a composite endpoint using both size criteria (WHO > RECIST) as well as MER. While MER may be robust in detecting early response, it may be less helpful in detecting early progression in the absence of size increase. If these data can be confirmed in a randomized study, early upfront therapy followed by possible resection of symptomatic, quiescent tumor may become a new standard of care. PF-03084014 represents a very promising, novel systemic therapy for this rare subset of often highly morbid tumors.

A



B

	Regimen / Clinical Benefit in Weeks					
Patient# - dose	1st regimen	2nd regimen	3rd regimen	4th regimen	5th regimen	6th regimen
7 - 150mg BID	GSI (183 weeks)	Off therapy w/o progression (69 weeks)				
6 - 130mg BID	Tam/Sulindac (260 weeks)	GSI (234 weeks)	Off therapy w/o progression (48 weeks)			
5 - 220mg BID	GSI (66 weeks)	Tam/sulindac (14 weeks)	Surgery (170 weeks)			
4 - 150mg BID	Vinorelbine (12 weeks)	GSI (64 weeks)	Off therapy w/o progression (231 weeks)			
3 - 100mg BID	Surgery (12 weeks)	Indomethacin (30 weeks)	Tam/sulindac (17 weeks)	GSI (229 weeks)	Off therapy w/o progression (84 weeks)	
2 - 80mg BID	MTX/Vinblastine (17 weeks)	Tam/sulindac (176 weeks)	Imatinib (25 weeks)	GSI (365 weeks)		
1 - 80mg BID	Surgery (26 weeks)	Tam/sulindac (39 weeks)	Vinorelbine (17 weeks)	Liposomal Doxorubicin (3 weeks)	Imatinib (13 weeks)	GSI (366 weeks)

FIG. 3 Chronologic clinical benefit. The bar graph shows the duration of clinical benefit for all therapies received since the time of diagnosis. This clinical benefit is calculated as time to initiating intervention to time of the start of another intervention. The blue bars represent active treatment with PF-03084014 (GSI), while the yellow bars represent time off treatment with PF-03084014 and without any further intervention. Arrows on the right indicate patients who are still free of a new intervention, either on (blue) or off (yellow) therapy. The table displays clinical benefit in weeks of each therapy and the color-coded regimen used. *GSI* gamma secretase inhibitor, *BID* twice daily, *MTX* methotrexate, *Tam* tamoxifen

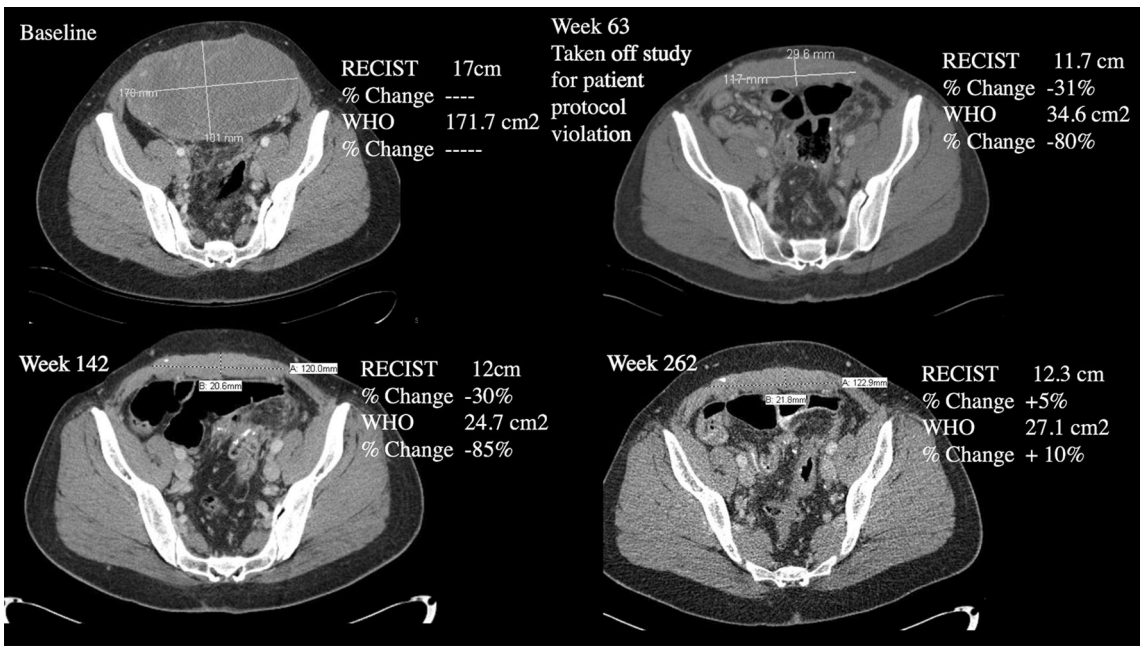
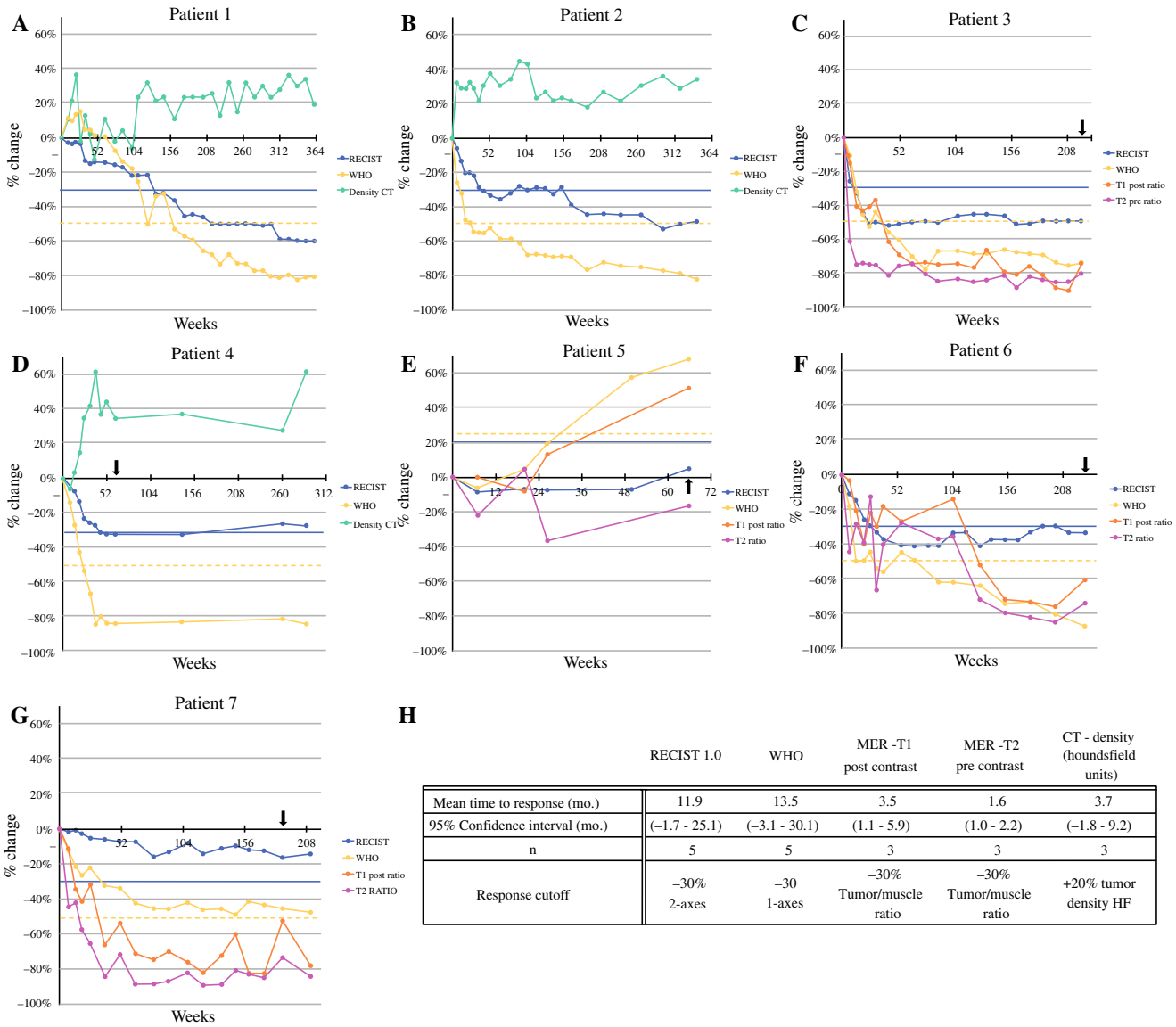


FIG. 4 WHO versus RECIST response. Patient 4 (+Gardener's syndrome): CT scans shown at baseline, and 63, 142, and 262 weeks. The patient was removed from the study at week 63 for a protocol violation but continues to be followed with scans and remains free of progression for over 4 years. Measurements show differences in best overall response using RECIST (−31%) versus WHO criteria (−85%). *WHO* World Health Organization, *RECIST* Response Evaluation Criteria in Solid Tumors, *CT* computed tomography



H

	RECIST 1.0	WHO	MER -T1 post contrast	MER -T2 pre contrast	CT - density (houndsfield units)
Mean time to response (mo.)	11.9	13.5	3.5	1.6	3.7
95% Confidence interval (mo.)	(–1.7 - 25.1)	(–3.1 - 30.1)	(1.1 - 5.9)	(1.0 - 2.2)	(–1.8 - 9.2)
n	5	5	3	3	3
Response cutoff	–30% 2-axes	–30 1-axes	–30% Tumor/muscle ratio	–30% Tumor/muscle ratio	+20% tumor density HF

FIG. 5 Different response endpoints. Spider plots tracking change from baseline of RECIST response (blue), WHO response (yellow), CT density change in HUs (green), T1 post-contrast MER (orange), and T2 pre-contrast (purple). Black arrows mark the time of discontinuation of PF-03084014. The hashed lines indicate partial response for WHO (−50%, yellow) and RECIST (−20%, blue). The table lists time to response for all the listed modalities using the cut-off for MER (−30%) and CT density (+20%). *WHO* World Health Organization, *RECIST* Response Evaluation Criteria in Solid Tumors, *CT* computed tomography, *HUs* Hounsfield units, *MER* magnetic resonance imaging enhancement ratio

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DISCLOSURE Victor Manuel Villalobos, Francis Hall, Antonio Jimeno, Lia Gore, Kenneth Kern, Rossano Cesari, Bo Huang, Jeffrey T. Schowinsky, Patrick Judson Blatchford, Brianna Hoffner, Anthony Elias, Wells Messersmith have nothing disclosures to declare.

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