Phase II Trial of the γ-secretase Inhibitor Nirogacestat (PF-03084014) in Adults with Desmoid Tumors/Aggressive Fibromatosis

Abbreviated Title: PhII PF-03084014 Desmoids

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Investigational Agent:	Nirogacestat (PF-03084014)
IND Number:	119,796
Sponsor:	Center for Cancer Research, National Cancer Institute

Roles: [A]obtains information by intervening or interacting with living individuals for research purposes; [B]obtains identifiable private information about living individuals; [C]obtains the voluntary informed consent of individuals to be subjects; [D]makes decisions about subject eligibility; [E]studies, interprets, or analyzes identifiable private information or data/specimens for research purposes

PRÉCIS

Background:

- Desmoid tumors (also known as aggressive fibromatosis), are rare, locally invasive, slow-growing soft-tissue tumors. The disease can be either asymptomatic or be associated with severe loss of organ function and significant morbidity.
- Treatment with the selective small-molecule γ-secretase inhibitor PF-03084014 caused significant tumor shrinkage in patients with unresectable desmoid tumors in an early-phase clinical trial
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- The Notch pathway is a key regulator of cell differentiation, proliferation and apoptosis; aberrant signaling via the Notch pathway is associated with carcinogenesis.

Objectives:

- *Primary:* Determine the response rate (CR+PR) of Nirogacestat in patients with desmoid tumors/aggressive fibromatosis
- *Exploratory:* Assess symptom measures at baseline and on study; perform genotyping for germline and somatic mutations in *APC* and *CTNNB1* genes; correlate clinical response to therapy with genotyping data; and assess modulation of the Notch pathway by evaluating notch response genes in tumor biopsies at baseline and after drug administration

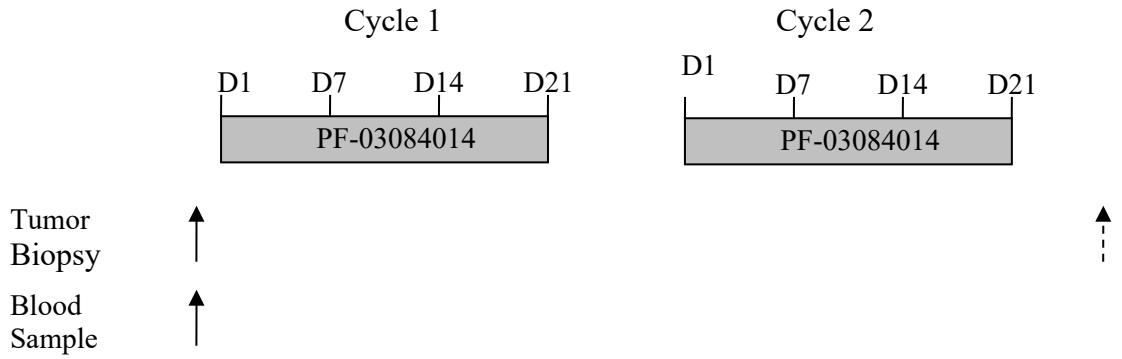
Eligibility:

- Age ≥18; histologically confirmed desmoid tumor not amenable to curative resection or definitive radiation therapy that has progressed after receiving at least one line of standard treatment; adequate organ function
- Willingness to provide blood samples and 10 unstained slides or a tumor block for genetic research studies

Study Design:

- This is an open-label Phase II trial of Nirogacestat; study drug will be administered orally at 150 mg twice a day in 21-day cycles
- Optional tumor biopsies for research purposes will be performed at baseline prior to study treatment and at the beginning of cycle 7 (+/- one cycle)
- Restaging scans (CT scan of the known site of disease) will be performed at baseline and then every 6 cycles (+/- one cycle).
- Optional MRI scans may be performed prior to start of study treatment, end of cycle 1, and every 6 cycles (at the same times as the CT scans)
- Health-related quality of life (HRQOL)/symptom questionnaires will be administered at baseline and at restaging

SCHEMA



Nirogacestat will be administered at 150 mg, orally, BID, in 21-day cycles

Tumor biopsies (optional) will be performed at baseline (pre-treatment) and at the beginning of cycle 7 (+/- one cycle)

Blood sample for germline analysis will be collected at baseline

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1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

- Determine the response rate (CR+PR) of Nirogacestat in patients with desmoid tumors/ aggressive fibromatosis

1.1.2 Exploratory Objectives:

- Assess symptoms at baseline and at intervals on study
- Perform genotyping for germline and somatic mutations in *APC* and *CTNNB1* genes
- Correlate clinical response to therapy with genotyping data
- Assess modulation of the Notch pathway by evaluating notch response genes in tumor biopsies at baseline and post-drug administration

1.2 BACKGROUND AND RATIONALE:

1.2.1 Desmoid Tumors

Desmoid tumors (also known as aggressive fibromatosis), are rare, locally invasive, slow-growing soft-tissue tumors. These tumors are considered benign; however, they are highly heterogeneous. The disease can be either asymptomatic requiring no intervention or be associated with severe loss of organ function and significant morbidity. Treatment options include wide surgical resection and radiotherapy, but not all tumors are amenable to resection and the post-surgical recurrence rate is high. Systemic chemotherapy may be indicated for inoperable or unresectable tumors, but watchful waiting may also be recommended as prolonged disease stabilization can occur [1-3].

Desmoid tumors frequently carry mutations in *CTNNB1*, the gene that encodes β-catenin, resulting in stabilization and nuclear accumulation of the protein [4-7]. β-catenin is an integral component of the Wnt/ β-catenin/Tcf signaling pathway, which is frequently dysregulated in cancer [8-10]. Patients with desmoid tumors carrying β-catenin mutations have a worse 5-year recurrence-free survival rate than patients with wild-type tumors [11, 12]. At least three different point mutations have been identified in exon 3 of *CTNNB1* (T41A, S45F, and S45P), one of which (S45F) may be a predictor of tumor recurrence after resection. All three oncogenic mutations limit phosphorylation and consequently degradation of β-catenin, resulting in the protein being translocated to the nucleus to activate Wnt pathway target genes [11].

Patients with familial adenomatous polyposis (FAP) can also develop desmoid tumors as a result of somatic and germline mutations in the adenomatous polyposis coli (*APC*) tumor suppressor gene; these patients have an 800-fold increased risk of developing desmoids [1, 13-15]. APC protein is critical for preventing constitutive activation of Wnt signaling by regulating levels of β-catenin. In normal cells a multiprotein complex of APC, axin, casein kinase 1α (CK1α) and glycogen synthase kinase (GSK3β) regulates the phosphorylation of β-catenin, resulting in its

degradation [14, 16]. Mutations in the *APC* gene can generate altered or truncated protein which is unable to phosphorylate β-catenin. This results in increased in β-catenin that is subsequently translocated to the nucleus, resulting in activation of T cell transcription factor 4 (Tcf-4) and aberrant gene expression [9, 17] (Figure 1).

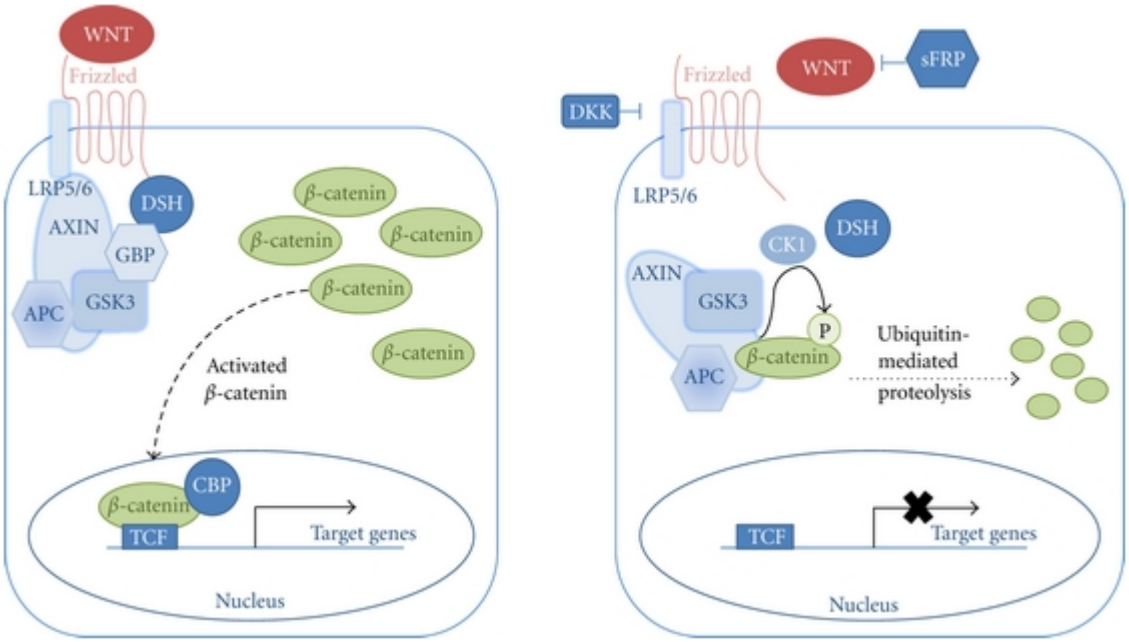

Figure 1: Model of the Wnt/APC/beta-catenin pathway. Wnt protein binds to its receptor on the cell surface to increase accumulation of β-catenin, which is translocated to the nucleus, resulting in activation of Wnt pathway transcription factors (left panel). If an active APC complex forms, the complex can bind and phosphorylate β-catenin, leading to its subsequent ubiquitin-mediated degradation (right panel). If an active APC complex cannot form due to mutations in either APC or β-catenin itself, β-catenin is not degraded and remains constitutively active (Figure from [15]).

A limited number of clinical studies have been done due in part to the rarity of desmoid tumors; clinical activity has been reported in trials of targeted agents. Penel et al. reported one complete response and three partial confirmed responses (3% and 9%) in 40 patients with recurrent or established desmoid tumors in a Phase II clinical trial of the tyrosine kinase inhibitor imatinib [18]. Partial responses (6/13) and stable disease (8/13) were also reported in patients treated on an expanded access study with the multikinase inhibitor sorafenib [19].

1.2.2 PF-03084014 (Nirogacestat)

Significant tumor shrinkage in patients with unresectable desmoid tumors was recently reported in a Phase I clinical trial of the small-molecule γ-secretase inhibitor PF-03084014 in patients with advanced solid tumors; four of nine evaluable patients with desmoid tumors experienced partial responses and the remaining five patients had some evidence of tumor shrinkage with prolonged disease stabilization [20, 21]. Gamma-secretase is required to activate intracellular

Notch signaling [22]. Notch pathway γ-secretase inhibitors have been postulated as a treatment for desmoid tumors as desmoid tumor-derived mesenchymal stromal cells express stem cell markers including BMI-1, a transcriptional repressor downstream of the Notch pathway [23]. A diagram outlining the complex potential interaction between components of the Notch and Wnt signaling pathways is presented in Figure 2 below:

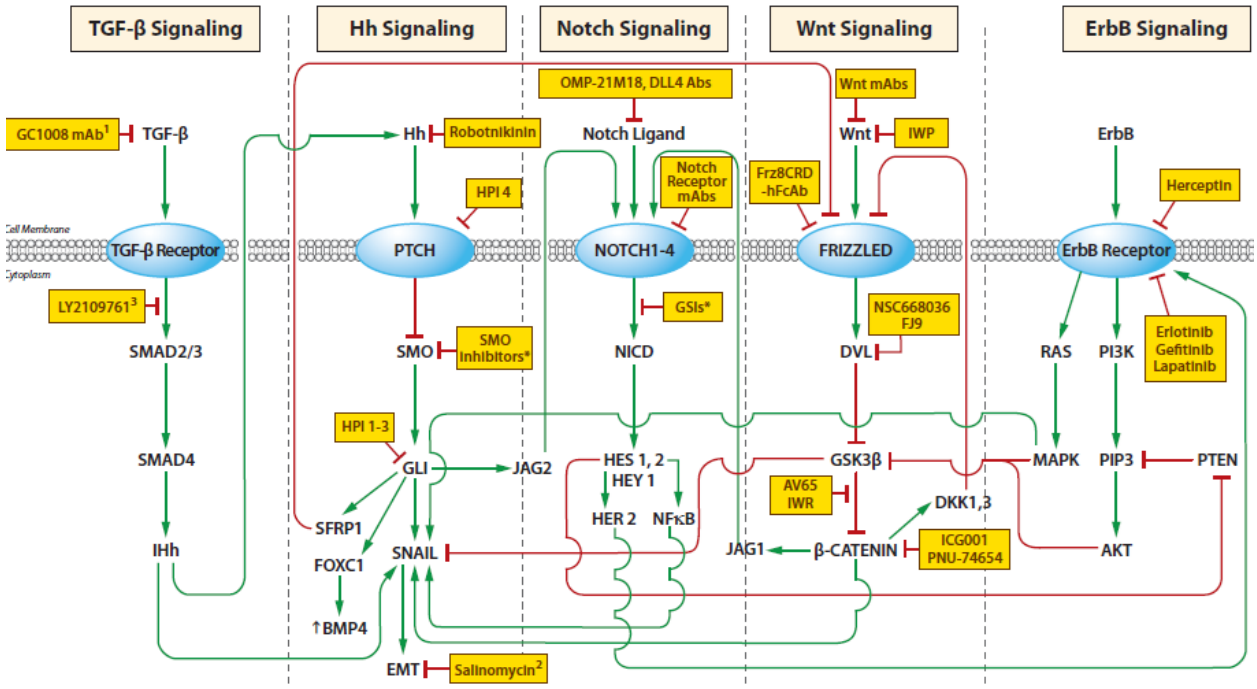

Figure 2: Some of the embryonic signalling pathways that may interact to initiate and promote carcinogenesis: transforming growth factor (TGF)-β, Hedgehog (Hh), Notch, Wnt, and ErbB. From Takebe et al 2011 [24].

Preclinical Pharmacokinetics

Single dose pharmacokinetics of PF-03084014 following intravenous (IV) and oral administration was assessed in the toxicology species (rat and dog). PF-03084014 demonstrates moderate systemic clearance in rat and dog, with $T_{1/2}$ values of 11.7 and 12.4 hour, respectively. Systemic exposure increased with increasing dose in rats (2 to 50 mg/kg/day) and dogs (2, 10, and 50→20 mg/kg/day) from 3-month toxicological studies. Although the increase was greater than dose proportionality in the rats on both Day 1 and 90 and in the dogs on Day 1, the exposure increase was dose proportional in the dog on Day 91.

Volume of distribution at steady state values of PF-03084014 were greater than total body water in rats and dogs, suggesting that this compound readily distributes to tissues in these species. PF-03084014 showed high plasma protein binding with average unbound fraction (%) of 0.64, 1.95, 4.22, and 2.61 for mice, rats, dogs, and humans, respectively, at nominal concentrations of 490 ng/mL for mouse and 1,000 ng/mL for rat, dog and human determinations.

In vitro metabolism of PF-03084014 is consistent across nonclinical species and humans. All circulating-metabolites observed in humans were present in one or more of the evaluated nonclinical species. PF-03084014 appears to be metabolized to several oxidative metabolites. In vitro, CYP 3A4 has been shown to catalyze the metabolism of PF-03084014. In rats, <1% of the administered dose is eliminated unchanged via biliary excretion or eliminated unchanged in urine or feces.

Preclinical Toxicology

PF-03084014 was administered to rats and dogs in oral studies up to 1 month in duration. The no-observed-adverse-effect level (NOAEL) in rats was 5 mg/kg, and the mean C_{max} and area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24}) were 19.3/42.7 ng/mL (male/female [M/F]) and 50.7/137 ng•h/mL (M/F), respectively. In dogs, the NOAEL was 10 mg/kg, and the mean C_{max} and AUC_{0-24} were 448 ng/mL and 1920 ng•h/mL, respectively. The target systems identified were the hematopoietic/immune, gastrointestinal (GI), musculoskeletal, reproductive, and hepatic systems.

Hematopoietic/immune effects were seen in both species and included decreases in B and T cells, natural killer lymphocytes (NK) cells, Immunoglobulin M (IgM) and Immunoglobulin D (IgD) expression on B cells (rat only), and lymphoid depletion in spleen, thymus (thymic cortical atrophy in dog), lymph nodes, and/or gut-associated lymphoid tissue (GALT). Treatment-related intestinal tract changes consisted of epithelial hyperplasia and, with higher exposures, epithelial degeneration and necrosis. In general, both the hematopoietic/immune and GI changes showed recoverability in rats when treatment was discontinued, except for decreases in T cells and IgD and IgM expression on B cells. These changes were considered mechanism-related due to the effects of PF-03084014 on Notch.

Increased retention of the hypertrophic zone of the growth plate and articular cartilage (sternum and joint), and ovarian atrophy, increased number of corpora lutea, and asynchrony of the estrus cycle were seen in rats only; partial recovery of these effects was evident after discontinuation of PF-03084014. These responses were similar to those observed with vascular endothelial growth factor (VEGF) inhibitors in nonclinical toxicologic studies. Whether the anti-angiogenic like effects of PF-03084014 are mechanism-related (i.e., a result of Notch inhibition or effects on other γ-secretase substrates) or are downstream effects on angiogenic growth factor signaling (i.e., VEGF), cannot be determined at this time. The fact the bone and ovary effects were seen in the rat and not the dog may be attributed to the fact the rat has an open growth plate, is actively developing, and the estrus cycle is more frequent in the rat compared with the dog. In addition, these nonclinical findings were not replicated observed in clinical studies with VEGF inhibitors (Investigators Brochure).

Hepatic vacuolation was observed in rats without changes in clinical chemical or hematologic effects, and no primary liver toxic effects were apparent. Inflammation of the liver in dogs was considered secondary to intestinal hyperplasia and a disruption of the intestinal mucosal barrier. Additional organs affected by treatment with PF-03084014 were the lung (increased number of foam cell foci in rats suggestive of phospholipidosis), kidney (protein casts in lumen in rat; hypertrophy of tubular epithelial cells and increased pigment in dog), and salivary gland (necrosis of glandular epithelial cells in rat). These latter changes were seen predominantly in

rats at high doses and exposures that exceed the estimated clinically efficacious concentration. There was no indication of adverse effects on the function of these organs and these changes were not evident in recovery animals.

PF-03084014 was also administered to rats and dogs in oral studies up to 3 months in duration followed by a 1-month recovery. In the rat study, based on ovarian atrophy, alterations in the estrous cycle and decreased cellularity in GALT in females and mesenteric lymph nodes in males and females at 5 mg/kg/day, a NOAEL was not identified. Adverse treatment-related effects were observed at all dose levels evaluated and included increased incidence and severity of chronic progressive nephropathy, pulmonary phospholipidosis, and salivary gland necrosis at ≥ 5 mg/kg/day, and morbidity/mortality and fibrinoid necrosis of the pulmonary arteries in both males and females at 50 mg/kg/day.

In the dog study, treatment-related effects of variable incidence and severity were noted in the dosing phase within the intestines, spleen, gall bladder, liver, kidney, testes, and ovary at doses ≥ 10 mg/kg/day (except oocyte mineralization which was noted at 2 mg/kg/day). The intestinal and liver findings were associated with generalized inflammation and associated clinical pathology changes in most of these animals. Based on oocyte mineralization noted at the lowest of 2 mg/kg/day, a NOAEL was not identified.

PF-03084014 was negative in genetic toxicology assays (bacterial mutagenicity and human lymphocyte cytogenetic assays) and safety pharmacology assessments. PF-03084014-01 was also evaluated for its effect in the human ether-a-go-go related gene (HeRG) potassium channel assay and determined to present minimal risk of electrocardiogram (QT) prolongation. No reproductive and developmental toxicity studies have been conducted with PF-03084014.

Current Human Experience

PF-03084014 (Nirogacestat) has been evaluated in three Phase I clinical studies in healthy adults and one ongoing Phase I study in patients with advanced solid tumors and refractory ALL. In healthy volunteer studies, single oral doses of PF-03084014 up to 120 mg (Studies A8641001 and A8641008) and multiple doses up to 95 mg (Study A8641002) once daily for up to 14-days administered were deemed safe and well tolerated. No maximum tolerated single or repeat dose was identified. Adverse events across the three studies were generally mild and transient: the most frequently observed adverse events were headache, dizziness, and fatigue. In studies with a lumbar puncture (Studies A8641002 and A8641008), back pain was also frequently observed. There were no clinically relevant treatment-related changes in vital signs or electrocardiograph endpoints. No clinically important changes were observed in clinical safety laboratory endpoints, including serum chemistry evaluations, hematological profiles (including T- and B-cell biomarkers), and urinalysis. There were dose-related trends for increases in eosinophils and immature B cell subsets observed after administration of PF-03084014 95 mg daily in Study A8641002, which returned to pretreatment values about 4 days after the final dose of study drug was administered.

Evaluation of pharmacokinetic characteristics indicated that PF-03084014 was rapidly absorbed, with median time of occurrence of Cmax (Tmax) values of 0.5 to 1 hour generally observed across the three Phase I studies. Exposure increased with escalating single and repeat doses,

with some evidence for greater than dose proportional increases observed across the dose range studied in trials A8641001 and A8641002. The terminal elimination half-life of PF-03084014 was approximately 19 hours after single doses and 26 hours after multiple doses (Investigators Brochure).

There is currently one ongoing clinical study with PF-03084014 (Study A8641014), an open-label, non-randomized, Phase I dose finding study in patients with advanced solid tumor malignancies and patients with relapsed/refractory acute T-ALL. In the dose-finding portion of the study, the maximum tolerated dose (MTD) of PF-03084014 administered twice daily continually for 21 days was established at 220 mg BID in patients with advanced solid tumors. Additional patients were subsequently enrolled in the expansion cohort at 150 mg or 220 mg BID. The Recommended Phase II Dose (RP2D) in patients with advanced solid tumors has been determined to be 150 mg BID by comparing the tolerability, pharmacokinetic and pharmacodynamic profile of PF-03084014 at these two doses. The MTD in patients with refractory or relapsed T-ALL/LBL leukemia has not been established.

Safety

As of the March 1, 2013 cut-off date, 64 adult patients with advanced solid tumor malignancies have data in the safety database, and six patients were still on treatment. The most common AEs independent of causality seen in patients with advanced solid tumors were diarrhea, nausea, fatigue, vomiting, hypophosphatemia, decreased appetite, cough and rash; all of these events were considered to be treatment related in some patients (Table 1). The majority of AEs were considered mild to moderate but treatment related Grade 3 hypophosphatemia, diarrhea, and rash have been frequently reported. The only treatment-related Grade 4 AE was anaphylactic shock reported in one patient, an event thought to be related to co-administration of intravenous morphine. No clinically relevant changes in vital signs or electrocardiograph endpoints have been reported. The severe hematology laboratory test abnormalities reported were low lymphocyte count and platelets. The most frequently reported severe serum chemistry abnormalities were hypophosphatemia, hypokalemia and hyperglycemia.

	Patients, n (%)	
Adverse event*	**Grade 1/2**	**Grade 3**
Diarrhea	29 (45)	6 (9)
Nausea	23 (36)	1 (2)
Fatigue	19 (30)	0
Hypophosphatemia	2 (3)	15 (23)
Vomiting	14 (22)	1 (2)
Rash (cumulative terms)	11 (17)	3 (5)
Decreased appetite	11 (17)	0

Table 1: Treatment-related AEs in patients with advanced solid tumors (N = 64; ≥ 10%)
* Gr 4 anaphylactic shock (n=1) likely related to morphine administration.

In the Phase I study, five first cycle dose-limiting toxicities (DLTs) were observed among the patients with advanced solid malignancies Grade 4 anaphylactic shock for one patient, thought to be related to intravenous morphine (100 mg BID); Grade 3 diarrhea for two patients (150 mg and 220 mg BID); Grade 3 rash; and inability to administer 80% of planned dose during Cycle 1 for one patient (330 mg BID).

Although efficacy is not the primary objective of the dose-finding study, patients with advanced solid tumors were evaluated for best response according to Response Criteria in Solid Tumors (RECIST) version 1.0. As of March 1, 2013, 46 patients were evaluable for response: a complete response was observed in one patient with papillary thyroid cancer; five patients (out of seven evaluable, overall response rate 71%) with desmoid tumors achieved a partial response (Figure 3). Stable disease was reported for 14 patients with a variety of tumor types, and 26 patients had objective progression as best overall response on study.

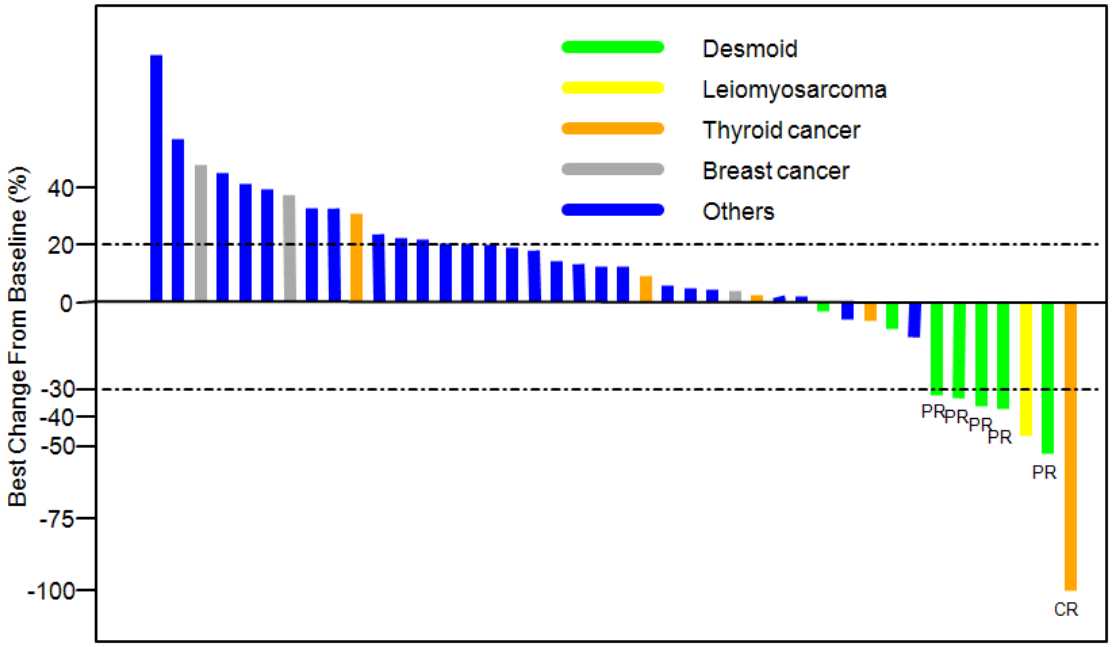

Figure 3: Waterfall plot for response in evaluable patients receiving PF-03084014 on the Phase I trial (data from Pfizer). Responses were measured after 6 to 9 months on study.

Clinical Pharmacokinetics

Evaluation of the pharmacokinetic characteristics of PF-03084014 indicated that it was rapidly absorbed, with median time of occurrence of C_{max} (T_{max}) values of 0.5 to 1 hour generally observed across the three clinical studies. PF-03084104 exposure increased with escalating single and repeat doses, with some evidence for greater than dose proportional increases observed across the dose range studied in trials A8641001 and A8641002. The terminal elimination half-life of PF-03084014 was approximately 19 hours after single doses and 26 hours after multiple doses.

Potential Drug Interactions

PF-03084014 induced CYP 3A4 in human hepatocytes in vitro. Nirogacestat does not inhibit CYP 1A2 at concentrations <30 µM, but weakly inhibits CYP 2C9, CYP 2C19 and CYP 2D6 in human liver microsomes with 50% inhibitory concentration (IC_{50}) values of 18.5 +/- 1.6 µM, 20.3 +/- 2.0 µM and 13.5 +/- 1.2 µM. PF-03084014 inhibits CYP 3A with an IC_{50} value of 4.6 +/- 0.3 µM. Additionally, preliminary assessment suggests that Nirogacestat is a weak time-dependent inhibitor of CYP 3A4 with an inhibition constant (Ki) value of 2.2 µM and a kinact rate of 0.059/min. In a healthy volunteer clinical drug-drug interaction study, Nirogacestat increased the area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) 58.9% and maximum observed plasma concentration (C_{max}) 30.7% of Midazolam following 9 days of dosing at 95 mg daily. In nonclinical studies conducted in *mdr1a/1b (-/-)* knockout and wild-type mice, PF-03084014 readily penetrates the blood-brain barrier and shows interaction with the efflux transporter P-glycoprotein (P-gp) at the blood-brain barrier.

Correlative Studies Background

Pre- and post-dose (cycle 1) blood and hair follicle samples were collected for pharmacodynamic analysis on the Phase I clinical trial in patients with advanced solid tumors. Changes in gene expression in these samples were measured by TaqManR qRT-PCR. Notch pathway modulation was demonstrated in all evaluable patients, with transcriptional repressor *Hes4* showing the most consistent regulation, with a greater than 2-fold down-regulation in an initial cohort of nine patients (Figure 4) [20]. *Hes4* is also one of several Notch pathway target genes down-regulated following Nirogacestat treatment in breast cancer xenograft models [25] (Figure 2).

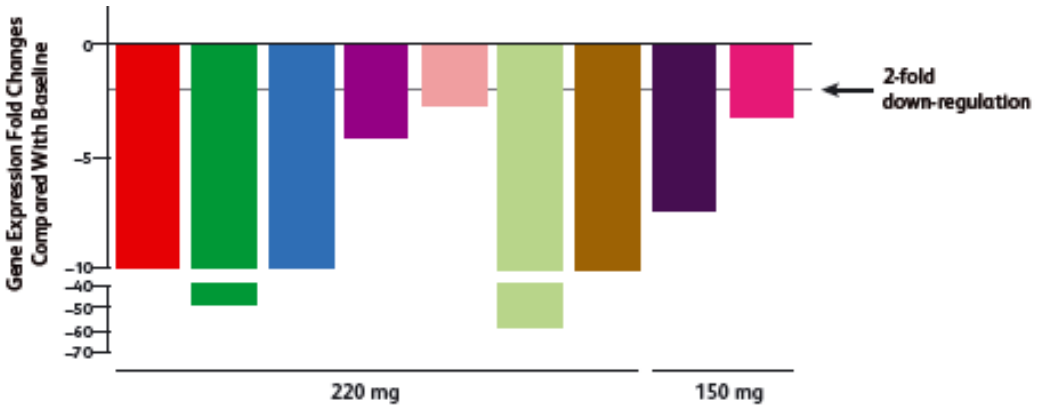

Figure 4: Changes in *Hes4* gene expression following treatment with Nirogacestat in samples from 9 patients on the Phase I trial [20].

In this current study, optional tumor biopsies will be collected at baseline and during cycle 7 to look at changes in the expression of Notch response genes in the Clinical Tumor Profiling Laboratory of Dr. Paul Meltzer, CCR. A blood sample will also be collected at baseline; blood and tumor biopsy samples will undergo genotyping for germline and somatic mutations in *APC* and *CTNNB1* genes.

Because prior studies have indicated that desmoid tumors may be aneuploid, copy number analysis will be performed on tumor biopsy DNA for correlative studies. Blood and tumor biopsy tissue will also be subject to whole exome sequencing for somatic mutations in genes

which may contribute to tumor formation. Samples will be delinked prior to performing any genotyping studies. Details of the correlative studies to be performed are provided in Section 5.1; none of the genetic information obtained will be used to inform clinical decision making or be shared with the patient. The potential risks associated with obtaining genetic information are discussed in Section 5.4. If sufficient biopsy material is available, the following assays will be performed to obtain comprehensive genomic profiling of these tumors: transcriptome sequencing and DNA methylation analysis.

Rationale

Based on the promising activity in desmoid tumors observed in patients on the Phase I trial, we propose a Phase II trial of Nirogacestat in patients with unresectable desmoid tumors to further evaluate the activity of this agent in this rare disease.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

Nirogacestat will be administered at the recommended Phase II dose of 150 mg BID orally, continually, in 21-day cycles. Optional tumor biopsies for research purposes will be performed at baseline prior to study treatment and at the beginning of cycle 7 (+/- one cycle).

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically confirmed desmoid tumor confirmed by the Laboratory of Pathology, NCI, that has progressed after receiving at least one line of standard treatment and that is not amenable to surgical resection or definitive radiation therapy.

2.1.1.2 Willingness to provide blood samples and 10 unstained slides or a tumor block for genetic research studies.

2.1.1.3 Any line of therapy with prior desmoid therapy, including radiotherapy, should have been completed at least 2 weeks before study entry and all toxicities must have resolved at least to eligibility levels.

2.1.1.4 Age ≥18 years; because no dosing or adverse event data are currently available on the use of Nirogacestat in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

2.1.1.5 ECOG performance status ≤2 (see Appendix A).

2.1.1.6 Life expectancy > 3 months.

2.1.1.7 Patients must have normal organ and marrow function as defined below:

absolute neutrophil count	≥ 1,500/mcL
platelets	≥ 100,000/mcL
total bilirubin	≤ 1.5 X institutional upper limit of normal
AST(SGOT)/ALT(SGPT)	≤ 5 X institutional upper limit of normal

creatinine	< 1.5 X institutional upper limit of normal
	OR
creatinine clearance	≥ 60 mL/min/1.73 m^2 for patients with creatinine levels >1.5 mg/dL
hemoglobin	≥ 9 g/dL

2.1.1.8 Patients must be able to swallow whole tablets or capsules with no GI condition affecting absorption; nasogastric or G-tube administration is not allowed.

2.1.1.9 The effects of Nirogacestat on the developing human fetus are unknown. For this reason and because γ-secretase inhibitors are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for at least 6 months after dosing with study drugs ceases. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and 6 months after completion of study drug administration.

2.1.1.10 Ability to understand and the willingness to sign a written informed consent document.

2.1.1.11 Evidence of measurable disease by CT scan. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents. Concurrent mediations that the patient is taking will be reviewed by the PI to assess safety and eligibility.

2.1.2.2 Prior treatment with γ-secretase inhibitors or anti-notch antibody therapy.

2.1.2.3 Uncontrolled intercurrent illness including, but not limited to, serious infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.4 QTc interval of >470 msec at study entry; congenital long QT syndrome.

2.1.2.5 Pregnant women are excluded from this study because Nirogacestat is a γ-secretase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Nirogacestat, breastfeeding should be discontinued if the mother is treated with Nirogacestat.

2.1.2.6 Patients with gastrointestinal conditions that might predispose for drug intolerability or poor drug absorption (e.g., inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, malabsorption syndrome, and active peptic ulcer disease) are excluded. Subjects with ulcerative colitis,

inflammatory bowel disease, or a partial or complete small bowel obstruction are also excluded, as are any patients who cannot swallow the tablet whole. Tablets must not be crushed or chewed; nasogastric or G-tube administration is not allowed.

2.1.2.7 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with Nirogacestat.

2.1.3 Recruitment Strategies

We have had multiple discussions with the Desmoid Tumor Research Foundation, Inc., who have various outreach efforts including patient meetings and webcasts. Senior executives of the Foundation have indicated strong interest in this trial and willingness to inform their members. We also have a network of referring physicians nationally that refers patients with solid tumors to our clinical program. Given our interest and trials for sarcomas, we have formed connections with centers that treat patients with mesenchymal malignancies. We will be informing all of these of the availability of this trial once it is open.

2.2 SCREENING EVALUATION

2.2.1.1 Histologic confirmation: A block or stained slides of tumor tissue from each participant to confirm diagnosis. All patients will be required to submit a tumor block or 10 unstained slides for genetic research purposes.

2.2.1.2 History and physical examination: Complete history and physical examination (including height, weight, vital signs, performance score, EKG) will be conducted within 72 hours prior to enrollment.

2.2.1.3 Imaging Studies (Baseline): Every participant should have an evaluation of known sites of disease as part of the baseline evaluation. All patients will be required to undergo a CT scan of the area of known disease; an MRI with diffusion weighting may be performed prior to start of study treatment, at the end of cycle 1, and at the time of restaging, per PI's discretion.

2.2.1.4 Laboratory Evaluation: Baseline laboratory data are to be obtained within 72 hours prior to enrollment:

- Hematological Profile: CBC with differential.
- Biochemical Profile: albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, phosphorus, SGOT[AST], SGPT[ALT], magnesium, potassium, and sodium.
- Coagulation Profile: PT, PTT, INR
- Urine and/or serum pregnancy test for female participants of childbearing potential.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of investigational agent. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours. .

Off Protocol Therapy and Off-Study Procedure: Authorized staff must notify the Central Registration Office (CRO) when a patient is taken off protocol therapy and when a patient is taken off-study. The Participant Status Updates Form from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to the NCI Central Registration Office (HOIS; ncicentralregistration-l@mail.nih.gov).

2.4 RANDOMIZATION PROCEDURES

N/A

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is an open-label Phase II trial of Nirogacestat. Study drug will be administered at 150 mg, orally, BID, continually, in 21-day cycles.

Labs (CBC with differential and serum chemistries, including electrolytes) will be monitored each week during cycle 1, and then every other cycle. History and physical examination will be performed before the start of every other cycle. For patients having a history and physical examination performed by their local physician, study drug will be held until receipt of results; this may result in an interruption of therapy. For patients on study for more than a year, history and physical examination and labs can be performed every 3 cycles (up to 2 weeks before the start of the cycle). EKG monitoring will be performed at baseline and then post-drug administration on study day 1. Additional EKG monitoring may be performed during cycle 1 as clinically indicated.

Response assessment will be performed using RECIST 1.1. Restaging scans (CT scans of the known site of disease) will be performed at baseline prior to starting study treatment and then every 6 cycles (+/- 1 cycle) as described in Section 5.5. An MRI with diffusion weighting may be performed prior to start of study treatment, end of cycle 1, and at the time of restaging, per PI's discretion.

Health-related quality of life (HRQOL)/symptom questionnaires will be administered at baseline and at restaging (response assessment) as described in Section 3.4.

Archival unstained slides or tumor block will be sent for genetic research studies as described in Section 5.4.

Blood for research (whole exome sequencing) will be collected at baseline as described in Section 5.2.

Optional tumor biopsies for research purposes will be performed at baseline prior to study treatment and at the beginning of cycle 7 (+/- one cycle) as described in Section 5.2.

3.2 DRUG ADMINISTRATION

Reported adverse events and potential risks are described in Section 11.1. Appropriate dose modifications are described in Section 3.3. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's tumor.

Patients will be asked to maintain a Study Medication Diary (Appendix B) and record each dose of medication. Patients will be given instructions for completing the medication diary and will be asked to return it to the clinic staff at their follow up visits. There is no restriction on taking the study drug with food; patients who miss a dose or vomit the drug will be instructed to not take an additional dose. A cycle will be considered completed if 90% of the planned dose is administered. Occasionally patients may miss a dose for non-medical reasons, but this should not have an impact in the overall conduct of the trial or be a risk to their safety.

3.3 DOSE MODIFICATIONS

- Grade 3 non-hematologic toxicities (other than alopecia; easily correctable electrolyte abnormalities) would require holding study drug until recovery to grade ≤ 2 or baseline, with reinstituting study drug at the next lower dose level (see below).
- Grade 2 or higher nausea, vomiting, or diarrhea would result in dose reduction only if not controlled by supportive measures.
- Any grade of allergic reaction would result in discontinuing study drug and taking patient off study.
- Grade 3 hematologic toxicities (except any grade lymphopenia, leucopenia in the absence of neutropenia) would result in dose being held till recovery to grade 2 or less with reinstitution of study drug at the next lower dose level. Anemia would require dose reduction if there is a drop in hemoglobin of ≥ 2 g/dL from baseline without other causes such as nutritional deficiency.

A maximum of 2 dose reductions will be allowed on study. Study drug can be held for a maximum of 3 weeks to allow recovery from toxicities. If toxicities do not resolve to retreatment criteria by the end of 3 weeks, the patient will only resume treatment at the discretion of the PI (i.e., if the patient is benefiting from therapy).

Dose Level	Dose (orally BID q 21-day cycles)
-1	100 mg

-2	80 mg

3.4 PATIENT REPORTED OUTCOME QUESTIONNAIRE

Participants on this study will be asked to complete health-related quality-of-life (HRQOL)/symptom questionnaires to assess the severity and associated interference caused by disease and treatment-related symptoms and track their severity and interference over the course of treatment. These patient-reported outcome (PRO) measures will capture the emergence or worsening of selected symptoms from baseline to study completion, thus improving the identification of treatment-emergent symptomatic toxicity and better capturing improvements in disease-related symptoms which may inform decisions about therapeutic response and clinical benefit Such patient-reported outcomes (PRO) allow participants to rate their own HRQOL, thereby providing a direct measure of each patient's experience of treatment over the course of the study [26, 27].

This protocol will use the psychometrically-validated M.D. Anderson Symptom Inventory (MDASI) to assess PRO disease and treatment-related symptoms [28]. MDASI uses a 0-10 numerical scale to assess, over the previous 24 hours, 13 symptoms commonly experienced by patients with cancer and 6 additional items that assess the extent to which these symptoms interfered with how patients felt and were able to function:

- 13 treatment symptoms assessed: pain, fatigue, nausea, disturbed sleep, distress (emotional), shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling
- 6 symptom interference items assessed: general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life

A copy of MDASI is provided in Appendix D. The questionnaires will be administered at baseline and at restaging. Completing the MDASI takes approximately 2-5 minutes and the symptom scale will take an additional 5 minutes to complete. All patients will complete these questionnaires under the supervision of a member of the clinic staff.

A component score representing symptom severity is obtained by taking the average of the 13 symptom items together. A component score representing symptom distress is obtaining by averaging the 6 symptom interference items. Questionnaires will be maintained in the research chart of each patient. The NCI has received permission to use MDASI by the copyright holder, The University of Texas MD Anderson Cancer Center.

3.5 STUDY CALENDAR

Baseline history and physical exam are to be conducted within 1 week prior to start of protocol therapy; laboratory evaluations must be done within 72 hours prior to start of protocol therapy. Scans and x-rays must be done ≤ 28 days prior to the start of therapy. The duration of a cycle will be 21 days (± 1 day for scheduling). The start of the next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. History and physical examination and laboratory

evaluations can be performed before the start of a cycle. For patients having their history and physical examination performed by their local physician, study drug will be held until receipt of results. For patients on study for more than a year, history, physical examination, and labs can be performed every 3 cycles (up to 2 weeks before the start of the cycle).

	Pre-Study	C1 W1 (D1-7)	C1 W2 (D8-14)	C1 W3 D15-21)	C2 W1 (D1-7)	C2 W2 (D8-14)	C2 W3 (D15-21)	C3 W1 on	Off Treat-ment
Nirogacestat **(PF-03084014)** [a]		X	X	X	X	X	X	X	
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X----------X							
Physical exam [b]	X							X	X
Vital signs [b]	X							X	X
Height	X								
Weight [b]	X							X	X
Performance status [b]	X							X	X
CBC w/diff, plts [c]	X		X	X				X	X
Serum chemistry [c]	X		X	X				X	X
Coagulation profile	X								
Adverse event evaluation		X----------X							X
Tumor measurements [d]	X								X
B-HCG [e]	X								
EKG [f]	X								
Tumor biopsies [g]	X								
Archival tissue [h]									
PG blood sampling [h]	X								
Questionnaire [i]	X								

a. PF-03084014 twice daily in 21-day cycles.
b. Should be performed on day 1 at the Clinical Center, and then at the start of every other cycle at the Clinical Center or by patient's local physician. For patients on study more than a year, history and physical examination can be performed every 3 cycles (up to 2 weeks before the start of the cycle).
c. Serum chemistry (albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, glucose, phosphorus, magnesium, potassium, SGOT [AST], SGPT [ALT], sodium) and CBC w/diff, platelets should be performed within 72 hours before enrollment (pre-study) and weekly during cycle 1, at the start of every other cycle and as clinically indicated. For patients on study more than a year, labs can be performed every 3 cycles (up to 2 weeks before the start of the cycle).
d. Tumor measurements are repeated every 6 cycles (±1 cycle). Documentation (radiologic) must be provided for patients removed from study for progressive disease. Optional MRI scans may be performed prior to start of study treatment, end of cycle 1, and every 6 cycles.
e. Serum or urine pregnancy test (women of childbearing potential) within 1 week prior to enrollment

f. EKG at baseline and then post-drug administration on day 1. Additional monitoring may be performed during cycle 1 as clinically indicated.
g. Tumor biopsies are optional at baseline and at the beginning of cycle 7
h. Archival tumor biopsy tissue and blood sample for pharmacogenomic analysis collected at baseline
i. Quality-of-life questionnaire to be administered at baseline and at restaging

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.6.1 Criteria for removal from protocol therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment
- Significant toxicity occurs despite 2 dose reductions as described in Section 3.3 or no lower dose level exists
- Pregnancy
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Toxicities felt to be possibly, probably, or definitely related to the study drugs that have not resolved or stabilized by Day 30 post-treatment will be followed until stabilization or resolution via phone calls as clinically indicated.

3.6.2 Off-Study Criteria

Patients will be removed from this study for one of the following reasons: completed 30-day follow-up period, toxicities are unresolved but stabilized, patient enrolls on another protocol, or patient receives standard of care. The reason for study removal and the date the patient was removed must be documented in the medical record.

3.6.3 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS

All patients will be provided with the best available supportive care. All concurrent medications should be documented prior to initiation of treatment, and be periodically reviewed with the patient. Particular attention must be paid to medications which may cause hemolytic anemia.

No other approved or investigational treatment for desmoid tumors will be permitted during the study period, including chemotherapy, biologic response modifiers, hormone therapy, immunotherapy, or radiotherapy.

Nausea/Vomiting
Anti-emetics will not be administered routinely prior to Nirogacestat. However, if a patient develops nausea/vomiting, anti-emetics such as but not limited to prochlorperazine, metoclopramide, 5-HT3 antagonists, or aprepitant may be given. In addition, if a patient develops nausea and/or vomiting that is Grade 2 or greater, anti-emetics may be instituted prophylactically at the discretion of the investigator. Nausea and vomiting will be considered refractory if it does not resolve to ≤ Grade 1 with treatment with a combination of at least 2 of the antiemetics within 24 hours.

Diarrhea
If diarrhea develops and does not have an identifiable cause other than study drug administration, anti-diarrheals such as Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to package insert or loperamide 4 mg po after the first unformed stool with 2 mg po every 2 hours as long as unformed stools continue (4 mg every 4 hours while asleep). No more than 16 mg of loperamide should be taken during a 24-hour period. This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours to Grade ≤ 2 with the above regimen ((loperamide ≤16 mg in a 24-hour period if there is resolution of the symptoms).

Neutropenia
Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode. Growth factors to prevent neutropenia will not be administered prophylactically. If necessary, they may be administered according to accepted American Society of Clinical Oncology (ASCO) guidelines to allow re-treatment.

Anemia
Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL. Use of erythropoietin will follow ASCO guidelines.

*Thrombocytopeni*a
Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤10,000/mm^3. If invasive procedure(s) is (are) planned, or the patient develops bleeding,

platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mm^3.

Hypophosphatemia
Institutional normal value for serum phosphate: 2.5-4.8 mg/dL. Mild to moderate hypophosphatemia (1.0–2.4 mg/dL) will be managed with oral replacement therapy; PHOS-NaK packet (280 mg K^+/160 mg Na^+/250 mg Phos) up to 1000 mg/day. In instances where patients are intolerant or refractory to oral replacement, intravenous replacement therapy with sodium phosphate infusion may be administered at a rate of 0.08-0.16 mmol/kg over 2-6 hours. For severe hypophosphatemia (< 1.0 mg/dL) or in patients with clinical sequelae of hypophosphatemia (e.g., hemolysis) will be managed with intravenous replacement therapy (0.08–0.16 mmol/kg) over 2-6 hours.

Hypokalemia
*In*stitutional normal value for serum potassium: 3.3-5.1 mmol/L. Mild to moderate hypokalemia (2.5–3.2 mmol/L) will be managed with oral replacement therapy; potassium chloride 20 mEq orally up to a maximum of 100 mEq/day. For severe hypokalemia (< 2.5 mmol/L) or in patients with mild to moderate hypokalemia with evidence of cardiac arrhythmia, intravenous potassium will be administered intravenously at 10 mEq/hour through a peripheral IV or up to 40m Eq/hour through a central catheter and with cardiac monitoring.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

In normal cells, the APC complex of APC, axin, Ck1α, and GSK3β regulates β-catenin levels, resulting in degradation of the protein [14]. More than 1000 mutations that lead to missense or frame shift mutations or premature stop codons and consequently synthesis of truncated APC protein have been described [17, 29] (listed in the Sanger Center COSMIC database at http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/). These mutations result in non-functional APC protein that cannot phosphorylate β-catenin for subsequent degradation; dysregulation of β-catenin levels results in protein accumulation in the nucleus and activation of Tcf-4. Prior studies of desmoid tumors indicate that aneuploidy does occur in some of these tumors [30]. There is no information available regarding cooperating mutations which may contribute to tumor progression.

5.2 PHARMACODYNAMICS

5.2.1 Laboratory Contact

At least 24 hours prior to biopsy or blood sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10:

E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov

Pager (preferred): 102-12798

Phone: 240-858-3963

Fax: 301-480-5871.

For biopsies, tubes pre-labeled with the participant ID, biopsy date, protocol number, and site of tissue biopsy will be provided. Initial processing and shipping of the samples will be completed as described below.

5.2.2 Tumor Biopsies

5.2.2.1 Timing of tumor biopsies

Optional biopsies will be collected:

- before drug administration on study (baseline),
- at the beginning of cycle 7 (+/- one cycle)

5.2.2.2 Biopsy Procedure

Serial tumor biopsies will be obtained through Interventional Radiology by a percutaneous approach. A maximum of 3 core biopsies 18-gauge in diameter and at least 1 cm in length will be obtained at each time point. Only percutaneous biopsies will be performed.

It is estimated that there will be between 2-5 million cells from each biopsy. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and Interventional Radiology, an attempt at biopsy will be made. Determination of a disease site amenable to biopsy will be determined on an individual case basis after discussion with an interventional radiologist. The biopsy procedure to be used in this protocol is described below; local anesthesia will be administered. Such biopsies can be safely performed as evidenced by literature reports [31] as well as our experience at the Clinical Center. Risks of the procedure include, but are not limited to, bleeding, infection, pain, and scarring. We will follow Clinical Center Interventional Radiology SOPs for coagulant panel and platelets.

- All biopsies will be by percutaneous approach
- No biopsy by an invasive (endoscopic, laparoscopic, or surgical) procedure will be performed

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, or MRI. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. All cases will be carefully reviewed with the interventional radiologists at NIH who have extensive experience in performing such procedures. Only if the procedure is considered to be low risk will we proceed with tumor biopsy in a given participant.

Tumor biopsies are optional. Baseline biopsies will be performed following patient enrolling on study. If the baseline biopsy is unsuccessful or the patient refuses to undergo subsequent biopsies, no further biopsies will be performed but the patient will

remain on study, receive study medication, and other correlative studies will be performed.

5.2.2.3 Solid Tumor Biopsy Processing

A maximum of three tissue cores will be collected. Biopsies will be fixed in formalin then sent to the Laboratory of Pathology, NCI. One 4-micron H&E-stained section and either a matching FFPE tissue block or 10 unstained slides will be sent to the Clinical Tumor Profiling Laboratory where an examination of tumor content will be performed by a designated pathologist:

Contact: Marbin Pineda
37/6138
301-496-5266
pinedama@mail.nih.gov; cc Paul Meltzer (pmeltzer@mail.nih.gov) and Keith Killian (killianj@mail.nih.gov).

Tumor content must exceed 40% and estimated tumor content will be recorded. The H&E section will serve to confirm original diagnosis and also estimate tumor nuclei content. The remaining biopsy will be extracted for nucleic acids using the Qiagen FFPET All-Prep procedure. DNA will be assessed for quantity and quality by spectroscopy (OD 260/280) and a PCR-based amplification quality assessment test. RNA will be assessed for quality by analysis on the Agilent Bioanalyzer.

10-20 ng of RNA will be analyzed from pre-treatment and cycle 7 biopsies to determine the level of Notch target gene *HES4* using a Taqman assay.

If sufficient samples are available, whole-exome sequencing will be performed on the DNA and transcriptome sequencing will be performed on the RNA, both done retrospectively for research purposes on samples unlinked from patient identifiers.

5.2.3 Blood Samples

A blood sample will be obtained at baseline for germline sequencing of *APC* and *CTNNB1*.

A minimum of 2 mL of whole blood is required for genetic sequencing. For this, 5 mL of blood will be collected in a purple top (EDTA) tube at baseline prior to starting treatment. The blood can be collected using a standard protocol. After blood draw, the sample should be aliquoted and frozen in 2-mL screw-top cryovials at -20°C. These samples need to be sent on dry ice to the following address. The samples should be labeled with only the unique patient ID. **Do NOT include patient identifiers (e.g., medical record number, patient name or initials) with the samples.**

Please e-mail contact person 24 hours prior to shipment.

Upon receipt at the Clinical Tumor Profiling Laboratory, genomic DNA will be extracted for clinical targeted sequencing.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.3.1 Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions. Information about each specimen will be recorded on a PK/PD collection worksheet.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers. Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: protocol number, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:

500 series: tumor biopsies
800 series: blood for pharmacogenomic analysis

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer or lack of dry ice in a shipping

container allows for extensive sample thawing, etc.) will be reported as such to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

All specimens obtained in the protocol are used as defined in the protocol, and any new use of these samples will require prospective IRB review and approval. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below; the study will remain open so long as sample or data analysis continues.

5.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.4.1 Description of the scope of genetic/genomic analysis

Optional biopsy samples will be collected at baseline and during cycle 7, but delinking will occur once a patient has come off study for one of the reasons listed in Section 3.6 or has had a response. At this point, patient identifiers will be de-linked and the Clinical Tumor Profiling Laboratory will perform whole exome sequencing on the de-identified samples; this lab is CLIA-certified for sample handling but not for the correlative studies that will be performed on this study. No genetic data will be shared with the patient. The process for de-identifying the samples is described further below.

A section of each biopsy will be stained for H&E and the stained slide scanned into an Aperio Image Database. For a tumor biopsy sample to be considered adequate, a minimum of 40% of the biopsy should have tumor content; biopsy samples with a lower tumor content will **not** undergo macrodissection or laser capture microdissection to enrich for tumor cells. In cases where sufficient tumor DNA is not obtained for analysis, the patient will be given the option to undergo a repeat tumor biopsy to obtain more tissue.

The remaining specimen will be extracted using Qiagen's AllPrep FFPET nucleic acid extraction methodology. Resultant DNA and RNA will be quantified by NanoDrop spectroscopy. 500 ng DNA will be analyzed for copy number variation on an Illumina CytoSNP array following standard protocols. If sufficient DNA is obtained, 500 ng will be used for sequencing library preparation using standard Illumina methods. The identical procedure will be applied to the blood sample. Both libraries will be sequenced on an Illumina HiSeq 2000 sequencer. If sample is sufficient, 1 µg of RNA from the ALLPrep extraction will be converted to cDNA and sequenced on the HiSeq2000. If available, 250-750 ng of tumor DNA will be analyzed using Illumina 450K methylation arrays.

5.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Archival tumor, blood, and optional tumor biopsy samples will be collected from participants on this study, but genetic analysis will only be performed on de-identified samples. Whole-exome sequencing (performed for research purposes) of tumor and blood can detect nonambiguous germline variants, which may raise health and privacy implications for the patient and his or her family. Whole exome sequencing on this study

will not be validated for clinical use and no clinical decisions can be made based on its results. No genetic data will be shared with the patient or his/her family. Given the uncertain clinical significance of some of these variants and the ethical implications, we will perform such research analysis on de-identified samples only.

Clinical information linked to the unique patient IDs will be stored in a bioinformatics database. Once the patient has been taken off study or at a defined time point determined by the study PI, the unique patient ID will be deleted and a new random ID generated (arbitrary or random alphanumeric code) in the database by the bioinformatics team, thereby un-linking the patient identifier from the information in the database. The Bioinformatics team will inform the Clinical Tumor Profiling Lab of the new random ID, all samples from a given patient will be transferred to the new ID, and the Clinical Tumor Profiling Lab will also break the link to the unique patient ID. The unique patient IDs will be discarded so there is no possibility of linking the samples to the sources. The Clinical Tumor Profiling Lab will proceed with whole exome sequencing on de-identified samples for research purposes only. Data reports sent to the clinical site will be summary reports with no identifiable patient IDs whatsoever.

This study affords a unique opportunity to collect information about mutations in genes associated with desmoids tumors, a rare and poorly characterized cancer, as well as how patients' tumors respond to this targeted therapy. The NIH IRB will be consulted and kept informed of progress of this study and other trials conducted with the study agent that may affect study design and conduct.

5.4.3 Management of Results

Given the uncertain clinical significance of some of the variants in genes of interest to this study and the ethical implications of these potential findings, we will perform genetic research analysis on de-identified samples only. No genetic data will be shared with the patient or his/her family. A Certificate of Confidentiality will not be obtained for this study.

5.4.4 Genetic counseling

N/A; all samples will be unlinked before analysis.

5.5 MAGNETIC RESONANCE IMAGING (MRI) – OPTIONAL ONLY

According to the National Comprehensive Cancer Network's guidelines on soft tissue sarcomas[32], MRI is a recommended imaging modality for patients with desmoids tumors and will be offered in cases where it is deemed appropriate. MR imaging will consist of 3 components: T2 weighted (T2W), diffusion weighted (DW) and Dynamic Contrast Enhanced MRI (DCE). Imaging will be performed at 3 Tesla in the Molecular Imaging Clinic. Each sequence contributes a different functional parameter to the study. It is estimated the scan time will be approximately 30 minutes. There are well known contraindications to MRI that will be observed (e.g., shrapnel, a pacemaker, etc.). For the gadolinium injection, the patient must have an eGFR > 30cc/min.

Here we describe the value of each imaging parameter:

T2W provides anatomic imaging of the lesion at high spatial resolution. T2W signal is also dependent on the amount of free water in the lesion. It is predicted that with increasing fibrosis, water content will decrease, thus shortening the T2 of the lesion, resulting in a darker lesion. The T2 value can be calculated and additionally, ratios of the tumor to an unaffected tissue (e.g., muscle) can provide a quantitative index of changes consistent with fibrosis over time.

DW depends on the Brownian motion of water within tissue. By using varying "b values", one can calculate the Apparent Diffusion Coefficient (ADC) which is an index of water diffusion in tissue (higher values indicate more water diffusion) Loose connective tissue is associated with free water migration resulting in high ADC values, whereas dense connective tissue associated with fibrosis would be predicted to restrict diffusion resulting in progressively lower ADC values. For this protocol, we will obtain serial ADC values at each time point.

DCE MRI consists of the rapid acquisition of T1 weighted images before, during and after the bolus administration of a gadolinium-containing MR contrast agent. Serial regions of interest are then placed over the tumor and time-signal curves are generated. By calculating the T1 of the tissue prior to injection, one can convert the signal intensity into the actual gadolinium concentration within the tissue over time. These gadolinium concentration-time curves can then be fit to a 2-compartment exponential model that generates parameters associated with the initial uptake of contrast (Ktrans) and with the washout of the contrast (kep), both of which are related to vascular permeability. In addition, heuristic measurements of the curve such as area under the curve (AUC) and time to peak (TTP) can be measured to add further data. Angiogenic inhibitors are predicted to decrease Ktrans, kep, AUC, and TTP and are especially useful when compared in the same patient over time. Gamma-secretase inhibitors have been shown to affect the leakiness of blood vessels; therefore, serial DCE-MRI measurements will be obtained in patients over time.

Optional MRI scans may be performed at baseline prior to study drug administration, at the end of cycle 1 and at the time of restaging, per PI's discretion. Although optional, every attempt to will be made to obtain MRI scans on patients when possible. To accommodate scheduling issues, scans can be performed +/- one week from the scheduled date.

5.6 HUMAN DATA SHARING PLAN

What data will be shared?

We will share human data generated in this research for future research as follows:

X De-identified data in an NIH-funded or approved public repository
X Identified data in BTRIS (automatic for activities in the Clinical Center)
X De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?

Data will be shared through:

X An NIH-funded or approved public repository: clinicaltrials.gov
X BTRIS (automatic for activities in the Clinical Center)

X Approved outside collaborators under appropriate individual agreements
X Publication and/or public presentations

When will the data be shared?
X At the time of publication or shortly thereafter

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

All data will be kept secure. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number.

All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

6.2 RESPONSE CRITERIA

CT restaging scans will be performed at baseline prior to study drug administration and then every 6 cycles (+/- one cycle). An MRI scan with diffusion weighting may be performed prior to start of study treatment, end of cycle 1, and at the time of restaging, per PI's discretion. In addition to a baseline scan, confirmatory CT scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [33]. Changes in the largest diameter (unidimensional measurement) of the tumor

lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.2.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with Nirogacestat.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.2.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions

with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all

scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in

cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.2.4 Response Criteria

6.2.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.2.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.2.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript [33] for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

6.2.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that

recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs). There will be no adverse event reporting on the extended follow-up portion of this trial.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events, and Policy 802: Non-Compliance in Human Subjects Research (found in https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs). Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here: https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP/IRB in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to the Clinical Director/designee at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 EXPEDITED ADVERSE EVENT REPORTING CRITERIA TO THE IND MANUFACTURER

All serious adverse events must be reported in the defined timelines to CCRsafety@mail.nih.gov. The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below:

Reporting of Serious Adverse Events. Within 24 hours of sponsor awareness of the event, the sponsor will report to SpringWorks by facsimile any Serious Adverse Event ("SAE," as defined in Section 7.1.4) that occurs during the SAE reporting period (as defined in Section 7.1) in a study subject assigned to receive Nirogacestat. The PI will report such SAEs using an FDA MEDWATCH form or equivalent. The *Reportable Event Fax Cover Sheet* provided by should also be provided. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

7.5 NIH OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)/INSTITUTIONAL BIOSAFETY COMMITTEE (IBC) REPORTING CRITERIA

N/A.

7.6 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.6.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose modification if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section 7.2.1 will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to Section **Error! Reference source not found.**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form

and instructions can be found at:
https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=157942842

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

Reporting will be per the collaborative agreement.

8.5 REPORTING PREGNANCY

8.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.5.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of Nirogacestat.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 30 days after the last dose should, if possible, be followed up and documented.

8.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL SECTION

This study will be conducted as a single stage Phase II trial to rule out an unacceptably low 10% clinical response rate (PR+CR; p0=0.10) in favor of a modestly high response rate of 35% (p1=0.35). If we assume a type I error rate (alpha, probability of accepting a poor treatment) of 0.10 when the response rate is 0.10 and a statistical power of 0.90 (beta=0.10, probability of rejecting a good treatment) when the true response rate is 0.35, then we plan to accrue a total of 17 patients. The null hypothesis will be rejected if 4 or more responses are observed in the 17 patients. It is anticipated that 1 patient per month may be enrolled onto this study. Thus, it will take approximately 17 months to complete enrollment.

10.1 STATISTICAL CONSIDERATIONS FOR EXPLORATORY CORRELATIVE STUDIES

Symptom measurements will be summarized by mean and standard deviation for continuous measurements and by frequency distributions for categorical measurements. Mutations in *APC* and *CTNNB1* will be summarized with frequency distributions, respectively. The clinical response rate will be compared between the mutated and non-mutated subgroups. Modulation of the Notch pathway will be assessed by a paired t-test for a change in expression from baseline to post-drug administration.

11 COLLABORATIVE AGREEMENTS

11.1 AGREEMENT TYPE

Springworks is providing the agent used in this study to the PI under a Collaborative Agreement (CTA); providing this agent constitutes the research support for this investigator-initiated study.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

Men and women of all races and ethnic groups are eligible for this trial.

12.2 PARTICIPATION OF CHILDREN

Because no dosing or adverse event data are currently available on the use of Nirogacestat in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

12.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

This study will be open to all individuals regardless of gender, ethnicity, or race, provided that the aforementioned inclusion and exclusion criteria are met. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

12.3.1 Patient Advocate

The patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at (301) 496-2626 in Building 10 of the Clinical Research Center, Room 1-3521, on the Bethesda NIH campus. Patients will be informed that they can contact the study PI or RN at any time with questions about their medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

12.4 RISKS/BENEFITS ANALYSIS

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of nirogacestat side effects (listed in Section 13.1.1), gene sequencing risks (Section 5.4.2), MRI imaging risks (Section 13.2), and phlebotomy and CT radiation and contrast agent risks (details below). The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Section 3. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication. This research

represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects.

Risks Related to CT Radiation: This study includes 2 optional CT-guided tumor biopsies and up to 3 CT restaging scans per year. These procedures confer radiation exposure at an effective dose of up to approximately 6 rem per year. This dose is above NIH RSC guidelines of less than 5.0 rem per year in adults.

Risks Related to Contrast Agents:

Risks for IV Contrast: Symptoms from the contrast infusion are usually mild and may include discomfort from the injection, feeling hot, a metallic taste, nausea or vomiting, and allergic reaction (ranging from mild itching or rash to severe trouble breathing, shock or, rarely, death). The contrast may also cause kidney problems.

Risks for Oral Contrast: Symptoms from oral contrast are usually mild and may include vomiting, nausea, cramping, bloating, constipation, or diarrhea.

Risks Related to Phlebotomy: There are no major risks involved with blood draws. Minor complications include bleeding, pain, bruising at the site of phlebotomy, vasovagal reactions or infections may rarely occur.

12.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to Medical Records; a copy will be placed in the research record. Patients will not be consented by telephone

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

When a hand signature on an electronic document is used for the documentation of consent, this study will use the iMedConsent platform (which is 21 CFR Part 11 compliant) to obtain the required signatures. Both the investigator and the participant will sign the electronic document using a finger, stylus, or mouse. Electronic signatures (i.e., “signatures” that are digitally generated) will not be used.

12.5.1 Participation of subjects unable to give consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (*i.e.*, long-term stabilization and/or improvement in the pain and physical impairment caused by desmoid tumors), all subjects ≥ age 18 at the NCI only will be offered the

opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 19-1 and NIH OHSRP Policy 403 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

13 PHARMACEUTICAL AND DEVICE INFORMATION

13.1 NIROGACESTAT (PF-03084014) (IND #119,769)

PF-03084014 is an investigational agent supplied by SpringWorks; the dihydrobromide salt form will be used in the clinical studies.

Molecular Weight: 651.47 (dihydrobromide salt)

Molecular Formula: $C_{27}H_{43}Br_2F_2N_5O$

Physical Description: white to off-white powder

Route: oral

Mechanism of Action: selective noncompetitive inhibitor of γ-secretase

Contraindications: none identified

Other Names: PF-4014

13.1.1 Nirogacestat Toxicity

Preclinical—The target systems reported in chronic oral dosing studies in dogs were the GI, hematopoietic/ immune, musculoskeletal, reproductive, and hepatic systems. Hematopoietic/immune effects were seen in both rat and dog, and included decreases in B and T cells, NK cells, IgM and IgD expression on B cells (rat only), and lymphoid depletion in spleen, thymus (thymic cortical atrophy in dog), lymph nodes, and/or gut-associated lymphoid tissue. Treatment-related intestinal tract changes consisted of epithelial hyperplasia and, with higher exposures, epithelial degeneration and necrosis (more detailed information is provided in Section 1.2.2).

Clinical—The most common AEs independent of causality seen in patients with advanced solid tumors were diarrhea, nausea, fatigue, vomiting, hypophosphatemia, decreased appetite, cough and rash; all of these events were considered to be treatment related in some patients. The majority of AEs were considered mild to moderate but treatment related Grade 3 hypophosphatemia, diarrhea, and rash have been frequently reported. The only treatment-related

Grade 4 AE was anaphylactic shock reported in one patient, an event thought to be related to co-administration of intravenous morphine.

No clinically relevant changes in vital signs or electrocardiograph endpoints have been reported. The severe hematology laboratory test abnormalities reported were low lymphocyte count and platelets. The most frequently reported severe serum chemistry abnormalities were hypophosphatemia, hypokalemia and hyperglycemia (more detailed information is provided in Section 1.2.2).

An IND/CIOMS safety report was issued to study sites on 18 December 2019 for a serious adverse event of "premature menopause" in a 25-year-old female participant on the randomized phase 3 study. Since this event was reported, 3 additional SAE reports for potential primary ovarian insufficiency have been reported to SpringWorks Therapeutics. SpringWorks has conducted a comprehensive review of adverse events entered into the electronic data capture (EDC) system and are actively following 2 additional cases of hot flashes/ facial flushing to determine if these are symptoms of primary ovarian insufficiency or due to other unrelated causes. SpringWorks, site investigators, and site staff remain blinded to study treatment and it is unknown if these participants were receiving nirogacestat or placebo, but "primary ovarian insufficiency" as a risk for women of childbearing potential has been added to the informed consent form with Amendment L.

As of June 21, 2021, the SpringWorks Global Safety Committee additionally designated hidradenitis suppurativa, folliculitis, and alopecia as “identified risks” in patients treated with nirogacestat. Of note, none of these risks met the criteria for being designated as “important” identified risks. These risks have been added to the informed consent form with Amendment N. The basis for the decision for each event is as follows:

- Recognized hidradenitis suppurativa as an identified risk based on
  - the validated signal process, analysis, and final Signal Assessment Report
  - Gamma secretase inhibition mechanism involving hair follicles described in the literature
- Recognized folliculitis as a validated signal and an identified risk
  - Observation during hidradenitis Safety Assessment Report analysis
  - Gamma secretase inhibition mechanism involving hair follicles shared with hidradenitis as described in the literature
- Recognized alopecia as a validated signal and an identified risk
  - Observation identified as part of the hidradenitis and folliculitis investigations
  - Gamma secretase inhibition mechanism involving hair follicles shared with hidradenitis as described in the literature
  - Decrease in estrogen due to ovarian insufficiency could lead to release of follicle from
  - telogen and loss of hair [34]
  - Estrogen depletion during menopause can lead to female pattern hair loss [35]

As of April 25, 2023, Springworks identified non-melanoma skin cancer (defined as the MedDRA Preferred terms of Basal cell carcinoma, Squamous cell carcinoma, and Squamous cell carcinoma of the skin) as an important potential risk for nirogacestat, based on occurrence in six nirogacestat trial participants. All participants have continued treatment with nirogacestat after

the report of their non-melanoma skin cancer [with three patients on extended treatment, up to 1448 days after onset of their non-melanoma skin cancer] with no reported occurrence of another non-melanoma skin cancer. No reports of malignant melanoma have been reported from participants in the nirogacestat development program. SpringWorks recommended that an association between treatment with nirogacestat and the appearance and diagnosis of non-melanoma skin cancer be recognized as an important potential risk for nirogacestat, and this risk has been added to the informed consent form with Amendment R (version date 5/18/2023).

13.1.2 Formulation and Preparation

Nirogacestat is available as 10 mg and 50 mg tablets. All tablets contain common compendial excipients.

13.1.3 Stability and Storage

Tablets should be stored at 15-25° C (59-77°F).

13.1.4 Incompatibilities/Drug Interactions

In vitro studies indicate that Nirogacestat is metabolized primarily by the drug-metabolizing enzyme, CYP3A4. Nirogacestat does not inhibit CYP1A2, weakly inhibits CYP2C9, CYP2C19 and CYP2D6, and causes induction of CYP3A4. Nirogacestat may however increase exposure to sensitive substrates of CYP2C9, CYP2C19, and CYP2D6, or CYP2C9, CYP2C19, and CYP2D6 substrates with a narrow therapeutic range.

- **Cytochrome P450 Inhibitors**: Co-administration of Nirogacestat with potent inhibitors of CYP3A4 may increase plasma Nirogacestat concentrations. Caution should be exercised in patients receiving Nirogacestat in combination with these and other potent CYP3A4 inhibitors (see Appendix C).
- **Cytochrome P450 Inducers:** Nirogacestat metabolism may be induced when taking potent CYP3A4 inducers resulting in reduced Nirogacestat plasma concentrations. Caution should be exercised in patients receiving Nirogacestat in combination with these and other potent CYP3A4 inducers (see Appendix C).
- **Cytochrome P450 Substrates:** Patients treated with Nirogacestat should avoid the use of CYP3A4 substrates with narrow therapeutic indices (see Appendix C).

13.2 MAGNETIC RESONANCE IMAGING SCANNER

The use of Magnetic Resonance Imaging scanners on this study for assessment of disease burden meets the requirements for an IDE exemption under Category 1. The devices in the Clinical Center are commercially obtained and FDA approved. The device is being used in accordance with FDA labeling and was not regulated as a device before the enactment of the Medical Device Amendments

13.2.1 Source

MRI scans will be performed using the devices available in the NIH Clinical Center.

13.2.2 MRI and Contrast Agent Toxicity

Risks associated with MRIs include the following: participants may be at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for participants to have an MRI scan if they have a pacemaker or other implanted electrical device, brain stimulator; some types of dental implants, aneurysm clips, and metallic prostheses (including metal pins and rods, heart valves, and cochlear implants); permanent eyeliner; implanted delivery pump; or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. Participants will be screened for such metal before having any scan. If they have any, you will not receive an MRI scan. If they have a question about metal in their body, they should inform the study investigators. Participants will be asked to complete an MRI screening form before each MRI scan they have.

All magnetic objects must be removed before entering the MRI scan room. This includes items like watches, coins, jewelry, and credit cards.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, participants should let us know right away.

Symptoms from the contrast infusion are usually mild and may include feeling hot, burning, or coldness in the arm during the injection, a metallic taste, headache, allergic reactions and nausea. In an extremely small number of individuals, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. Unless specifically allowed by the protocol, participants will not receive gadolinium-based contrast agents for research purposes if they have previously had an allergic reaction to them. Individuals with a history of anaphylaxis to other agents or chronic asthma requiring treatment will not receive gadolinium under this protocol unless they have previously received gadolinium and tolerated it well. Participants will be asked about such allergic reactions and history of asthma before a contrast agent is administered.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis,” which has resulted in a very small number of deaths. If subjects are 60 years old or greater or have diabetes, kidney disease or liver disease, blood work to assess kidney function will be performed within 4 weeks before any MRI scan with gadolinium contrast. Participants may not receive gadolinium for a research MRI scan if kidney function is not normal. There is no evidence for the potential of gadolinium-related toxicity in people with normal kidney function. This protocol follows NIH Clinical Center guidelines for kidney-function screening related to gadolinium administration.

Most of the gadolinium contrast is eliminated in the urine. However, recent studies have found very small amounts of residual gadolinium in the body, including the brain, by imaging and at autopsy. Macrocyclic gadolinium-containing contrast agents are substantially less likely to leave gadolinium behind than linear agents. The use of macrocyclic vs. linear agents in this study is delineated in the procedures section above. There is presently no evidence that the retained gadolinium is associated with any adverse effects.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		
Grade	Descriptions	Percent
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100
		90
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80
		70
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60
		50
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40
		30
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20
		10
5	Dead.	0

APPENDIX B: PATIENT'S MEDICATION DIARY

INSTRUCTIONS

1. Complete one form for each cycle of treatment.
2. Swallow study drugs whole with a full glass of water. There is no restriction on taking the study drug with food. Do not chew the tablets.
3. Record the date and time you took the drugs.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottle of drugs when you return for your appointment.
6. In case you make a mistake when filling in his form, please place a single slash mark through the error (~~error~~) and initial it. Please do not white out any errors or scribble them out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.

Today's Date _____Cycle #_____ Nirogacestat Dose _____mg

Patient Name_____(*initials are acceptable)* **Patient Study ID**_____

Day	Date	Time of dose AM	PM	Number of Tablets Taken	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					

Patient's signature: _____

Patient Study Calendar

Nirogacestat treatment is given over periods called cycles. All cycles are 3 weeks (21 days) long. Treatment cycles will be repeated as long as you are tolerating the drug and your cancer is either stable or getting better. Each cycle is numbered in consecutive order.

The chart below shows what will happen during Cycle 1 and future cycles. The left-hand column shows the day in the cycle, and the right-hand column tells you what will happen on that day. This schedule shows what will happen to you after you sign the consent and start the study.

Day	What to do and what will happen to you
Before starting study drug	• Check in at the Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider • Get routine blood and urine tests • Have a research blood sample taken • Pregnancy test for women who are able to become pregnant • Take a health questionnaire • CT scan of the known site of disease will be done o Research tumor biopsy may be taken (optional)
Cycle 1, Day 1	• Admitted to Clinical Center • Begin taking Nirogacestat by mouth twice a day each day • EKG will be done
Cycle 1, Days 2-20	• Continue taking Nirogacestat by mouth twice a day each day • Get routine blood tests each week during cycle 1
Cycle 1, Day 21	• Continue taking Nirogacestat by mouth twice a day each day • An optional MRI scan to measure how your tumors are responding to Nirogacestat treatment may be performed per PI's discretion
Cycle 2, Week 1	• Check in at the Outpatient Clinic • Get routine blood tests at the start of each new cycle • Continue taking Nirogacestat by mouth twice a day each day
Cycle 3 and onwards	• Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider at the start of every other cycle (if you have been on the study for more than a year, this will be done every 3 cycles, up to 2 weeks before the start of the cycle) • Get routine blood tests every other cycle (if you have been on the study for more than a year, this will be done every 3 cycles, up to 2 weeks before the start of the cycle) • Continue taking Nirogacestat by mouth twice a day each day

Day	What to do and what will happen to you
Cycle 6 **Day 21**	• Continue taking Nirogacestat by mouth twice a day each day • CT scan to measure how your tumors are responding to Nirogacestat treatment will be done every 6 cycles (+/- 1 cycle) (about 4 months) • An optional MRI scan to measure how your tumors are responding to Nirogacestat treatment may be done every 6 cycles (about 4 months) per PI's discretion • Take a health questionnaire when we measure how your tumors are responding to Nirogacestat treatment (every 6 cycles, about 4 months)
Cycle 7 **Day 1**	• Continue taking Nirogacestat by mouth twice a day each day **Only for patients who undergo research tumor biopsies (optional)** • Check in at the Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider o Research tumor biopsy may be taken (optional)

APPENDIX C: POTENTIAL DRUG INTERACTIONS

Co-administration of Nirogacestat with potent inhibitors of CYP3A4 may increase plasma concentrations. Nirogacestat metabolism may be induced when taking potent CYP3A4 inducers, resulting in reduced plasma concentrations. Patients treated with Nirogacestat should also avoid the use of CYP3A4 substrates with narrow therapeutic indices.

CYP2C19 Inhibitors

Amiodarone	Felbamate	Methoxsalen	Ritonavir
Amitriptyline	Fenofibrate	Methsuximide	Rosiglitazone
Amprenavir	Fluconazole	Miconazole	Saquinavir
Aprepitant	Fluoxetine	Moclobemide	Selegiline
Azelastine	Fluvoxamine	Modafinil	Sertraline
Bortezomib	Fosamprenavir	Nelfinavir	Sildenafil
Buprenorphine	Gefitinib	Nicardipine	Sulconazole
Cholecalciferol/Vitamin D_3	Gemfibrozil	Nilutamide	Telmisartan
Cimetidine	Imipramine	Olanzapine	Ticlopidine
Citalopram	Indinavir	Omeprazole	Tioconazole
Clotrimazole	Indomethacin	Orphenadrine	Topiramate
Clozapine	Isoniazid	Oxcarbazepine	Torsemide
Delavirdine	Ketoconazole	Paroxetine	Tranylcypromine
Diazepam	Lansoprazole	Pentamidine	Valdecoxib
Dimethyl sulfoxide	Letrozole	Pimozide	Valproic acid
Drospirenone	Loratadine	Pioglitazone	Voriconazole
Efavirenz	Losartan	Probenecid	Warfarin
Entacapone	Mephobarbital	Progesterone	Zafirlukast
Ethinyl estradiol	Mestranol	Propofol	
Ethotoin	Methimazole	Rabeprazole	

CYP2C19 Inducers

Aminoglutethimide Carbamazepine	Fosphenytoin Phenytoin	Rifampin	St. John's wort

CYP2C19 Substrates

Carisoprodol	Escitalopram	Methsuximide	Phenobarbital
Cilostazol	Esomeprazole	Moclobemide	Phenytoin
Citalopram	Fosphenytoin	Nelfinavir	Progesterone
Clobazam	Imipramine	Nilutamide	Rabeprazole
Clomipramine	Lansoprazole	Omeprazole	Sertraline
Desogestrel	Mephenytoin	Pantoprazole	Trimipramine
Diazepam	Mephobarbital	Pentamidine	Voriconazole

Only major substrates and effective inducers are listed. Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

CYP3A4 Inhibitors

Acetazolamide	Diclofenac	Lomustine	Primaquine
Amiodarone	Dihydroergotamine	Losartan	Progesterone
Amlodipine	Diltiazem	Lovastatin	Propofol
Amprenavir	Disulfiram	Mefloquine	Propoxyphene
Anastrozole	Docetaxel	Mestranol	Quinidine
Aprepitant	Doxorubicin	Methadone	Quinine
Atazanavir	Doxycycline	Methimazole	Quinupristin
Atorvastatin	Drospirenone	Methoxsalen	Rabeprazole
Azelastine	Efavirenz	Methylprednisolone	Ranolazine
Azithromycin	Enoxacin	Metronidazole	Risperidone
Betamethasone	Entacapone	Miconazole	Ritonavir
Bortezomib	Ergotamine	Midazolam	Saquinavir
Bromocriptine	Erythromycin	Mifepristone	Selegiline
Caffeine	Ethinyl estradiol	Mirtazapine	Sertraline
Cerivastatin	Etoposide	Mitoxantrone	Sildenafil
Chloramphenicol	Felodipine	Modafinil	Sirolimus
Chlorzoxazone	Fentanyl	Nefazodone	Sulconazole
Cimetidine	Fluconazole	Nelfinavir	Tacrolimus
Ciprofloxacin	Fluoxetine	Nevirapine	Tamoxifen
Cisapride	Fluvastatin	Nicardipine	Telithromycin
Clarithromycin	Fluvoxamine	Nifedipine	Teniposide
Clemastine	Fosamprenavir	Nisoldipine	Testosterone
Clofazimine	Glyburide	Nizatidine	Tetracycline
Clotrimazole	Grapefruit juice	Norfloxacin	Ticlopidine
Clozapine	Haloperidol	Olanzapine	Tranylcypromine
Cocaine	Hydralazine	Omeprazole	Trazodone
Conivaptan	Ifosfamide	Orphenadrine	Troleandomycin
Cyclophosphamide	Imatinib	Oxybutynin	Valproic acid
Cyclosporine	Indinavir	Paroxetine	Venlafaxine
Danazol	Irbesartan	Pentamidine	Verapamil
Dasatinib	Isoniazid	Pergolide	Vinblastine
Delavirdine	Isradipine	Phencyclidine	Vincristine
Desipramine	Itraconazole	Pilocarpine	Vinorelbine
Dexmedetomidine	Ketoconazole	Pimozide	Voriconazole
Diazepam	Lansoprazole	Pravastatin	Zafirlukast
	Lidocaine	Prednisolone	Ziprasidone

CYP3A4 Inducers

Aminoglutethimide	Nafcillin	Pentobarbital	Primidone	Rifapentine
Carbamazepine	Nevirapine	Phenobarbital	Rifabutin	St. John’s wort
Fosphenytoin	Oxcarbazepine	Phenytoin	Rifampin	

CYP3A4 Substrates

Albuterol	Docetaxel	Ketamine	Progesterone
Alfentanil	Doxepin	Ketoconazole	Quetiapine
Alprazolam	Doxorubicin	Lansoprazole	Quinidine
Amlodipine	Doxycycline	Letrozole	Rabeprazole
Amprenavir	Efavirenz	Levomethadyl acetate hydrochloride	Repaglinide
Aprepitant	Eletriptan	Levonorgestrel	Rifabutin
Aripiprazole	Enalapril	Lidocaine	Rifampin
Atazanavir	Eplerenone	Losartan	Ritonavir
Atorvastatin	Ergoloid mesylates	Lovastatin	Saquinavir
Benzphetamine	Ergonovine	Medroxyprogesterone	Sertraline
Bisoprolol	Ergotamine	Mefloquine	Sibutramine
Bortezomib	Erythromycin	Mestranol	Sildenafil
Bosentan	Escitalopram	Methadone	Simvastatin
Bromazepam	Estradiol	Methylergonovine	Sirolimus
Bromocriptine	Estrogens, conj., synthetic	Methysergide	Sufentanil
Buprenorphine	Estrogens, conj., equine	Miconazole	Tacrolimus
Buspirone	Estrogens, conj., esterified	Midazolam	Tamoxifen
Busulfan	Estrone	Miglustat	Tamsulosin
Carbamazepine	Estropipate	Mirtazapine	Telithromycin
Cerivastatin	Ethinyl estradiol	Modafinil	Teniposide
Chlordiazepoxide	Ethosuximide	Montelukast	Terbinafine
Chloroquine	Etoposide	Moricizine	Tetracycline
Chlorpheniramine	Felbamate	Nateglinide	Theophylline
Cisapride	Felodipine	Nefazodone	Tiagabine
Citalopram	Fentanyl	Nelfinavir	Ticlopidine
Clarithromycin	Flurazepam	Nevirapine	Tolterodine
Clobazam	Flutamide	Nicardipine	Toremifene
Clonazepam	Fosamprenavir	Nifedipine	Trazodone
Clorazepate	Fulvestrant	Nimodipine	Triazolam
Cocaine	Gefitinib	Nisoldipine	Trimethoprim
Colchicine	Halofantrine	Nitrendipine	Trimipramine
Cyclophosphamide	Haloperidol	Norethindrone	Troleandomycin
Cyclosporine	Ifosfamide	Norgestrel	Vardenafil
Dantrolene	Imatinib	Ondansetron	Venlafaxine
Dapsone	Indinavir	Paclitaxel	Verapamil
Delavirdine	Irinotecan	Pergolide	Vinblastine
Diazepam	Isosorbide dinitrate	Phencyclidine	Vincristine
Digitoxin	Isosorbide mononitrate	Pimozide	Vinorelbine
Dihydroergotamine	Isradipine	Pioglitazone	Zolpidem
Diltiazem	Itraconazole	Primaquine	Zonisamide
Disopyramide			Zopiclone

CYP2C8/9 Inhibitors

Amiodarone	Felodipine	Modafinil	Sertraline
Amitriptyline	Fluconazole	Montelukast	Sildenafil
Amlodipine	Fluoxetine	Nateglinide	Simvastatin
Anastrozole	Fluphenazine	Nelfinavir	Sulconazole
Aprepitant	Flurbiprofen	Nicardipine	Sulfadiazine
Atazanavir	Fluvastatin	Nifedipine	Sulfamethoxazole
Azelastine	Fluvoxamine	Olanzapine	Sulfinpyrazone
Bortezomib	Gemfibrozil	Omeprazole	Sulfisoxazole
Candesartan	Ibuprofen	Ondansetron	Tamoxifen
Chloramphenicol	Imatinib	Orphenadrine	Teniposide
Cholecalciferol (Vitamin D_3)	Indinavir	Pantoprazole	Thioridazine
Cimetidine	Indomethacin	Paroxetine	Ticlopidine
Clopidogrel	Irbesartan	Pentamidine	Tioconazole
Clotrimazole	Isoniazid	Pioglitazone	Tolbutamide
Clozapine	Ketoconazole	Piroxicam	Tolcapone
Cyclosporine	Ketoprofen	Pravastatin	Tranylcypromine
Delavirdine	Lansoprazole	Progesterone	Tretinoin
Dexmedetomidine	Leflunomide	Propafenone	Triazolam
Diclofenac	Losartan	Propofol	Trimethoprim
Diltiazem	Lovastatin	Propoxyphene	Valdecoxib
Dimethyl sulfoxide	Mefenamic acid	Pyrimethamine	Valproic acid
Disulfiram	Meloxicam	Quinidine	Valsartan
Drospirenone	Methimazole	Quinine	Verapamil
Efavirenz	Methoxsalen	Ritonavir	Voriconazole
Entacapone	Metronidazole	Rosiglitazone	Warfarin
Eprosartan	Miconazole	Saquinavir	Zafirlukast
Etoposide	Midazolam	Selegiline	

CYP2C8/9 Inducers

Carbamazepine	Phenobarbital	Primidone	Rifapentine
Fosphenytoin	Phenytoin	Rifampin	Secobarbital

CYP2C8/9 Substrates

Alosetron	Losartan	Rifampin	Tolbutamide
Amiodarone	Mephenytoin	Rosiglitazone	Torsemide
Bosentan	Mestranol	Selegiline	Trimethoprim
Carvedilol	Montelukast	Sertraline	Voriconazole
Fluoxetine	Nateglinide	Sulfadiazine	Warfarin
Fosphenytoin	Paclitaxel	Sulfamethoxazole	Zafirlukast
Glimepiride	Phenytoin	Sulfinpyrazone	Zopiclone
Glipizide	Pioglitazone	Sulfisoxazole	
Ketamine	Propofol	Tamoxifen	

CYP2D6 Substrates

Amitriptyline	Diphenhydramine	Maprotiline	Propranolol
Atomoxetine	Dolasetron	Metoclopramide	Protriptyline
Carvedilol	Doxepin	Metoprolol	Risperidone
Chlorpheniramine	Duloxetine	Mexiletine	Tamoxifen
Chlorpromazine	Flecainide	Nortriptyline	Thioridazine
Clomipramine	Fluoxetine	Palonosetron	Timolol
Codeine	Fluvoxamine	Paroxetine	Tolterodine
Desipramine	Haloperidol	Perhexiline	Tramadol
Dextromethorphan	Hydrocodone	Promethazine	Trazodone
Dihydrocodeine	Imipramine	Propafenone	Venlafaxine

APPENDIX D: QUALITY-OF-LIFE QUESTIONNAIRE

Date:
Subject Initials: Study Subject #

M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interefered Completely 10
14. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
15. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
16. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
17. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
18. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
19. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

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OTHER SYMPTOMS

Do you have any other symptoms that you wish to report?

○ Yes ○ No

Please list these other symptoms in the chart below and rate the severity each symptom by filling in a circle from 0 (symptom not present) to 10 (symptom was as bad as you can imagine)

	What was the severity of this symptom at its WORST? *not present*										*as bad as you can imagine*
List any other symptoms	0	1	2	3	4	5	6	7	8	9	10
1.	○	○	○	○	○	○	○	○	○	○	○
2.	○	○	○	○	○	○	○	○	○	○	○
3.	○	○	○	○	○	○	○	○	○	○	○
4.	○	○	○	○	○	○	○	○	○	○	○
5.	○	○	○	○	○	○	○	○	○	○	○
6	○	○	○	○	○	○	○	○	○	○	○

APPENDIX E: QTC PROLONGATION

The following table presents a list of drugs that prolong, may prolong, or are unlikely to prolong the QTc. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website:
http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine /Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram /Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine /Anafranil®
Bepridil /Vascor®	Chloral hydrate /Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril®	Diphenhydramine /Benadryl®
Chlorpromazine /Thorazine®	Dolasetron /Anzemet®	Diphenhydramine /Nytol®
Cisapride /Propulsid®	Dronedarone /Multaq®	Doxepin /Sinequan®
Clarithromycin /Biaxin®	Felbamate /Felbatrol®	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor®	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx®	Galantamine /Reminyl®
Droperidol /Inapsine®	Gatifloxacin /Tequin®	Imipramine /Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporanox®
Erythromycin /E.E.S.®	Granisetron /Kytril®	Ketoconazole /Nizoral®
Halofantrine /Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil®
Haloperidol /Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl /Orlaam®	Lapatinib /Tyverb®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Levofloxacin /Levaquin®	Sertraline /Zoloft®

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Methadone /Dolophine®	Lithium /Lithobid®	Solifenacin /VESIcare®
Methadone /Methadose®	Lithium /Eskalith®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Moxifloxacin /Avelox®	Trimipramine /Surmontil®
Pimozide /Orap®	Nicardipine /Cardene®	
Probucol /Lorelco®	Nilotinib /Tasigna®	
Procainamide /Pronestyl®	Octreotide /Sandostatin®	
Procainamide /Procan®	Ofloxacin /Floxin®	
Quinidine /Cardioquin®	Ondansetron /Zofran®	
Quinidine /Quinaglute®	Oxytocin /Pitocin®	
Sotalol /Betapace®	Paliperidone /Invega®	
Sparfloxacin /Zagam®	Perflutren lipid microspheres /Definity	
Terfenadine /Seldane®	Quetiapine /Seroquel®	
Thioridazine /Mellaril®	Ranolazine /Ranexa®	
	Risperidone /Risperdal®	
	Roxithromycin* /Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend®	
	Ziprasidone /Geodon®	

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