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A Phase I, Dose-Finding Study in Patients with Advanced Solid Malignancies of the Oral γ-Secretase Inhibitor PF-03084014

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Abstract

Purpose: To estimate the maximum tolerated dose (MTD) for continuous oral administration of the γ-secretase inhibitor PF-03084014, determine the recommended phase II dose (RP2D), and evaluate safety and preliminary activity in patients with advanced solid tumors.

Experimental Design: This open-label, phase I study consisted of a dose-finding portion based on a 3+3 design, followed by an expansion cohort. PF-03084014 was administered orally, twice daily (BID) for 21 continuous days. Tested doses ranged from 20 to 330 mg BID. In the expansion cohort, patients were to receive the estimated MTD or a lower dose of PF-03084014.

Results: A total of 64 patients received treatment. The MTD was estimated to be 220 mg BID. The RP2D was determined to be 150 mg BID, based on the better safety profile versus the 220-mg BID dose, given comparable NOTCH-related target inhibition. The most common treatment-related adverse events were diarrhea, nausea, fatigue, hypophosphatemia, vomiting, rash, and decreased appetite, which were generally mild to moderate in severity. One patient with advanced thyroid cancer had a complete response, and five of seven response-evaluable patients with desmoid tumor achieved a partial response (71.4% objective response rate). Tumor responses were mostly durable, ranging from 1.74+ to 24+ months. PF-03084014 demonstrated a generally dose-dependent pharmacokinetic profile at doses ranging from 20 to 330 mg BID. Consistent downmodulation of NOTCH-related *HES4* gene expression was observed in peripheral blood from all evaluable patients.

Conclusion: Further development of PF-03084014 for the treatment of patients with advanced solid tumors is warranted and currently under evaluation. *Clin Cancer Res; 21(1); 60–67. ©2014 AACR.*

See related commentary by Hughes et al., p. 7

Introduction

Signaling through the NOTCH pathway facilitates tumor growth and dissemination, by acting on multiple tumor-associated processes, including cancer cell proliferation, survival, and differentiation, as well as on endothelial cell function and angiogenesis (1–3). Activating mutations or translocations in *NOTCH* family members have been identified in both hematologic malignancies (e.g., T-cell acute lymphoblastic leukemia) and in solid tumors (e.g., breast cancer; refs. 4, 5). NOTCH may also play a tumor-suppressive role in certain tumors, such as in squamous cancers of the oropharyngeal tract (6–8).

The NOTCH family consists of four receptors (NOTCH 1-4), which interact with the delta-like and JAGGED families of ligands that are normally bound to the cell membrane. Upon ligand binding to the NOTCH receptor, the enzyme complex γ-secretase mediates proteolytic cleavage of the NOTCH intracellular domain (NICD). Subsequently, after migration into the nucleus, the NICD modulates gene expression of a number of target genes (1, 2, 9).

γ-secretase is a multicomponent enzyme of the intramembrane cleaving protease family (I-CLiPs). Inhibition of γ-secretase represents an attractive therapeutic target expected to result in inhibition of the aberrant NOTCH signaling noted in several cancer types and, consequently, of the associated downstream tumor-related processes (10–13). γ-Secretase inhibitors were also developed for the treatment of Alzheimer disease, although results from randomized trials did not show benefit (14, 15). In one of these studies evaluating the γ-secretase inhibitor LY450139 in patients with Alzheimer disease, NOTCH inhibition was associated with the occurrence of squamous-cell cancers of the skin in elderly patients (15). These findings further indicate a potential tumor-suppressive role for NOTCH signaling in the skin, mediated by induction of terminal differentiation in keratinocytes (16).

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Translational Relevance

NOTCH pathway signaling drives multiple cancer-related processes in a variety of hematologic malignancies and solid tumor types, and it can be disrupted by γ-secretase inhibition, which prevents proteolytic cleavage of the NOTCH intracellular domain and its subsequent nuclear translocation. This first-in-human, phase I dose-finding study established the tolerability, maximum tolerated dose (MTD), recommended phase II dose (RP2D), and pharmacokinetic profile of PF-03084014, a novel, selective, reversible inhibitor of γ-secretase, in patients with advanced solid tumors. At the MTD and RP2D, there was consistent reduction in *HES4* expression in peripheral blood, indicating target inhibition. Complete or partial responses were observed in thyroid cancer, leiomyosarcoma, and in five of seven patients with desmoid tumor. These results lay the groundwork for further evaluation of PF-03084014 in desmoid tumor, a disease in which NOTCH signaling has been implicated, and in other advanced solid malignancies.

PF-03084014 is a selective, noncompetitive, reversible inhibitor of γ-secretase that has demonstrated substantial antitumor activity in multiple, NOTCH-dependent, preclinical models at well-tolerated doses (17–20). Single- and multiple-dose administration of PF-03084014 was deemed to be safe and well tolerated at the tested dose levels, based on the results of phase I studies conducted in healthy volunteers.

This first-in-patient, dose-finding study estimated the maximum tolerated dose (MTD) and determined the recommended phase II dose (RP2D) for continuous, oral administration of PF-03084014 in patients with advanced solid tumors, and evaluated safety and preliminary antitumor activity in this patient population.

Patients and Methods

Study design and patient selection

This multicenter, open-label phase I study of PF-03084014 consisted of an initial dose-finding portion, followed by an expansion cohort. For inclusion in the study, patients had to have advanced solid tumors resistant to standard therapy or for which no therapy was available; measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) was required for patients enrolled in the expansion cohort. Patients were excluded from the study if they had received prior treatment with a γ-secretase inhibitor or an anti-NOTCH receptor antibody, had central nervous system metastases or a corrected QT (QTc) interval >470 msec, and/or had current use or anticipated need for treatment with moderate/strong cytochrome P450 (CYP) 3A4 inhibitors or strong CYP3A4 inducers.

Approval was obtained from the ethics committees at the participating institutions and regulatory authorities. Patients gave written informed consent. The study followed the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study was supported by Pfizer Inc and registered at ClinicalTrials.gov (ID: NCT00878189).

The MTD was estimated using the standard 3+3 method. Dose-limiting toxicities (DLT) included all of the following adverse events potentially related to treatment with PF-03084014: (i) grade ≥3 maximally treated nonhematologic adverse events, (ii) treatment delays ≥7 days due to treatment-related adverse events, (iii) inability to deliver at least 80% of planned dose in cycle 1 due to adverse events, (iv) grade 4 neutropenia lasting >7 days, (v) febrile neutropenia, (vi) grade ≥3 neutropenic infection, and (vii) grade ≥3 thrombocytopenia with bleeding. The RP2D was determined taking into account the estimated MTD, the overall treatment tolerability, and the pharmacokinetic and pharmacodynamic profiles. Secondary endpoints included safety and tolerability of PF-03084014, single-dose and multiple-dose pharmacokinetics (including the effect of food), pharmacodynamics, antitumor activity, and QTc interval.

Treatment

Oral PF-03084014 was administered at a starting dose of 20 mg twice daily (BID) for 21 continuous days. In cycle 1 only, patients received 21 days of continuous BID dosing followed by 7 days off treatment to allow for pharmacokinetic assessments; the afternoon dose was not administered on day 21 of cycle 21. The initial 20-mg BID dose was escalated to 40, 80, 100, 130, 150, 220, and 330 mg BID. In the expansion cohort, patients were to receive the MTD or a lower dose of PF-03084014. Study drug administration was continued until disease progression, unacceptable toxicity, a treatment delay of >2 weeks or more than two dose-level reductions in the absence of clinical benefit. A combination with dexamethasone, originally planned to help control potential gastrointestinal toxicity, was not evaluated, as diarrhea and other gastrointestinal adverse events were manageable at the tested dose levels.

Assessments

Safety.

Patients were assessed for safety at baseline, on days 1, 8, 15, and 21 of cycle 1, on days 1 and 15 of cycles 2 to 8, on day 1 of the subsequent cycles, and at the end of treatment. Adverse events were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 3.0).

Antitumor activity.

Tumor assessments were performed by CT or MRI within 4 weeks of study entry, at the beginning of cycle 3, and every 2 cycles thereafter. After cycle 9, patients were evaluated for treatment efficacy as clinically indicated, until disease progression.

Pharmacokinetics.

Blood samples for pharmacokinetic assessments were collected on days 1, 8, 15, 18, 20, and 21 of cycle 1; on days 1 and 15 of cycles 2 to 8; and at the end of treatment. Samples were analyzed for PF-03084014 serum concentrations using a validated analytical method. Additional blood samples were collected on day 1 of cycle 2 from a subset of patients treated with PF-03084014 for food-effect pharmacokinetic analyses.

Pharmacodynamics.

Blood samples for pharmacodynamic analyses were collected at baseline and on days 8 and 21 of cycle 1; tumor biopsies were to

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be performed at baseline and on day 21 of cycle 1. Biopsies were optional in the dose-finding portion of the study and mandatory in the expansion cohort, with exceptions granted by the sponsor. The screening biopsy could be replaced by an archival biopsy in the dose-finding phase. Gene expression analyses were performed by the Pfizer Clinical Pharmacogenomics Laboratory using custom TaqMan low-density arrays run on the Applied Biosystems 7900HT Fast Real-Time PCR System (Life Technologies). Data were analyzed using the Applied Biosystems DataAssist 3.0 program (Life Technologies).

Sample size and statistical analysis

At least 3 and up to 6 DLT-evaluable patients were to be enrolled at each tested PF-03084014 dose level, for evaluation of treatment effects in the dose-finding part of the study following the 3+3 method. An estimated 22 additional patients with solid tumors were to be included in the expansion cohort to confirm the MTD and determine the RP2D. Descriptive statistics were used throughout the study for continuous, categorical, and time-to-event variables. A two-sided 95% confidence interval (CI) was calculated for the objective response rate (ORR) using an exact method. Time to progression, duration of response, time to response, and PFS were analyzed using the Kaplan–Meier method, and the 95% CI of median calculated using the Brookmeyer–Crowley method. Results of pharmacodynamic evaluations were analyzed using descriptive statistics.

Results

Patients

A total of 64 patients with solid tumors were enrolled and received study treatment, including 41 in the dose-finding portion of the study. Patient characteristics are presented in Table 1. Nine (14%) patients had desmoid tumor, with median disease duration of 4.1 years from histopathologic diagnosis. Other tumor types diagnosed in at least two patients each were breast, colon, colorectal, lung, pancreatic, and thyroid cancer; hepatic malignancies; and leiomyosarcoma of the endometrium. The majority of patients had advanced stage disease (92.2% had stage IV). Because of the lack of a general consensus on desmoid tumor staging, extent of disease in desmoid tumor patients was based on tumor assessments at study sites.

Table 1. Patient baseline demographics and clinical characteristics

Parameter	Patients ($N = 64$), n (%)[a]
Median age, y (range)	61.0 (23–80)
Male:female ratio	31:33
Race	
White	57 (89.1)
Black	4 (6.3)
Asian	1 (1.6)
Other	2 (3.1)
ECOG PS	
0	20 (31.3)
1	44 (68.8)
≥2	0
Measurable disease	
Yes	60 (93.8)
No	3 (4.7)
Not reported	1 (1.6)
Disease stage	
III	2 (3.1)
IV	59 (92.2)
Unknown	3 (4.7)
Primary tumor	
Colon/colorectal cancer	11 (17.0)
Desmoid tumor	9 (14.1)
Breast cancer	7 (10.9)
Thyroid cancer	6 (9.4)
Lung cancer	5 (7.8)
Endometrial leiomyosarcoma	3 (4.7)
Pancreatic cancer	2 (3.1)
Hepatic malignant neoplasm	2 (3.1)
Other	19 (29.7)
Prior surgeries	64 (100)
Prior radiation therapy	
Yes	33 (51.6)
No	30 (46.9)
Unreported	1 (1.6)
Prior systemic therapies	
Yes	60 (93.7)
No	4 (6.3)
Number of systemic regimens	
1	6 (9.6)
2	10 (15.6)
3	9 (14.1)
>3	35 (54.7)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]Except where noted.

Dose-limiting toxicity and MTD

Nine of the 41 patients enrolled in the first part of the study did not meet the prespecified threshold for dose administration (e.g., 80% of planned dose) and were, therefore, not evaluable for DLT. Five of the 32 DLT-evaluable patients experienced DLTs during the dose-finding part of the study: one patient had grade 4 anaphylactic shock at 100 mg BID ($n = 6$), 2 patients had grade 3 diarrhea at 150 mg BID ($n = 6$) and at 220 mg BID ($n = 6$), respectively (Table 2). The grade 4 anaphylactic shock event was considered related to intravenous treatment with morphine for pain control because this adverse event started 25 minutes after morphine administration. However, treatment-related causality could not be excluded because the patient had received the first dose of study drug before intravenous administration of morphine. Of the two DLT-evaluable patients dosed at 330 mg BID, one had grade 3 rash and the other patient was unable to complete 80% of the planned dose due to grade 1 palpitations and grade 1 oropharyngeal pain attributed to PF-03084014 treatment. Thus, the MTD was estimated to be 220 mg BID. Enrollment was expanded to a total of 16 patients in the 220-mg BID group and to a total of 23 patients in the 150-mg BID group (dose-finding plus expansion cohorts) to confirm the MTD and define the RP2D.

Safety

Sixty-two (96.9%) of the 64 patients on study experienced at least one all-cause adverse event and 54 (84.4%) had at least one treatment-related adverse event. The most common treatment-related adverse events were diarrhea (54.7%), nausea (37.5%), fatigue (29.7%), hypophosphatemia (26.6%), vomiting (23.4%), rash (20.3%), and decreased appetite (17.2%); the majority of these adverse events were low grade (Table 3).

Thirty-one (48.4%) patients experienced all-cause grade 3 adverse events, with 23 (35.9%) patients experiencing a treatment-related grade 3 adverse event. The most common treatment-related grade 3 adverse events were hypophosphatemia (23.4%), diarrhea (9.4%), rash (3.1%), and nausea, vomiting,

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Table 2. Dose-limiting toxicities by dose level

Dose level for 21 days, mg BID	Number of DLT-evaluable patients	Number (%) of patients with DLTs	DLTs
20	3	0	None
40	3	0	None
80	3	0	None
100	6	1 (16.7)	Grade 4 anaphylactic shock[a]
130	3	0	None
150	6	1 (16.7)	Grade 3 diarrhea
220	6	1 (16.7)	Grade 3 diarrhea
330	2	2 (100)	Grade 3 rash ($n = 1$) Unable to complete 80% of the planned dose owing to grade 1 palpitations and grade 1 oropharyngeal pain ($n = 1$)

[a]This patient had also received a first dose of intravenous morphine for pain control.

drug hypersensitivity, or hypokalemia (1.6% each). Treatment-related grade 3 adverse events were reported in 62.5% of patients in the 220-mg BID group compared with 34.8% in the 150-mg BID group combining the dose-finding part and the expansion cohort.

Seven (10.9%) patients had all-cause grade 4 adverse events, with only one patient (1.6%) experiencing a grade 4 adverse event deemed to be treatment related (anaphylactic shock, after also receiving an initial dose of morphine). All four on-study deaths were due to disease progression. The mean QTc changes observed in the study were not considered clinically significant and there did not seem to be a dose-dependent effect on the QTc interval.

Treatment exposure

Median treatment duration ranged from 1 to 1,108 days. The mean percentage of the planned dose received by patients ranged from 86.5% (100 mg BID) to 97.6% (80 mg BID), and it was 90.6% for the 150-mg BID and 90.5% for the 220-mg BID dose levels. Dose reductions due to treatment-related adverse events were infrequent and reported in 9 (14.1%) patients at various times on treatment (from cycle 1 to cycle 10). Across dose levels, 5 (7.8%) patients had grade 2 or 3 diarrhea that resolved with dose reduction. Temporary discontinuation occurred in 21 (32.8%) patients, 13 (20.3%) of which were for a treatment-related adverse event. All treatment-related adverse events leading to temporary discontinuation (diarrhea, hypophosphatemia, rash, nausea, vomiting, and fatigue) or dose reduction were grade 1 to 3, and most resolved following temporary discontinuation or dose reduction.

Overall, 7 (10.9%) patients permanently discontinued treatment primarily owing to an adverse event; of these, 4 (6.3%) patients discontinued for a treatment-related adverse event: one each for grade 4 anaphylactic shock (100 mg BID), grade 1 visual impairment (150 mg BID), grade 3 drug hypersensitivity (220 mg BID), and grade 3 rash (330 mg BID). The hypersensitivity reaction (rash associated with chest tightening and shortness of breath) resolved with intravenous steroid therapy after discontinuation of study treatment. Six patients were still on treatment at the data cutoff date (January 2013).

Efficacy

The ORR was 13% (95% CI, 4.9–26.3) among the 46 response-evaluable patients, with one complete response in a patient with thyroid cancer (20-mg BID dose) and five partial responses (2 at 80 mg BID and one each at 150 mg, 220 mg, and 330 mg BID). All 5 patients with partial responses had desmoid tumor, for an ORR of 71.4% (95% CI, 29.0–96.3) among the 7 evaluable patients in this subgroup (Fig. 1 and Supplementary Table S1). Stable disease was noted as best overall response in 14 (30.4%) patients, including 2 patients with desmoid tumor (Supplementary Table S1).

Median duration of response was not reached (range, 1.7+ to 24.2+ months) because of censoring of all 6 responders at data cutoff in January 2013 (Fig. 2). All 5 responders with desmoid tumor had not progressed and were censored at the time of data cutoff; 4 patients were still on study and one discontinued because of noncompliance with study protocol. The patient with thyroid cancer who achieved a complete response was taken off-study for suspected disease recurrence (mediastinal adenopathy), but, upon discontinuation of study drug, the lymphadenopathy resolved and he was progression free radiologically and biochemically (negative thyroglobulin) for 22.77+ months. This patient was censored at last evaluation due to missed tumor assessment. The median time to response for the five responders with desmoid tumor was 8.5 months (95% CI, 2.9–30.4) with significant variability among the different patients.

Among all patients, the median time to progression was 1.6 (95% CI, 1.4–4.2) months, median PFS was 1.6 (95% CI, 1.4–4.2) months, and PFS at 12 months was 29.8% (95% CI, 17.1%–43.7%). Both median time to progression and PFS were 1.6 months in the 150-mg BID group and 1.5 months in the 220-mg BID group.

Table 3. Treatment-related adverse events in ≥5% patients on study

Adverse event	All grades[a] *n* (%)	Grade 3[b] *n* (%)	Grade 4[c] *n* (%)
Diarrhea	35 (54.7)	6 (9.4)	0
Nausea	24 (37.5)	1 (1.6)	0
Fatigue	19 (29.7)	0	0
Hypophosphatemia	17 (26.6)	15 (23.4)	0
Vomiting	15 (23.4)	1 (1.6)	0
Rash[d]	13 (20.3)	2 (3.1)	0
Decreased appetite	11 (17.2)	0	0
Mucosal inflammation	6 (9.4)	0	0
Dry mouth	5 (7.8)	0	0
Headache	5 (7.8)	0	0
Hypokalemia	4 (6.3)	1 (1.6)	0
Pruritus	4 (6.3)	0	0
Dyspepsia	4 (6.3)	0	0

[a]No grade 5 treatment-related adverse events were reported.
[b]One patient experienced grade 3 drug hypersensitivity.
[c]One patient experienced grade 4 anaphylactic shock.
[d]Rash included erythematous rash, maculo-papular rash, macular rash, and pruritic rash.

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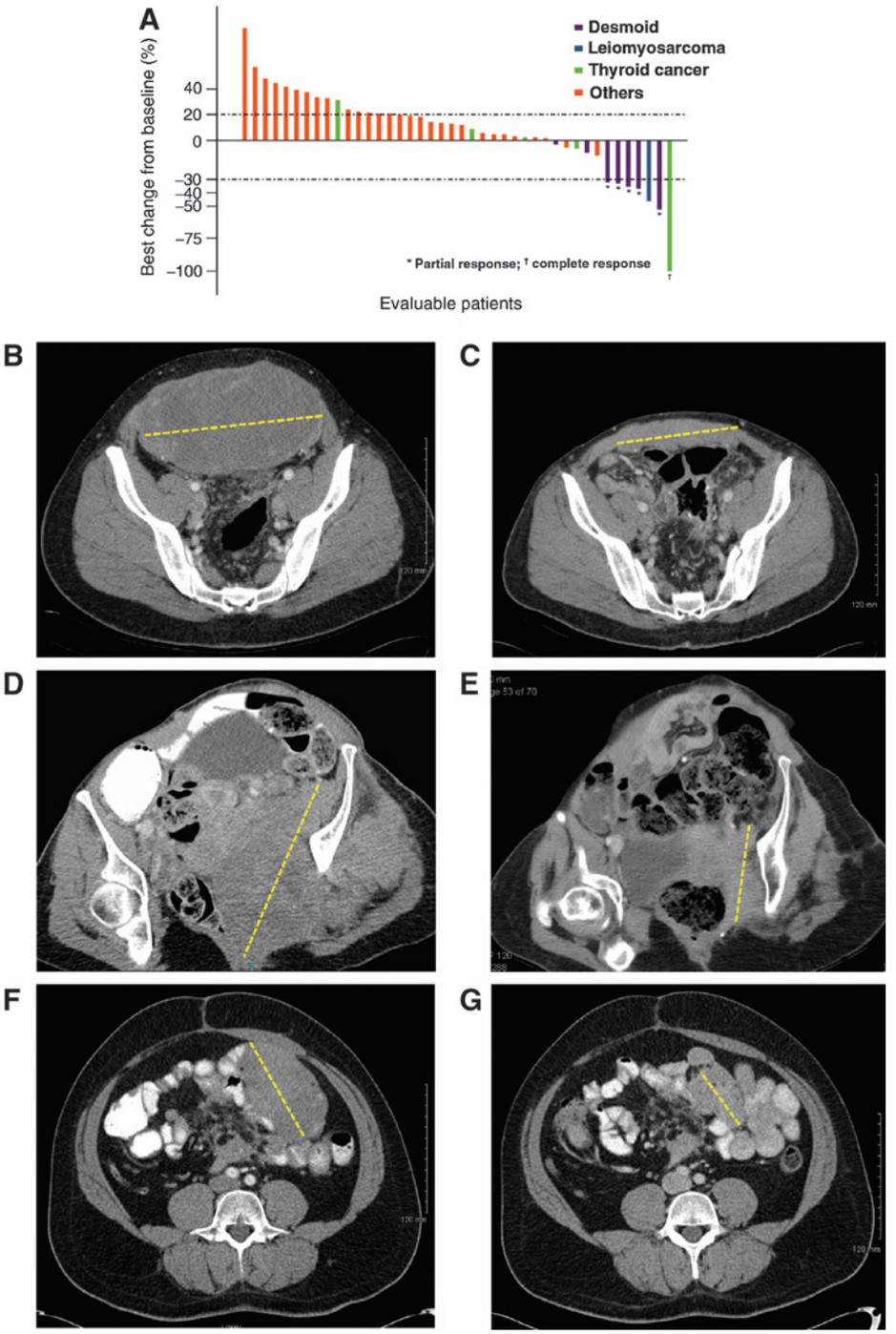

Figure 1.
A, best tumor size change from baseline following treatment with PF-03084014. The partial response observed in the patient with leiomyosarcoma could not be confirmed because of progression at a later tumor assessment. CR, complete response; PR, partial response. B–G, computed tomography images at baseline and following treatment with PF-03084014 in a patient with Gardner syndrome and abdominal desmoid tumor (B, 4/28/2011; C, 7/12/2012), a patient with pelvic desmoid tumor (D, 12/3/2009 and E, 10/24/2013) and a patient with abdominal desmoid tumor (F, 1/13/2010; G, 12/29/2012).

Pharmacokinetics

PF-03084014 was detected in the serum of all patients on day 1 of cycle 1, following oral administration. Median serum concentration–time profiles after single and multiple dosing are presented in Supplementary Fig. S1. Following a single dose, the time to peak plasma concentrations (T_{max}) of PF-03084014 ranged from 1 to 2.5 hours. After multiple dosing to steady state, T_{max} ranged from 1 to 3.7 hours. Steady state was achieved by day 8 of pharmacokinetic assessment, following BID dosing. The apparent volume of distribution was large, indicating extensive tissue distribution for PF-03084014 or low oral bioavailability. The mean terminal half-life was approximately 22 to 40 hours after multiple dosing. Mean exposure for area under the concentration–time curve (AUC_{tau}) and maximum concentration (C_{max}) increased in a generally dose-dependent manner over the dose range of 20 to 330 mg BID, following a single dose or after multiple dosing to steady state. For the food-effect assessment, although variability was observed in both C_{max} and AUC_{tau},

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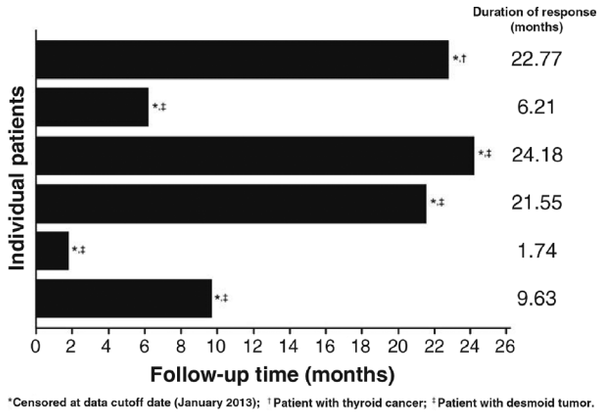

Figure 2.
Duration of response following treatment with PF-03084014 in objective responders with solid malignancies. Bars, individual patients.

overall, the drug exposure seemed to be similar in the fed versus the fasted state.

Pharmacodynamics

Expression analysis of the 28 *NOTCH* pathway-related genes in peripheral blood samples obtained from 11 patients in the 150-mg BID group and 7 patients in the 220-mg BID group demonstrated downregulation in all patients of the Hairy and enhancer of split-4 (*HES4*) gene on days 8 and 21 of treatment cycle 1 (Fig. 3), but not in the other genes analyzed. No consistent changes in NOTCH-related gene expression patterns were identified in the analysis of tumor biopsies, due to the small number of available samples ($n = 5$). Exploratory pharmacokinetic/pharmacodynamic analysis demonstrated that a >70% decrease in peripheral blood expression levels of the NOTCH-related target gene *HES4* was consistently achieved across the 150-mg BID and 220-mg BID dose levels at steady state on day 21 of cycle 1 in 8 of the 9 evaluable patients (Supplementary Fig. S2).

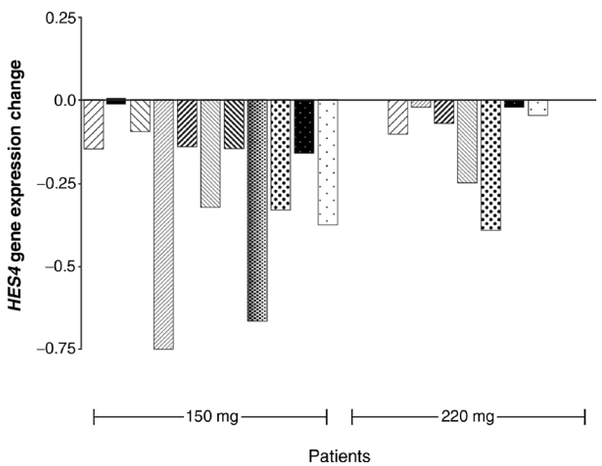

Figure 3.
Downregulation of *HES4* gene expression following treatment with PF-03084014 in patients with solid malignancies. Changes in the *HES4* gene expression ratio at day 8 of cycle 1 versus baseline: bars represent individual patients; dose groups are indicated below the figure. The solid line on the *x*-axis indicates a patient with complete inhibition of *HES4* expression.

Discussion

Evaluation of PF-03084014 in this first-in-patient study demonstrated that this novel, selective γ-secretase inhibitor is generally safe and well tolerated following oral administration at doses equal to or below 150 mg BID. In addition, preliminary evidence of antitumor activity was observed in patients with advanced solid malignancies, including thyroid cancer (complete response), desmoid tumor (partial responses), and endometrial leiomyosarcoma (unconfirmed response).

The estimated MTD for PF-03084014 administration was 220 mg BID. The RP2D was determined to be 150 mg BID, based on the better safety profile observed at this dose level compared with the 220-mg BID dose, given comparable NOTCH-related target inhibition (>70% inhibition at steady state compared with baseline for *HES4* gene expression). Treatment at 220 mg BID was associated with a greater incidence of grade 3 treatment-related adverse events compared with the 150-mg BID dose level, combining the dose-finding part and the expansion cohort (62.5% vs. 34.8%, respectively).

The most common treatment-related adverse events were diarrhea, nausea, fatigue, hypophosphatemia, vomiting, rash, and decreased appetite. They were generally mild to moderate in severity, and led to dose reduction and/or treatment discontinuation in a limited number of cases. Grade 3 diarrhea was generally manageable with anti-diarrheal therapy, dose interruption, or dose reduction. None of the on-study deaths was attributed by the study investigators to treatment with PF-03084014. No formation of squamous cell skin cancer has been observed after treatment with PF-03084014. The observed safety profile seems more favorable than those reported for two other investigational γ-secretase inhibitors, R04929097 and MK-0752, evaluated in phase I studies (21–25). Administration of these agents seemed limited by severe gastrointestinal toxicity (e.g., diarrhea), a finding that has not been observed with PF-03084014 treatment, which was associated with less severe and more manageable diarrhea.

Pharmacokinetic analyses demonstrated a generally dose-proportional exposure to PF-03084014 over the dose range tested, indicating that the exposures were predictable based on the dose administered. Conversely, the unsatisfactory pharmacokinetic properties of R04929097 limited further clinical development of this agent (24). The consistent downmodulation of *HES4* gene expression observed in peripheral blood from all evaluable patients suggests that this gene can be used as a pharmacodynamic marker of pathway activity and supports the use of a tissue surrogate such as blood for pharmacodynamic analyses.

Responses were observed across dose levels from 20 to 330 mg BID. One patient with advanced thyroid cancer achieved a complete response and 5 of 7 response-evaluable patients with desmoid tumor had a partial response (71.4% ORR in this tumor type; 95% CI, 29.0–96.3). The other two patients with desmoid tumor on study had stable disease. Tumor responses were mostly durable in the patients with desmoid tumor, ranging from 1.74+ to 24+ months. The complete response in the patient with thyroid cancer lasted for 22.77+ months.

Although considered benign in the early phase of growth, recurrent desmoid tumors may acquire aggressive features, with substantial local infiltration and disease burden that often mandate multiple surgical resections and the potential for limb loss or

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organ ablation in affected patients. In this setting, a systemic approach to treatment would be of great benefit to patients (26). Single-agent and combination chemotherapy regimens, including doxorubicin, cyclophosphamide, vinblastine, vinorelbine, or methotrexate, have demonstrated >50% response rate in patients with desmoid tumor, although the associated treatment-related toxicities (e.g., neutropenia, infections, and peripheral neuropathy) limit use in this patient population (26, 27).

Recent studies have demonstrated that treatment with targeted agents may have beneficial effects in patients with desmoid tumor. However, as few as approximately 10% to 25% of these patients had an objective response to treatment with the tyrosine kinase inhibitor imatinib (26) or the multiple kinase inhibitor sorafenib (28). Clinical responses to imatinib therapy had a median duration of 11 month in patients with desmoid tumor (29). These findings suggest that the future availability of a novel, oral agent potentially able to induce durable responses in a high proportion of patients (ORR >70% was observed in a small number of patients with desmoid tumor in this study), with a better tolerability compared with single-agent or combination chemotherapy, would represent substantial progress in this therapeutic setting.

Patients with desmoid tumor were enrolled in this study due to the known prevalence of β-catenin mutations in this malignancy, as well as the known cross-talk between the NOTCH and Wnt signaling pathways. In addition, molecular studies in both familial adenomatous polyposis-associated and sporadic desmoid tumors have demonstrated aberrant regulation of the NOTCH pathway. This work focused on desmoid tumor-derived mesenchymal stromal cells, which have been shown to express NOTCH1 and its activation target HES1, as well as the downstream transcriptional repressor BMI-1. In fact, BMI-1–mediated transcriptional repression is relieved by γ-secretase inhibition (30). These studies, therefore, support γ-secretase inhibition as a NOTCH receptor-targeted therapeutic approach in desmoid tumor. Nonetheless, future investigations are needed to fully understand the molecular mechanisms underlying tumor response to PF-03084014 in patients with desmoid tumor and in patients with other responsive malignancies.

In conclusion, PF-03084014, an orally administered γ-secretase inhibitor, was generally safe and well tolerated, and displayed a dose-dependent pharmacokinetic profile. Preliminary evidence of clinical efficacy was demonstrated in patients with solid tumors, as well as in one patient with recurrent acute T-cell lymphoblastic leukemia (treated at 150 mg BID) in a separate T-cell lymphoblastic leukemia/lymphoma cohort (manuscript in preparation). Further development of PF-03084014 for the treatment of patients with advanced solid tumors is ongoing in advanced triple-negative breast cancer (in combination with docetaxel) and in metastatic pancreatic cancer (in combination with gemcitabine and nab-paclitaxel). The National Cancer Institute (Bethesda, MD; NIH) is conducting a study with PF-03084014 as single-agent treatment for patients with desmoid tumor.

Disclosure of Potential Conflicts of Interest

W.A. Messersmith reports receiving commercial research support from Pfizer. B. Huang, M. Naveed Shaik, R. Cesari, X. Zheng, J. M. Reynolds, P.A. English, K.R. McLachlan, and K.A. Kern were full-time employees of Pfizer Inc. during the conduct of this study. P.A. English reports ownership interests (including patents) in Pfizer. No potential conflicts of interest were disclosed by the other authors.

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