SUMMARY OF CHANGES

Date: 05APR2019

Document: NCI Protocol **9664**: "*Pilot Study for the Treatment of Steroid-Refractory Sclerodermatous Chronic Graft-Versus-Host Disease (GVHD) with GDC-0449 (GDC-0449)*."

Note: The following is a Summary of Changes for the 05APR2019 protocol version #13

Protocol Changes:

Section	Description of Change
All pages	Updated to reflect current version date.
Title Page	Updated to reflect current version information and update study staff
9.1.2 Definition of Response to Therapy	Added definitions for GVHD assessments to define response to therapy.
10.1 Study Design/Study Endpoints	Added a secondary endpoint to clarify that response to therapy is a secondary endpoint.
10.2 Sample Size/Accrual Rate/Other Statistical Considerations	Updated to describe how response assessment data will be reported.
ICF	No changes to the Informed Consent Document. ICF version date has been updated to 05APR2019

NCI Protocol #: **9664**

IRB #: **84584**

Lead Org. ID #: **Huntsman Cancer Institute/University of Utah**

TITLE: PILOT STUDY FOR THE TREATMENT OF STEROID-REFRACTORY SCLERODERMATOUS CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD) WITH GDC-0449 (GDC-0449)

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NCI Supplied Agent: GDC-0449 (NSC 747691)

Historical Protocol Versions
Original (NCI Version 4): 6-14-2015
Version #5: 07-16-2015
Version #6: 08-03-2015
Version #7: 08-10-2015
Version #8: 11-24-2015
Version #9: 05-17-2016
Version #10: 06-29-2017
Version #11: 04-12-2018
Version #12: 07-09-2018
Version #13: 04-05-2019

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
Allo	Allogeneic
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BCC	Basal Cell Carcinoma
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRC	Colorectal Cancer
CRF	Case report form

Abbreviation or Term[1]	Definition/Explanation
CTCAE	Common Toxicity Criteria for Adverse Events
CRF	Case report form
CSS	Clinical Study Synopsis
CV	Curriculum Vitae
CYP	Cytochrome P450
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
ECM	Extra Cellular Matrix
EMA	European Medicines Agency
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FFS	Failure-Free Survival
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good laboratory practice
GVHD	Graft-Versus-Host Disease
HDL	High Density Lipoprotein
HH/h	Hedgehog Signaling Pathway
HIV	Human immunodeficiency virus
hr	Hour or hours
HSCT	Hematopoietic Stem Cell Transplantation
i.e.	Id est (that is)
INR	International normalized ratio
IPF	Interstitial Pulmonary Fibrosis
IRB	Institutional review board
LDH	Lactate dehydrogenase
LDL	Low Density Lipoprotein

Abbreviation or Term[1]	Definition/Explanation
MMH	Mohs Micrographic Surgery
MTD	Maximum tolerated dose
NIH	National Institutes of Health
NRM	Non-Relapse Mortality
OS	Overall Survival
PD	Progressive Disease
PDE	Prednisone Dose Equivalent
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
QOL	Quality of Life
QTc	QT interval corrected
RSS	Regulatory Support System
SAE	Serious adverse event
SD	Standard deviation or stable disease
SMO	Smoothened
$T_{1/2}$	Terminal elimination half-life
T_{max}	Time of maximum observed concentration
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

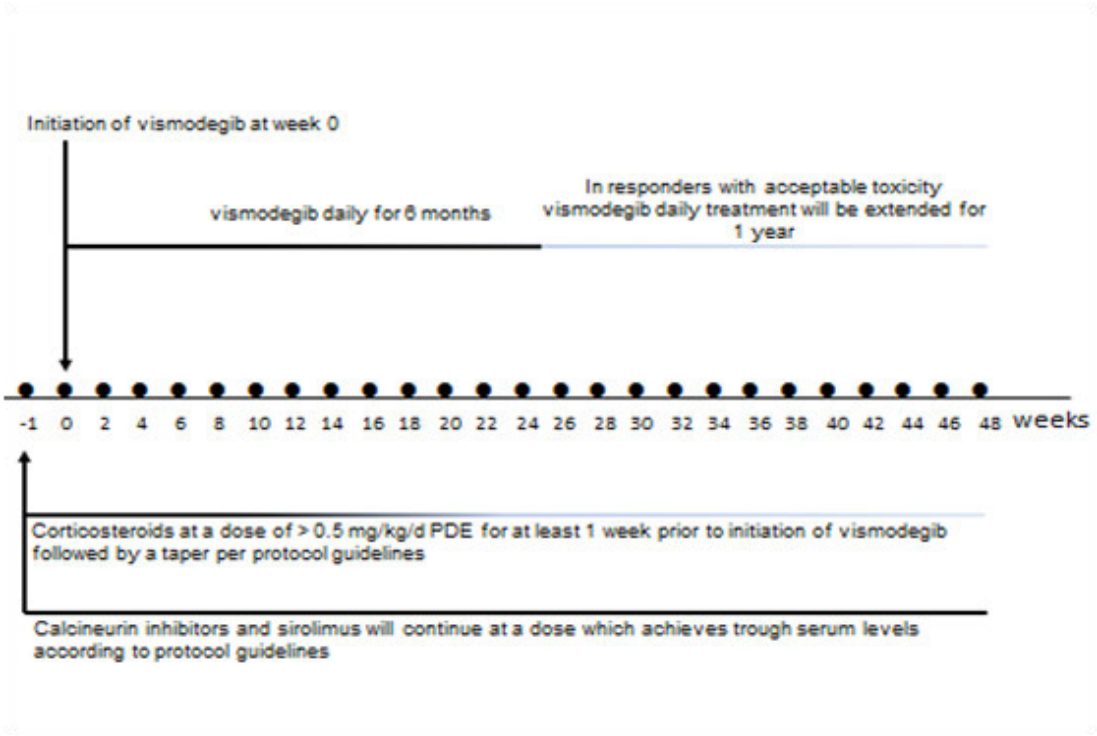
STUDY SUMMARY

Title	Pilot Study for the Treatment of Steroid-Refractory Sclerodermatous Chronic Graft-Versus-Host Disease (GVHD) with GDC-0449
Short Title	GDC-0449 for the treatment of GVHD
IRB Number	84584
Phase	Pilot
Design	This is an open label non-randomized pilot study to the clinical effects and safety of GCD-0449 in patients with hematologic malignancies who have undergone Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) and have been diagnosed with chronic GVHD.
Study Duration	Two years
Study Center(s)	Single Center – Huntsman Cancer Institute
Objectives	Primary Objectives: • To determine the clinical effects of GDC-0449, in steroid-refractory chronic graft versus host disease (GVHD) Secondary Objectives: • To determine the safety of GDC-0449 in patients with steroid-refractory GVHD • To determine the change in National Institutes of Health (NIH) Consensus Criteria (CC) global score of chronic GVHD at 6 and 12 months from baseline • To determine one-year non relapse mortality (NRM) and one-year relapse rate • To determine one-year failure-free survival (FFS) and one-year overall survival (OS) • To determine baseline clinical characteristics that may be associated with decreased FFS

Number of Subjects	12 patients
Diagnosis and Main Eligibility Criteria	Inclusion: 1. Patients with chronic GVHD diagnosed within 3 years after hematopoietic stem cell transplant (HSCT) for any disease, with any graft, and any conditioning regimen with at least one manifestation secondary to fibrosis, including: sclerodermatous skin changes, dry mouth, dry eye, esophageal strictures, or vaginal GVHD 2. Failure to respond to corticosteroids, defined as: • Progression of chronic GVHD despite optimal first line therapy (> 0.5 mg/kg/day of prednisone dose equivalent (PDE) for two weeks) or; • No improvement after 4-8 weeks of sustained therapy. Sustained therapy should include 2 weeks of > 0.5 mg/kg/day of PDE or; • Inability to taper steroid dosage to less than 0.5 mg/kg/day of PDE without worsening of chronic GVHD or; • Need for second or third line therapy beyond corticosteroids and calcineurin inhibitors or sirolimus, irrespective of other criteria listed under the current section Exclusion: 1. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. 2. More than 2 lines of therapy beyond

	corticosteroids with or without calcineurin inhibitors or sirolimus 3. Relapsed malignancy after transplantation
Study Product, Dose, Route, Regimen	GDC-0449 will be given orally at 150 mg daily for a total of 6 months. Dosing will start at 150 mg daily. Dose reductions may be made in the case of intolerable toxicities that do not meet discontinuation criteria. Dose Level -1: 150 mg every other day Dose Level -2: 150 mg every three days Dose Level -3: 150 mg twice a week In patients who are responsive to therapy with acceptable toxicity, the treatment period will be extended to 12 months.
Statistical Methodology	This is a pilot study that will include 12 patients. FFS, the primary endpoint, will be evaluated using the Kaplan-Meier method. The impact of different covariates on FFS will be analyzed using descriptive statistics, t-test, and Fisher's exact test where applicable. Differences in NIH scores will be analyzed using Wilcoxon signed-rank test. Differences in biomarkers will be assessed using Wilcoxon rank-sum test. The proportion of subjects who experience adverse events and serious adverse events will be summarized descriptively; no inferential tests will be performed.

SCHEMA


Initiation of vismodegib at week 0
vismodegib daily for 6 months
In responders with acceptable toxicity vismodegib daily treatment will be extended for 1 year
-1 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 weeks
Corticosteroids at a dose of > 0.5 mg/kg/d PDE for at least 1 week prior to initiation of vismodegib followed by a taper per protocol guidelines
Calcineurin inhibitors and sirolimus will continue at a dose which achieves trough serum levels according to protocol guidelines

1 OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the clinical effects of GDC-0449, in steroid-refractory chronic graft versus host disease (GVHD)

1.2 Secondary Objectives

1.1.2 To determine the safety of GDC-0449 in patients with steroid-refractory GVHD
1.1.3 To determine the change in National Institutes of Health (NIH) Consensus Criteria (CC) global score of chronic GVHD at 6 and 12 months from baseline
1.1.4 To determine one-year non relapse mortality (NRM) and one-year relapse rate
1.1.5 To determine one-year failure-free survival (FFS) and one-year overall survival (OS)
1.1.6 To determine baseline clinical characteristics that may be associated with decreased FFS

2 BACKGROUND

2.1 Chronic GVHD

Allogeneic (Allo) Hematopoietic Stem Cell Transplantation (HSCT) is a potentially curative treatment modality for patients with hematologic malignancies who would otherwise have a poor outcome with other conventional treatment approaches alone. Allo HSCT causes donor-derived immune responses that can result in the desired graft-versus-tumor effect as well as the undesired complication, Graft versus Host Disease (GVHD). Chronic GVHD is the main complication for long term survivors of a successful AlloHSCT. Chronic GVHD occurs in more than 50 % of all patients who undergo an allo HSCT and the majority of patients who develop acute GVHD as a complication of their allo HSCT. Chronic GVHD can involve multiple organs and require prolonged immunosuppressive therapy. Advanced chronic GVHD is typically manifested by significant fibrous tissue deposition in different organs, leading to disabling symptoms, most commonly as a consequence of sicca syndrome and sclerodermatous forms of the disease. Sicca syndrome can lead to severe pain, visual impairment, and mucositis leading to malnutrition. Sclerodermatous chronic GVHD can cause dramatic limitations in the range of motion, with different degrees of immobility, and occasionally restrictive pulmonary disease. At this stage, current treatment strategies are almost always ineffective, at least in part due to the irreversibility of manifestations related to fibrosis. The mainstay of first-line immunosuppressive therapy in patients with chronic GVHD is systemic glucocorticoids and there are no standard second-line therapies. Systemic glucocorticoids have limited efficacy and significant long term complications. Despite the many alternative immunosuppressive agents to systemic glucocorticoids, no single class of immunosuppressive agents has persistently produced a steroid-sparing effect in patients with chronic GVHD [1-7]. In conclusion, Chronic GVHD and its current standard therapy have a major negative impact on the quality of life (QOL) and survival in patients in whom allo

HSCT was able to achieve a cure from their original hematologic malignancy. Therefore, there is a desperate need for more effective agents in treating chronic GVHD.

2.2 CTEP Agent

2.2.1 GDC-0449

The hedgehog (Hh) signaling pathway is a crucial mediator of embryogenesis [8]. Signaling is initiated by the binding of the secreted morphogen, Hh, to its receptor, patched 1 (Ptch1). In the unbound state, Ptch1 inhibits Smoothened (SMO), a G-protein coupled phosphoprotein receptor, by preventing its localization to the cell surface; however, in the presence of the Hh ligand, the Hh-Ptch1 complex is internalized and the repression of Ptch1 on SMO is relieved. Surface localization of SMO is thought to initiate a signaling cascade, leading to the activation of the glioma-associated (Gli) family of zinc finger transcription factors, many of which are involved in proliferation, survival, and angiogenesis.

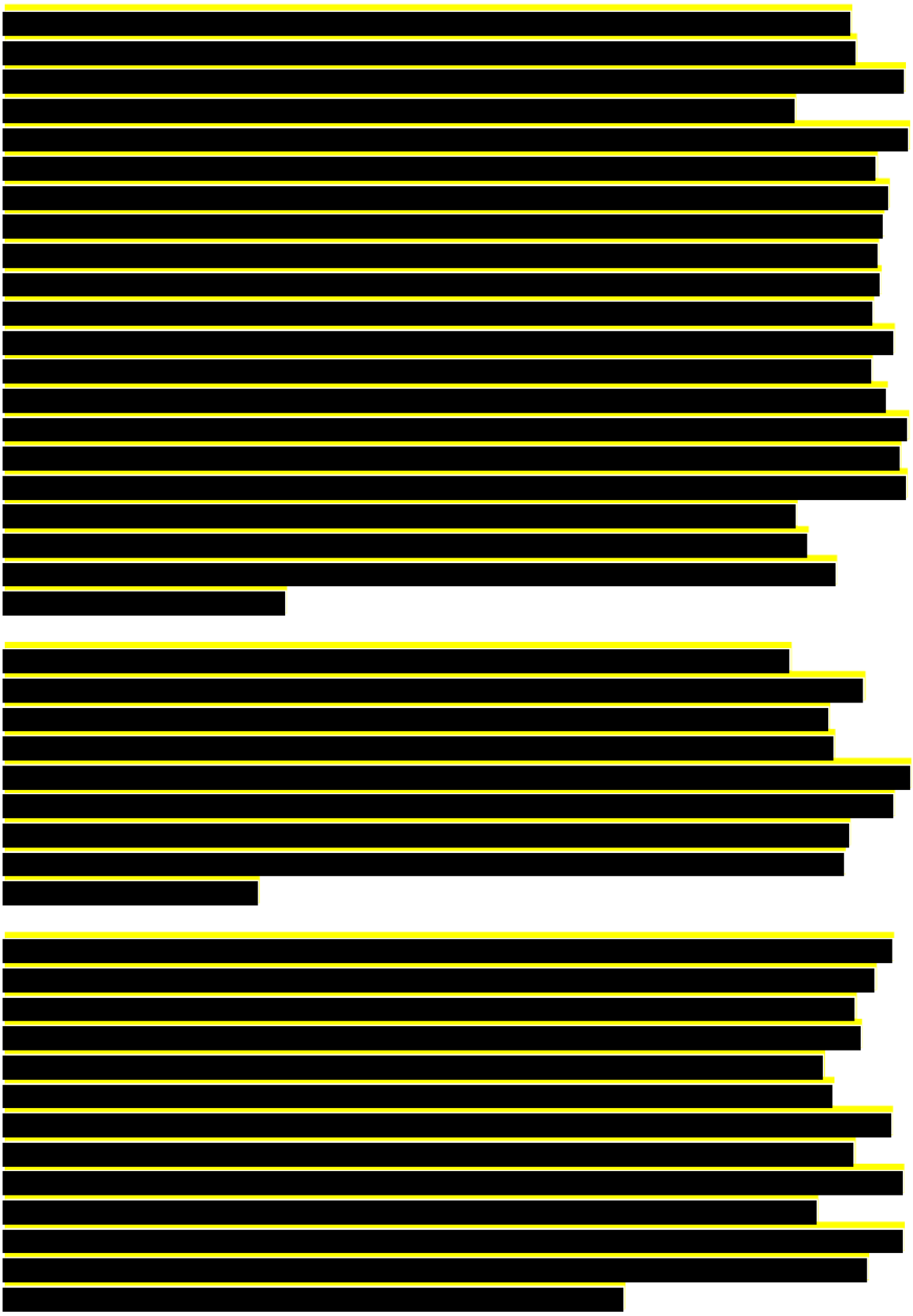
Aberrant activation of the Hh pathway in cancers is caused by mutations in the pathway or through Hh overexpression, termed either ligand-independent or ligand-dependent, respectively [9, 10]. Past studies have identified mutations in the Hh receptor components, Ptch1 or SMO in basal cell carcinoma (BCC) and medulloblastoma, resulting in constitutive pathway activation [11, 12]. Excessive or inappropriate expression of the Hh ligand has been found in a significant proportion of patients with sporadic cancers of the gastrointestinal tract, pancreas, lung and prostate, suggesting that disruption of Hh signal transduction could potentially be beneficial in a broad array of tumor types [13-16]. Evidence suggests that antagonism of excessive Hh signaling may provide a route to unique mechanism-based anticancer therapies, blocking tumor growth and stimulating tumor regression without toxic effects on normal adjacent tissue [17].

GDC-0449 binds to and inhibits SMO, whose only established function is to transmit the Hh signal. Specific SMO mutations have been identified that alter the ability of GDC-0449 to bind and inhibit the activity of SMO, thereby directly linking the action of GDC-0449 to SMO (Investigator's Brochure, 2015).GDC-0449 has demonstrated efficacy against a variety of primary human tumor xenografts, including colorectal cancer (CRC) and pancreatic adenocarcinoma, and tumor cell-line xenograft models. Inhibition of Hh signaling in xenograft models has been correlated with a decrease in tumor growth.

GDC-0449 has been studied in a number of Phase I and Phase II studies. These studies have evaluated the dose and schedule, pharmacokinetic (PK) profile, and efficacy of GDC-0449 in a number of indications, including first-line metastatic colorectal cancer (mCRC), ovarian cancer in second or third complete remission, and advanced basal cell carcinoma (aBCC). Clinical pharmacology studies have examined the potential of GDC-0449 for DDIs; dose-schedule optimization; effect of GDC-0449 on QTc interval prolongation; effect of food on the PK of GDC-0449; and the absorption, distribution, metabolism, and excretion of GDC-0449. A Phase I study in patients with varying degrees of renal and hepatic function has also been completed (Study GP27839). On 30

January 2012, the U.S. Food and Drug Administration (FDA) approved ERIVEDGE® (GDC-0449, or GDC-0449) capsules for the treatment of adults with mBCC, or with laBCC that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. On 12 July 2013, GDC-0449 was approved for the treatment of adult patients with symptomatic mBCC and laBCC inappropriate for surgery or radiotherapy based on a conditional marketing authorization from the European Medicines Agency (EMA). The approval was on the basis of results from Study SHH4476g, a single-arm, 2-cohort trial that enrolled 104 patients. Efficacy was evaluated in 96 patients with confirmed BCC[18].

Summary of Nonclinical Data



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Clinical Experience

Vismodegib has been studied, is currently being studied, or is planned to be studied in 22 Phase I, II, and IV clinical studies by the Sponsor (Investigator Brochure, 2015). To date, 15 studies have been completed and closed. Another four studies are ongoing and two are pending. One study (Study GO28852) was prematurely terminated, based on discontinuation of enrollment, by the Sponsor due to lower than anticipated efficacy. No safety issues were identified in this study to date. Thirty-four of a planned 60 patients have been enrolled and completed vismodegib treatment, and have been requested to continue safety and survival follow-up per protocol. Studies that have a CSR or a Clinical Study Synopsis (CSS) are briefly summarized in the sections below. Phase II studies

evaluating the efficacy and safety of vismodegib in first-line mCRC (Study SHH4429g), ovarian cancer in second or third complete remission (Study SHH4489g), and in aBCC (Study SHH4476g) have been completed. The expanded access study in the United States (Study SHH4811) has been completed, because vismodegib is available commercially. The global safety study (Study MO25616) continues after conditional approval in the EU to further evaluate safety and efficacy of vismodegib in aBCC. Studies analyzing vismodegib in operable BCC (Study SHH4812g) and drug-drug interactions of vismodegib with a combined P-glycoprotein (P-gp)/cytochrome P450 (CYP) 3A4 inhibitor or a CYP2C9 inhibitor (Study GP28465) have been completed. A Phase Ib, open-label, PK and safety study (Study GP27839) of vismodegib in patients with advanced solid tumors, including hepatocellular carcinoma, with varying degrees of renal or hepatic function has been completed. An extension study (Study SHH4437g) has been completed, which had been opened to permit patients deriving clinical benefit at the time of closure of Genentech-sponsored parent studies to continue receiving vismodegib. Other Phase II and IV studies evaluating the efficacy and safety of vismodegib in multiple BCC (Study MO28295) and in BCC preceding excision by Mohs micrographic surgery (MMS), as well as an observational study of treatment patterns, effectiveness, and safety outcomes in advanced BCC and BCCNS patients (Study ML28296/RegiSONIC) are ongoing. Additionally, vismodegib is being studied in 15 clinical trials under a Collaborative Research and Development Agreement Letter of Intent with the NCI Division of Cancer Treatment and Diagnosis and under agreements for four ISTs, which comprise multiple Phase I and Phase II studies. For a current list of NCI-sponsored and investigator-sponsored studies, refer to http://www.clinicaltrials.gov. A Phase II study (Study GB29298) that will evaluate the efficacy and safety of vismodegib in patients with IPF is being planned.

Reproductive and Developmental Toxicity

Fertility

Dedicated studies to assess the potential of vismodegib to affect fertility have not been performed. However, data from studies in rats and dogs indicate that male and female fertility may be compromised by treatment with vismodegib.

Increased numbers of degenerating germ cells and hypospermia were observed in relatively young dogs treated for 4 weeks at ≥ 50 mg/kg/day (corresponding to 2.2-fold greater than the average AUC0-24h steady-state exposure at the recommended human dose), which were not fully reversed by the end of a 4-week recovery period. No corresponding findings were observed at similar doses in 13-week and 26-week toxicity studies with sexually mature dogs. A relative decrease in percent motile sperm was observed in some male rats treated for 26 weeks at ≥ 15 mg/kg/day (corresponding to 34% of the average AUC0-24h steady-state exposure at the recommended human dose), which was not reversed by the end of an 8-week recovery period. No corresponding microscopic changes in the testis or epididymis or changes in sperm count, staging, or morphology were observed. A decrease in the number of corpora lutea was observed in female rats treated for 26 weeks at 100 mg/kg/day (corresponding to 1.1-fold of the average AUC0-24h steady-state exposure at the recommended human dose), which was not reversed by the end of an 8-week recovery period.

Teratogenicity

In an embryo-fetal development study in which pregnant rats were administered vismodegib daily during organogenesis, vismodegib crossed the placenta and was severely toxic to the conceptus. Malformations, including craniofacial anomalies, open perineum, and absent and/or fused digits, were observed in fetuses of dams at 10 mg/kg/day (corresponding to 20% of the average AUC0-24hr steady-state exposure at the recommended human dose). The incidence of fetal retardations or variations and incompletely or unossified sternal elements, centra of cervical vertebrae, or proximal phalanges and claws was also increased at 10 mg/kg/day. Vismodegib was embryo-lethal at ≥ 60 mg/kg/day (corresponding to 2.8-fold of the average AUC0-24h steady-state exposure at the recommended human dose). Findings in toxicity studies with vismodegib indicated a risk of adverse effects during post-natal development. Administration of vismodegib to rats resulted in irreversible changes in growing teeth (degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in the dental pulp, ossification of the root canal, and hemorrhage) and closure of the epiphyseal growth plate.

2.3 Hedgehog (HH) pathway and fibrosis

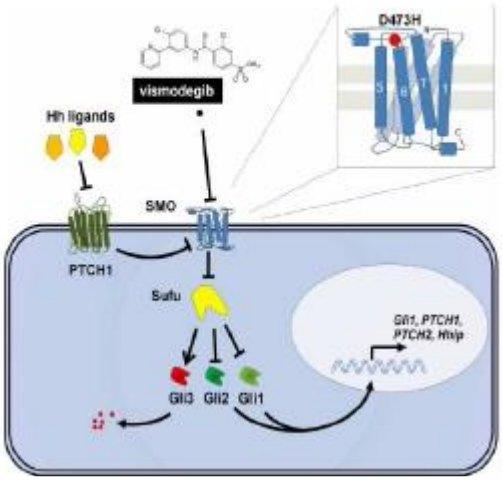
The HH pathway is considered a major morphogen in embryonic development, but it remains silent in most adult tissues [6]. There are three HH proteins: Sonic HH (Shh), Indian HH (Ihh) and Desert HH (Dhh). Shh is the most frequent ligand in the skin. In the absence of this ligand, the HH receptor Patched homologue-1 (Ptch-1) prevents activation of the HH pathway through inhibition of the co-receptor Smoothened (Smo). Mutations at the level of Ptch-1 or uncontrolled expression of the HH ligands can result in abnormal activation of HH in adults, releasing the inhibition of Smo by Ptch-1. Smo then induces stabilization of Gli transcription factors such as Gli-1 and Gli-2. Gli-1 and Gli-2 stimulate the transcription of HH target genes and activation of the HH pathway [34].Carcinogenesis and fibro proliferative disorders, including basal cell carcinoma of the skin, interstitial systemic sclerosis, interstitial pulmonary fibrosis (IPF), cirrhosis and human and murine chronic GVHD, have recently been associated with the activation of the HH pathway[34-39].This association has led to HH pathway inhibition emerging as a new therapeutic target.

2.4 Rationale for HH pathway inhibition as a new therapeutic target

As aforementioned, activation of the HH pathway has recently been linked to carcinogenesis and fibro proliferative disorders. In basal cell carcinoma of the skin, significant advancement has been made in understanding the role of HH signaling pathway[35]. This advancement has led to the rapid development of preclinical and clinical testing of targeted hedgehog pathway inhibitors which led to the US Food and Drug Administration (FDA) approval of GDC-0449, the first hedgehog pathway inhibitor for the treatment of advanced basal cell carcinoma[40, 41]. In a vital phase 2 trial, GDC-0449 was associated with tumor responses in 96 patients with locally advanced or metastatic basal-cell carcinoma[18].In systemic sclerosis, Shh was found to be overexpressed, with accumulation of Gli-1 and Gli-2. This activated phenotype led to the differentiation of resting fibroblasts into my fibroblasts, and in turn increased production of collagen [36]. Therefore, the HH pathway is a profibrotic pathway in systemic sclerosis. Furthermore, HH pathway inhibition had strong antifibrotic effects in preclinical models of systemic sclerosis in both the preventive and therapeutic settings [37]. In IPF, cross talk between TGF-B1, a central profibrotic cytokine, and the HH pathway was described in normal and IPF fibroblasts, where TGF-B1 modulated the expression of key components of the HH pathway. In addition, a functional HH pathway as well as GLI-dependent transcription in the nucleus was required for TGF-B1 effects on both normal and IPF fibroblasts during myofibroblastic differentiation [38] . Therefore, these data identified the GLI transcription factors as potential therapeutic targets in IPF. In human and murine chronic GVHD, HH pathway signaling was recently found to be activated with increased expression of Shh and accumulation of the transcription factors Gli-1 and Gli-2 [34]. Inhibition of the HH pathway with selective Smo inhibitor, LDE223 had effective antifibrotic effects both in the preventive and therapeutic settings of murine sclerodermatous chronic GVHD without affecting the potential benefits of a graft-versus leukemia response [34]. In conclusion, HH pathway activation has profibrotic effects and targeted HH pathway inhibition has potential antifibrotic effects in basal cell carcinoma, systemic sclerosis, IPF and sclerodermatous chronic GVHD.

2.5 GDC-0449 in steroid-refractory sclerodermatous chronic GVHD

Inhibition of the HH pathway has emerged as a new therapeutic target with antifibrotic effects. GDC-0449, a small molecule that binds and inhibits Smo, has been approved by the FDA for the treatment of advanced basal cell carcinoma [40]. As aforementioned, Active Smo signals downstream promoting the release of Gli family transcription factors which activate transcription of multiple target genes, including key regulators of the HH pathway, notably Gli1 and Ptch-1 (Figure adapted from [40]).



GDC-0449 binds to the extracellular domain of SMO, markedly inhibiting downstream signaling, even in the absence of Ptch-1. The first documented mechanism of clinical acquired resistance to GDC-0449 is a secondary mutation in the extracellular domain of Smo, D473H (indicated in the inset in the figure as a red circle), which prevents GDC-0449 binding. GDC-0449's safety was assessed in phase 1 trials in patients with refractory, locally advanced or metastatic solid tumors and in patients with advanced basal cell carcinoma [42, 43]. There was no maximum tolerated dose (MTD) reached. The recommended phase 2 trials dose was 150 mg/day, based on maximal plasma concentration achievement and pharmacodynamic response at this dose. In a phase 2 trial of GDC-0449 in patients with locally advanced or metastatic basal-cell carcinoma, all patients had at least one adverse effect [18]. More than half the treated patients (57%) had only grade 1 or 2 adverse events. Adverse events occurring in more than 30% of patients were muscle spasms, alopecia, dysgeusia (taste disturbance), weight loss, and fatigue. Serious adverse events were reported in 25% of patients, but the relationship between the drug and these deaths is unknown. In summary, given the need for more effective agents in treating chronic GVHD, the potential antifibrotic effect of HH inhibition in chronic GVHD, and the established safety and efficacy of GDC-0449, a SMO inhibitor, we hypothesize that target therapy of steroid refractory sclerodermatous chronic GVHD with GDC-0449 has the potential of preventing or reversing fibrosis and sparing steroid use.

2.6 Correlative Studies/Biomarkers Background

The pathophysiology of chronic GVHD is poorly understood, to date biomarkers to predict the disease course or guide therapy are not available. Moreover, the current therapeutic approaches have limited efficacy, particularly in patients with advanced chronic GVHD. Advanced chronic GVHD is defined by extensive fibrous tissue deposition in different organs, leading to considerable morbidity and mortality. Therefore, early diagnosis and treatment of chronic GVHD could prevent irreversible fibrotic damage and decrease morbidity and

mortality. Thus, this emphasizes the need for biomarkers to risk stratify patients with chronic GVHD and guide the optimal timing and intensity of therapy in these patients.

We hypothesize that chronic GVHD is a fibro proliferative process and thus patients with chronic GVHD will have changes in the production and/or turnover of the ECM. These changes can provide more understanding of the pathophysiology of chronic GVHD and introduce biomarkers for risk stratification and targeted therapy. We previously evaluated ECM turnover biomarkers in 112 patients with newly diagnosed chronic GVHD. Biomarkers were classified according to their role in fibrogenesis. Levels of three profibrotic proteins (CCL2, IGF-1, IL-13Ra) significantly correlated with TGF-B levels. TGF-B provided the strongest association with clinical outcomes one year after the diagnosis of chronic GVHD. Low levels of TGF-B were associated with more relapse, more NRM, lower progression free survival (PFS), and lower overall survival (OS) than high levels of TGF-B. High TGF-B levels and high IL-13 levels were associated with development of sclerotic chronic GVHD. Low levels of MMP2, an antifibrotic metalloproteinase, were associated with development of sclerotic chronic GVHD. These results suggested that ECM turnover is active at the time of chronic GVHD onset, even prior to the development of clinically apparent sclerosis [44]. Therefore, further investigation of changes in the production and/or turnover of the ECM at baseline, and following treatment may provide a better understanding of the pathophysiology of chronic GVHD and help develop new biomarker opportunities for risk stratification and targeted treatment of chronic GVHD.

3 STUDY DESIGN

3.1 Description

This is an open label non-randomized pilot study to determine the clinical effects and safety of GCD-0449 in patients with hematologic malignancies who have undergone Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) and have been diagnosed with chronic GVHD.

GDC-0449 will be given orally for a total of 6 months. In patients who are responsive to therapy with acceptable toxicity, the treatment period will be extended to 12 months. The initial dose will be given at 150 mg po daily. If Grade 2 hematologic or non-hematologic toxicities attributable to the study drug are observed, three different, consecutive dose reduction levels may be utilized:

- Level -1 (150 mg po every other day)
- Level -2 (150 mg po every three days)
- Level -3 (150 mg po twice a week)

All initial dose reductions will start at Level -1 and proceed to the next level if the toxicity in question persists. Dosing schedules will be dependent on what day of the week the patient starts the dose reduction level; for example, patients on Dose Level -1 with a Monday start would dose on Wednesday, Friday, Sunday, and so on.

3.2 Number of Patients

Twelve patients will be enrolled in this study. Sample size: 12 patients. Accrual rate: 1-2 patients monthly.

3.3 Number of Study Centers

This will be a single center study performed at the Huntsman Cancer Institute.

3.4 Study Duration

Estimated duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study) is approximately two years. The accrual rate is estimated to be 1-2 patients per month. Patients will remain on study treatment for 6-12 months and will complete all study procedures in 12-18 months.

4 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with signature in the patient research chart.

Patient No. _____
Patient's Initials: (L,F,M) _____

4.1 *Inclusion Criteria*

Yes/No (Response of "no" = patient ineligible)

4.1.1 _____ Age ≥18 years.
Because no dosing or adverse event data are currently available on the use of GDC-0449 in patients <18 years of age, children are excluded from this study.

4.1.2 _____ ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

4.1.3 _____ Life expectancy of greater than 12 months

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

☐ Leukocytes	≥3,000/mcL
☐ Absolute neutrophil count	≥1,500/mcL
☐ Platelets	≥50,000/mcL
☐ Total Bilirubin	within normal institutional limits
☐ AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
☐ Creatinine	≤1.5 mg/dl
	OR
☐ Creatinine Clearance	≥55 mL/min using the Cockcroft-Gault equation for patients with creatinine

levels above 1.5 mg/dl.

4.1.5 _____ Patients with chronic GVHD diagnosed within 3 years after hematopoietic stem cell transplant (HSCT) for any disease, with any graft, and any conditioning regimen with at least one manifestation secondary to fibrosis, including: sclerodermatous skin changes, dry mouth, dry eye, esophageal strictures, or vaginal GVHD

4.1.6 _____ Failure to respond to corticosteroids, defined as:

- ☐ Progression of chronic GVHD despite optimal first line therapy (> 0.5 mg/kg/day of prednisone dose equivalent (PDE) for two weeks) or;
- ☐ No improvement after 4-8 weeks of sustained therapy. Sustained therapy should include 2 weeks of > 0.5 mg/kg/day of PDE or;
- ☐ Inability to taper steroid dosage to less than 0.5 mg/kg/day of PDE without worsening of chronic GVHD or;
- ☐ Need for second or third line therapy beyond corticosteroids and calcineurin inhibitors or sirolimus, irrespective of other criteria listed under the current section.

4.1.7 _____ The effects of GDC-0449 on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because Hh signal pathway inhibitors are known to cause interruption of the embryonic signaling pathway and may lead to serious or life-threatening birth defects, including brain deformities, facial malformation, heart problems, or abnormal organs. Therefore, women of child-bearing potential and men must use two forms of contraception (i.e., barrier contraception and one other method of contraception) at least 4 weeks prior to study entry, for the duration of study participation, and for at least 24 months post-treatment. For appropriate methods of contraception considered acceptable see Appendix B. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Pregnancy Testing. Women of childbearing potential are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 7 days prior to the first dose of GDC-0449 (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks if their menstrual cycles are regular or every 2 weeks if their cycles are irregular while on study within the 24-hour period prior to the administration of GDC-0449. A positive urine test must be confirmed by a serum pregnancy test. Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of GDC-0449 cause serious or life-threatening birth defects. Patients must continue highly effective contraception during therapy and for 24 months after the last dose of GDC-0449

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 12 months in a woman > 45 years old.

Male patients should use condoms with spermicide, even after a vasectomy, during sexual intercourse with female partners while being treated with GDC-0449 and for 3 months after the last dose to avoid exposing an embryo or fetus to GDC-0449

4.1.8 _____HIV-positive patients on combination antiretroviral therapy are eligible provided that they meet the following criteria in addition to the other protocol criteria:

- ☐ Cancer as the only AIDS-defining condition
- ☐ CD4 cell count ≥250,
- ☐ Treatment sensitive HIV and prospects for long term survival on the basis of HIV disease alone
- ☐ Willing to take anti-HIV therapy that will have minimal potential for pharmacokinetic interactions with GDC-0449.

4.2 Exclusion Criteria

4.2.1 _____ Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

4.2.2 _____ Patients who are receiving any other investigational agents.

4.2.3 _____ Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

4.2.4 _____ History of allergic reactions attributed to compounds of similar chemical or biologic composition to GDC-0449

4.2.5 _____ Patients receiving any medications or substances that are strong inducers/inhibitors or substrates of CYP3A4/5, CYP2C9, CYP2C8, or CYP2C19 are ineligible. Because the lists of these agents are constantly changing, it is

important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

4.2.6 _____ Patients with malabsorption syndrome or other condition that would interfere with intestinal absorption. Patients must be able to swallow capsules.

4.2.7 _____ Patients with clinically important history of liver disease, including viral or other hepatitis or cirrhosis are ineligible.

4.2.8 _____ Patients with uncontrolled hypocalcemia, hypomagnesemia, hyponatremia or hypokalemia defined as less than the lower limit of normal for the institution, despite adequate electrolyte supplementation are excluded from this study.

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

4.2.10 _____ Pregnant women are excluded from this study because GDC-0449 is a Hh pathway inhibiting agent with the potential for serious or life-threatening birth defects or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with GDC-0449, breastfeeding should be discontinued if the mother is treated with GDC-0449. These potential risks may also apply to other agents used in this study.

4.2.11 _____ More than 2 lines of therapy beyond corticosteroids with or without calcineurin inhibitors or sirolimus.

4.2.12 _____ Relapsed malignancy after transplantation

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____	_____	_____
Investigator Signature	**Date**	**Time**

4.3 Inclusion of Women and Minorities

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

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	-	-	-	-	-
Asian	1	1	-	-	**2**
Native Hawaiian or Other Pacific Islander	-	-	-	-	-
Black or African American	1	1	-	-	**2**
White	3	3	1	1	**8**
More Than One Race	-	-	-	-	-
Total	**5**	**5**	**1**	**1**	**12**

5 TREATMENT PLAN

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 14. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Administration Schedule

- GDC-0449 is an oral drug. Patients should take GDC-0449 at approximately the same time according to their dose level, with or without food. Capsules should not be opened. If a patient misses a dose, he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses should not be made up. Patients will be instructed to bring all unused capsules and their medication diary (refer to Appendix D) to each study visit for assessment of compliance.

- Patients should be warned not to share their supply of GDC-0449.

- Investigators may dispense no more than a 32-day supply of GDC-0449.

- GDC-0449 will be given orally for a total of 6 months. In patients who are responsive to therapy with acceptable toxicity, the treatment period will be extended to 12 months. The initial dose will be given at 150 mg po daily. If Grade 2 hematologic or non-hematologic toxicities attributable to the study drug are observed, three different, consecutive dose reduction levels may be utilized:

  - Level -1 (150 mg po every other day)
  - Level -2 (150 mg po every three days)
  - Level -3 (150 mg po twice a week)

  All initial dose reductions will start at Level -1 and proceed to the next level if the toxicity in question persists. Dosing schedules will be dependent on what day of the week the patient starts the dose reduction level; for example, patients on Dose Level -1 with a Monday start would dose on Wednesday, Friday, Sunday, and so on.

5.2 CTEP Agent

5.2.1 GDC-0449 (NSC 747691)

Chemical Name or Amino Acid Sequence: 2-chloro-N-[4-chloro-3-pyridin-2-yl-phenyl]-4-(methanesulfonyl)benzamide

Other Names: Systemic Hedgehog Pathway Antagonist, G-025897, G-025897.1, and GDC-0449.1, GDC-0449

Classification: Hedgehog Pathway Antagonist

CAS Registry Number: 879085-55-9

Molecular Formula: $C_{19}H_{14}Cl_2N_2O_3S$ **M.W.:** 421.3 g/mol

Mode of Action: GDC-0449 provides anticancer responses by inhibiting the hedgehog pathway. The Hedgehog signaling pathway controls cell differentiation, growth, and proliferation. It is most active during embryogenesis but may also play a role in the regulation of adult stem cells involved in the maintenance and regeneration of adult tissues.

How Supplied: GDC-0449 is supplied by Genentech and distributed by the CTEP, NCI. It is available as 150-mg grey and pink size 1 capsules containing microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, povidone K29/32, talc, sodium starch glycolate, and magnesium stearate. The capsule shell consists of gelatin, red iron oxide, black iron oxide, and titanium dioxide. A compendial-grade black printing ink may be used.

Capsules are packaged in 75-mL round, white, high-density polyethylene (HDPE) bottles and closed with 38/400 two-piece HDPE child-resistant caps. Each bottle contains 32 capsules.

Storage: Store GDC-0449 at room temperature between 59°F and 86°F (15°C and 30°C).

Stability: Stability testing is ongoing.

Route(s) **of Administration:** Oral

5.2.2 Preparation and Administration

Drug Administration: Patients should take GDC-0449 at approximately the same time according to their dose level, with or without food. If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses should not be made up.

Patient Care Implications: The terminal half-life of GDC-0449 is currently unknown, but is expected to be longer than 1 week, and may be as high as 2 to 3 weeks. If plasma levels of GDC-0449 need to be lowered emergently, animal studies suggest that oral administration of activated charcoal may lower drug plasma levels more quickly than dose cessation alone.

Drug Interactions: Avoid any concurrent drug metabolized by cytochrome P450 that has a narrow therapeutic index.

5.2.3 Accountability and Compliance

GDC-0449 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

GDC-0449 is provided to the NCI under a Collaborative Agreement between Genentech and the DCTD, NCI (see Section 12.3).

Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Oral Drug Accountability Form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

5.3 Other Immunosuppression

5.3.1 Corticosteroids

Corticosteroids at a dose of >0.5 mg/kg/d PDE for at least 1 week prior to initiation of GDC-0449. After initiation of GDC-0449, the corticosteroids will be tapered according to protocol guidelines in the following table, in order to minimize heterogeneity and subsequent potential for confounding:

Week	PDE (mg/kg)
0 Start of therapy	1 daily until at least 1 week after clinical improvement
1 to 2 (starting at least 1 week after clinical improvement)	1alternating with 0.5
3 to 4	1alternating with 0.25
5 to 6	1 every other day (maintain until resolution of GVHD)
7 to 8 (start after resolution or near resolution of GVHD)	0.7 every other day
9 to 10	0.5 every other day
11 to 12	0.4 every other day
13 to 14	0.3 every other day
15 to 16	0.2 every other day
17 to18	0.1 every other day

5.3.2 Calcineurin inhibitor and sirolimus

Therapy will continue at a dose which achieves the following trough serum levels:

- Tacrolimus: 5-10 ng/mL
- Cyclosporine: 120-200 ng/mL
- Sirolimus: 5-10 ng/mL

5.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of GDC-0449 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix E presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

5.4.1 Concomitant Medications

GDC-0449 inhibits CYP2C8, CYP2C9, and CYP2C19 drug metabolism enzymes in vitro at concentrations that may be clinically relevant. Caution should be exercised when dosing GDC-0449 concurrently with medications that are substrates of CYP2C8, CYP2C9, and CYP2C19 and have narrow therapeutic windows. The table below lists clinically significant substrates of CYP2C8, CYP2C9, and CYP2C19. The table below represents medications to be used with caution. Only medications or substances that are strong inducers/inhibitors or strong substrates of CYP3A4/5, CYP2C9, CYP2C8, or CYP2C19 are prohibited. See exclusion criteria 4.2.5 for additional information.

2C8	2C9	2C19
Miscellaneous	NSAIDs	Proton-pump inhibitors
Repaglinide	Diclofenac	Omeprazole
Rosiglitazone	Ibuprofen	Lansoprazole
	Piroxicam	Pantoprazole
	Naproxen	Rabeprazole

Celecoxib	Esoprazole
Oral hypoglycemic agents	Anti-epileptics
Glipizide	Diazepam
Tolbutamide	Phenytoin
Angiotensin II blockers	Phenobarbitone
Irbesartan	Miscellaneous
Iosartan	Amitriptyline
NOT candesartan	Clomipramine
NOT valsartan	Clopidogrel
Miscellaneous	Cyclophosphamide
Fluvastatin	
Phenytoin	
Sulfamethoxazole	
Tamoxifen	
Torsemide	
Warfarin	

NSAIDs = Non-steroidal anti-inflammatory drugs

Clinically significant PK interactions between vismodegib and CYP450 inhibitors are not expected. Results from Study GP28465 demonstrated no clinically significant PK interaction between vismodegib and fluconazole (a moderate CYP2C9 inhibitor) or itraconazole (a strong CYP3A4 inhibitor) in healthy volunteers. Inducers of CYP3A4 are not predicted to alter vismodegib systemic exposure since similar steady-state plasma vismodegib concentrations were observed in patients in clinical studies concomitantly treated with CYP3A4 inducers (i.e., carbamazepine, modafinil, phenobarbital) and those concomitantly treated with CYP3A4 inhibitors (i.e.,erythromycin, fluconazole).

If plasma levels need to be lowered emergently, animal studies have suggested that oral administration of activated charcoal may lower drug plasma levels more quickly than drug cessation alone.

5.4.2 Pregnancy and Reproductive Concerns

Women of childbearing potential (defined in Appendix B) are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 7 days prior to the first dose of GDC-0449 (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks if their menstrual cycles are regular or every 2 weeks if their cycles are irregular while on study within the 24-hour period prior to the administration of GDC-0449. Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the of GDC-0449 to cause spontaneous abortion or birth defects.

Female patients are required to use two forms of acceptable contraception (refer to Appendix B), including one barrier method **during participation in the study and for the 24 months following the last dose**. All patients should receive contraceptive counseling either by the investigator, or by an obstetrician (OB)/gynecologist or other physician who is qualified in this area of expertise. If a woman of childbearing potential believes that her contraceptive method has failed, emergency contraception should be considered.

If a patient is suspected to be pregnant, GDC-0449 should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing with GDC-0449.

If a female patient becomes pregnant during therapy or within 24 months after the last dose of GDC-0449, or if the female partner of a male patient exposed to the drug becomes pregnant while the male patient is receiving GDC-0449 or within 3 months after the last dose of GDC-0449, the investigator must be notified in order to facilitate outcome follow-up.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any congenital anomaly/birth defect in a child conceived during the study or within 24 months after the last dose of GDC-0449 to a female patient or to a female partner of a male patient exposed to the agent during treatment or within 3 months after the last dose of GDC-0449 should be recorded and reported as an SAE.

- Female patients should not breastfeed a baby while on this study.
- Female patients must NEVER donate ova while being treated with GDC-0449.
- All sexually active male subjects (including those who have undergone vasectomy) should utilize a barrier form of contraception **during study treatment and for 3 months after the last dose** as it is not known whether GDC-0449 that may be present in seminal fluid would cause serious or life-threatening birth defects in a fetus born to the female partner of a male subject. Males should also not donate sperm during treatment or up to 3 months after the last dose.
- All patients are prohibited from donating blood for 24 months after the last dose of GDC-0449.

5.4.3 Supportive Care Guidelines

Supportive care, including infection prophylaxis will be conducted as per the current University of Utah institutional BMT program clinical practice guidelines.

Steroids can be re-introduced for supportive care once the taper begins as long as it is cleared with the Principle Investigator, is not for the treatment of GVHD progression AND does not exceed 0.5 mg/kg/d PDE.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for up to 12 cycles (i.e. 12 months) if there is clinical benefit (i.e. PR or CR) after the first 6 cycles, (i.e. 6 months) or until one of the following criteria applies:

- Chronic GVHD or malignancy progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) (see section 6.1)
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.6 Duration of Follow Up

Patients will be followed for a total of 6 months after removal from study treatment or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form. In addition, early stopping criteria are defined in Section 9.

6 DOSING DELAYS, DOSE MODIFICATIONS AND EARLY STOPPING CRITERIA

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for adverse event and serious adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded: (**http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx**).

6.1 Dose Modifications

In the case of any Grade 2 hematologic or non-hematologic toxicity attributable to the study drug, dose reductions can be performed to up to 3 different, consecutive levels as detailed below. All initial dose reductions will start at level -1, and proceed to the immediately lower level if the toxicity in question persists for at least 1 week. Dosing

schedules will be dependent on what day of the week the patient starts the dose reduction level; for example, patients on Dose Level -1 with a Monday start would dose on Wednesday, Friday, Sunday, and so on.

Dose reduction levels are:

- Level -1 (150 mg every other day)
- Level -2 (150 mg every three days)
- Level -3 (150 mg twice a week)

- GDC-0449 will be discontinued under the following circumstance:

  - Grade 3 or 4 non-hematologic or hematologic toxicity attributable to study treatment by Common Terminology Criteria for Adverse Events (CTCAE) version 4.

7 STUDY CALENDAR

	Screening/ baseline	Monthly for 3 months*	At 4 and 6 months*	At 8, 10 and 12 months[3]*	1 month after last date of treatment	9 months/ 15 months[3]*	12 months/ 18 months[3]*
Informed consent	x						
Medical history	x	x	x	x		x/x	x/x
Demographics	x						
Eligibility criteria	x						
Concomitant Medications	x	x	x	x	x	x	x
Physical exam	x	x	x	x		x/x	x/x
Vital signs	x	x	x	x		x/x	x/x
Performance status	x						
Pregnancy test[5]*	x						
Hematology	x	x	x	x		x/x	x/x
Serum chemistries	x	x	x	x		x/x	x/x
Pulmonary function tests	x	x**	x**	x**	x**	x**	x**
Correlative studies[6*]	x	At 3 months	At 6 months			x	x
Chronic GVHD assessment	x	x	x	x		x/x	x/x
Endpoint assessments Primary & secondary		x	x	x		x/x	x/x
Adverse events[4*]	x	x	x	x	x	x	x
AM-PAC[7]		x	x	x	x	x	x

*These represent the minimum number of visits per protocol
**Pulmonary function tests during these time points are only performed in patients with a diagnosis of chronic GVHD of the lung
[3]*These are monitoring time points for patients receiving 12 months of therapy. Patients will be followed every 3 months for 6 months after discontinuation of study treatment.
[4]* Adverse Events are monitored while the patient is receiving study drug (i.e. up to 12 months for those patients receiving 1 year of therapy) until 30 days post the last dose of study treatment.
[5]*Women of childbearing potential (defined in Appendix B) are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 7 days prior to the first dose of GDC-0449 (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks if their menstrual cycles are regular or every 2 weeks if their cycles are irregular while on study within the 24-hour period prior to the administration of GDC-0449. Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the of GDC-0449 to cause spontaneous abortion or birth defects
[6*] Blood and Plasma will be collected at baseline, 3, 6, 9, and 12 months post first dose. Skin punch biopsies will be collected at baseline and 6 months post first dose. See table in section 13.1 for additional details.
[7] The AM-PAC score (Activity Measure for Post-Acute Care) will be captured at each designated study visit as part of routine clinical assessment.

8 STUDY PROCEDURES

Patient registration for this trial will be managed by the Research Compliance Office at the Huntsman Cancer Institute.

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

8.1 Screening Procedures

All screening procedures must be performed within 7 days prior to registration unless otherwise stated. The screening procedures include:

- Informed Consent
- Medical history - Complete medical and surgical history, including history of infections
- Demographics - Age, gender, race, ethnicity
- Review subject eligibility criteria
- Review previous and concomitant medications
- Physical exam including vital signs, height and weight - Vital signs (temperature, pulse, respirations, blood pressure)
- Performance status - Evaluated prior to study entry according to Appendix A.
- Adverse event assessment - Baseline adverse events will be assessed. See Section 14.0 for Adverse Event monitoring and reporting.
- Hematology
  - Complete blood count (CBC) with differential and platelet count.
- Blood draw for correlative studies
  - See Section 13.0 for details.
- Blood Serum chemistries
  - Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphates, Alanine Amino transferase/Serum Glutamic Pyruvic Transaminase(ALT/SGPT), Aspartate Amino transferase/ Serum Glutamic Oxaloacetic Transaminase(AST/SGOT), BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.
  - Serum Magnesium (Mg) and Phosphorus (Phos).
  - Serum Lactate dehydrogenase (LDH).
  - Pregnancy test (for females of child bearing potential)
- Chronic GVHD assessment
- To be performed using the NIH global score which will be defined by using the NIH consensus criteria for assessment of chronic GVHD severity [46].

Other tests

- Baseline pulmonary function tests.

8.2 Procedures During Treatment

Clinical assessment visits - Will be scheduled monthly for the first 3 months, then months 4, 6, 8 10, 12 while patients are receiving GDC-0449 and will include history and physical exam (H&P) including vital signs, height and weight, directed evaluation of chronic GVHD assessment as per 8.1, directed evaluation of treatment effect as per 9.0, directed evaluation of adverse events as per 14.0, hematology as per 8.1, serum chemistries as per Section 8.1.

Study endpoint assessments - Will be study specific and will include comprehensive evaluations of chronic GVHD and evaluations of correlative studies as in table in section 7.

8.3 Follow-Up Procedures

Patients will be followed every 3 months from the first day the patient is no longer receiving GDC-0449 through 6 months from the completion of GDC-0449.

Follow-up visits will include H&P including vital signs, height and weight, directed evaluation of chronic GVHD assessment, directed evaluation of treatment effect, directed evaluation of adverse events, hematology and serum chemistries following the same guidelines above in section 8.1.

8.4 Time and Events Table

The time of assessments is shown in months, as it facilitates better comprehension, preventing potential errors, in the interpretation of the exact timing for each assessment. On the other hand, in order to facilitate integration with the weekly-based schedule of corticosteroids taper, and also budget considerations, we use the following transformation between weeks and months when addressing the schedule of assessments:

1 month: Week 4+/-1 week
2 months: Week 8+/-1 Week
3 months: Week 12+/-1 week
4 months: Week 16+/-1 week
6 months: Week 24 +/-1week
8 months: Week 32+/- 1 week
9 months: Week 36 +/-1 week
10 months: Week 40 +/- 1 week
12 months or 1 year: Week 52 +/-1week
15 months: Week 64 +/-1 week
18 months: Week 72+/-1 week

9 CRITERIA FOR EVALUATION AND ENDPOINT

9.1 Measurement of Effect

Response to therapy will be assessed at clinical assessment visits every 3 months from the first day of treatment with GDC-0449 through 12 months from the initiation of GDC-0449. Response will be defined as FFS at 6 months [23].

9.1.1 Failure Free Survival Definition

FFS is defined as being alive and:

- No relapse of malignancy
- No addition of any other systemic treatment for chronic GVHD
- Steroid dose at 6 months ≤ 0.2 mg/kg/day PDE

The need for addition of therapy while on GDC-0449 is one of the criteria for failure, and consequently the patient will be taken off study. In order to minimize differences in practice that might impact the primary endpoint, we established minimal indispensable criteria to initiate additional immunosuppressive therapy during the first six months of GDC-0449 treatment.

9.1.2 Definition of Response to Therapy

1. Stable disease (SD) (no change in chronic GVHD) according to NIH consensus response criteria for a total of 1month [46]. This criteria is irrespective of any response obtained initially, prior to the month of stability.
2. Progressive Disease: This is defined as any one of the following:
   - Skin: Increase in NIH Skin Score by 1 or more points, except 0 to 1.
   - Eyes: Increase in NIH Eye Score by 1 or more points, except 0 to 1.
   - Mouth: Increase in NIH Modified Oral Mucosa Rating Score of 2 or more points.
   - Esophagus: Increase in NIH Esophagus Score by 1 or more points, except 0 to 1.
   - Upper GI: Increase in NIH Upper GI Score by 1 or more points, except 0 to 1.
   - Lower GI: Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1.
   - Liver: Increase by 2x ULN ALT, alkaline phosphatase, and Total bilirubin.
   - Lungs: Decrease by 10% predicted absolute value of %FEV1. If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1.
   - Joints and Fascia: Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site.
   - Global: Clinician overall severity score increases by 2 or more points on a 0 – 10 scale
3. Partial Response: This is defined as any one of the following:
   - Skin: Decrease in NIH Skin Score by 1 or more points
   - Eyes: Decrease in NIH Eye Score by 1 or more points
   - Mouth: Decrease in NIH Modified Oral Mucosa Rating Score of 2 or more points.
   - Esophagus: Decrease in NIH Esophagus Score by 1 or more points.
   - Upper GI: Decrease in NIH Upper GI Score by 1 or more points
   - Lower GI: Decrease in NIH Lower GI Score by 1 or more points.
   - Liver: Decrease by 50% ALT, alkaline phosphatase, and Total bilirubin.
   - Lungs: Increase by 10% predicted absolute value of %FEV1. If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points.
   - Joints and Fascia: Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site.

- Global: Clinician overall severity score decreases by 2 or more points on a 0 – 10 scale.

4. Complete Response: This is defined as any one of the following:
   - Skin: NIH Skin Score 0 after previous involvement.
   - Eyes: NIH Eye Score 0 after previous involvement.
   - Mouth: NIH Modified Oral Mucosa Rating Score 0 after previous involvement.
   - Esophagus: NIH Esophagus Score 0 after previous involvement.
   - Upper GI: NIH Upper GI Score 0 after previous involvement.
   - Lower GI: NIH Lower GI Score 0 after previous involvement.
   - Liver: Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of one or more.
   - Lungs: Normal %FEV1 after previous involvement. If PFTs not available, NIH Lung Symptom Score 0 after previous involvement.
   - Joints and Fascia: Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least one measure.
   - Global: Clinician overall severity score 0.

Patients under categories 1 and 2 require the addition of other systemic treatment for chronic GVHD. These conditions should be attributable to chronic GVHD, with exclusion of other relevant causes in the differential diagnosis when applicable. The addition of other systemic treatment excludes the patient from the current clinical study.

9.2 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained per the study calendar.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted on the study calendar.

9.3 Stopping Rules/Interim Analysis

Safety was assessed after 1 cycle in the first 4 subjects to ensure that no more than one grade 3-5 drug reaction occurred and that no more than 4 of 6 subjects required a dose reduction for grade 2-4 drug reactions. At the initial dose of 150 mg daily, dose reductions to 150 mg every

other day for Grade 2 drug reactions were required. As such, the dosing schema was updated to the following:

> The initial dose will be given at 150 mg po daily. If Grade 2 hematologic or non-hematologic toxicities attributable to the study drug are observed, three different, consecutive dose reduction levels may be utilized (below). All initial dose reductions will start at Level -1 and proceed to the next level if the toxicity in question persists. Dosing schedules will be dependent on what day of the week the patient starts the dose reduction level; for example, patients on Dose Level -1 with a Monday start would dose on Wednesday, Friday, Sunday, and so on.
>
> - Level -1 (150 mg po every other day)
> - Level -2 (150 mg po every three days)
> - Level -3 (150 mg po twice a week)

Starting with patient 05, safety will be assessed to ensure that no more than 4 subjects (50% of the number of patients left to meet the enrollment target of 12) discontinue GDC-0449 after reducing to Level -3 due to adverse effects attributable to study drug. Safety will be reviewed monthly and at the time of each grade 3-5 reaction.

GDC-0449 will be discontinued under the following circumstance:

- If no more than 4 subjects (50% of the number of patients left to meet the enrollment target of 12) enrolled discontinue GDC-0449 after reducing to Level -3 due to adverse effects attributable to study drug.

10 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a pilot study of GDC-0449 in steroid refractory chronic GVHD. This is a single-institution study that will be performed at the Huntsman Cancer Institute. Total duration of study will be 2 years.

10.1.1 Primary Endpoint

- FFS at 6 months after initiation of therapy with GDC-0449
  FFS is defined as absence of NRM, no recurrent malignancy, steroid dose at 6 months ≤ 0.2 mg/kg/d of PDE, and no addition of new systemic treatment for chronic GVHD (Adapted from [45]). Criteria for addition of new systemic treatment for chronic GVHD are defined as per section 9.0.

10.1.2 Secondary Endpoints

- Safety of GDC-0449 in patients with steroid-refractory chronic GVHD

- Change in NIH global score of chronic GVHD from baseline at 6 and 12 months after the initiation of the protocol therapy

    - NIH global score will be defined by using the NIH consensus criteria for assessment of chronic GVHD severity [46].

- One-year NRM and one-year relapse rate

    - Relapse will be defined as malignancy relapse or as the initiation of any unintended intervention including an unplanned taper of immunosuppressant therapy to prevent malignancy progression due to any signs of recurrent, residual or new malignant disease after transplantation.

- One-year FFS and one-year OS

    - FFS is defined as in section 10.1.1 (Primary Endpoint).

- Clinical characteristics that may be associated with decreased FFS including the presence of high-risk disease at transplantation; high-intensity conditioning with total-body irradiation; > 3 involved sites with chronic GVHD, lower gastrointestinal involvement by GVHD and severe NIH global score at initiation of protocol treatment; and thrombocytopenia, hyperbilirubinemia, and steroid doses >1 mg/kg per day immediately before treatment failure requiring treatment change.

- Clinical response to GDC-0449 at 6 months as defined in section 9.1.2.

10.1.3 Exploratory Endpoints

- Fibrocyte numbers, leukocyte subsets and T cell cytokine profiles will be determined at baseline and in response to GDC-0449 at 3, 6, 9 and 12 months using flow cytometry.
- Cytokine profiles and ECM biomarkers present in plasma will be determined at baseline and in response to GDC-0449 at 3, 6, 9 and 12 months using ELISA and the fibroplex assay
- Mesenchymal cell phenotypes cultured from skin biopsies of cutaneous cGVHD patients pre- and post-GDC-0449 will be determined at baseline and in response to GDC-0449 at 6 months using immunohistochemistry studies and mesenchymal cell cultures
- Levels of TGFβ and hedgehog activation will be determined on skin biopsies at baseline and in response to GDC-0449 at 6 months, using different staining and other techniques.

10.2 Sample Size/Accrual Rate/Other Statistical Considerations

Sample size: 12 patients. Accrual rate: 1-2 patients monthly.
This is a pilot study that will include 12 patients. FFS, the primary endpoint, will be evaluated using the Kaplan-Meier method. The impact of different covariates on FFS will be analyzed using descriptive statistics, t-test, and Fisher's exact test where applicable. Differences in NIH scores will be analyzed using Wilcoxon signed-rank test. Differences in biomarkers will be assessed using Wilcoxon rank-sum test.

Overall clinical response (PD, SD, PR, CR) according to NIH criteria will be tabulated and described based on organ response and overall response.

The proportion of subjects who experience adverse events and serious adverse events will be summarized descriptively; no inferential tests will be performed.

10.3 Stratification Factors

N/A

10.4 Analysis of Secondary Endpoints

See Sections 10.1.

11 REGISTRATION GUIDELINES

11.1 Investigator and Research Associate Registration with CTEP

11.1.1 CTEP Registration Procedures
Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed **Supplemental Investigator Data Form** (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions about Investigator Registration, please contact the **CTEP Investigator Registration Help Desk** by email at pmbregpend@ctep.nci.nih.gov

11.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is required to access all CTEP applications and, if applicable (e.g., all Network trials), all Cancer Trials Support Unit (CTSU) applications and websites.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm.

11.2 Patient Registration:

Patients must meet all of the eligibility requirements listed in Section 4 prior to registration.

Study related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

Treatment should start within 5-7 business days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

IWRS

Patient Enrollment will be facilitated using the Interactive Web Response System (IWRS). IWRS is a web-based registration system available to users on a 24/7 basis. On a successful registration, IWRS will assign a patient number and assign the treatment. Patient enrollment data entered by Registrars in IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave. IWRS will provide a printable confirmation of registration and treatment information. Please print this confirmation for your records.

- Users must have a valid CTEP-IAM account (i.e., CTEP username and password) to access the IWRS system.
- Users defined with the Registrar role will have the ability to register patient in the study.
- Users defined with the Client Administrator role will have the ability to manage accrual limits, open and close treatment assignments as well as approve slot reservations, if applicable to the study.
- For trials with slot reservation requirements, Registrars will have the ability to request to reserve a slot, which may require approval from users at the lead institution defined as a 'Client Administrator' for the study.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 14.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/CTMS. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

12.2 CTEP Multicenter Guidelines

N/A

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said

other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

13.1 Biomarker Studies

All studies in this section are ancillary/exploratory. The aim of these studies is to determine the impact of GDC-0449 treatment on parameters of ECM turnover and immunologic changes in the circulation, as well as on markers of HH signaling in cGVHD skin biopsies.

13.1.1 Proteomic chronic GVHD analysis in Plasma:

Plasma will be collected for proteomic analysis of chronic GVHD biomarkers and extracellular matrix production and turnover. Analysis will include, but not be limited to, osteopontin, ST2, BAFF, MMP3, TGF-β, and CXCL9.

13.1.2 Immunologic Monitoring in Peripheral Blood:

Immunological monitoring will be performed using peripheral blood mononuclear cells collected prior to the initiation of therapy and then at 3, 6, 9 and 12 months (5 time points per patient)

13.1.2.1 Immune Cell Subsets:

The main objectives of the monitoring will be to characterize changes in immune subsets with well-defined or emerging roles in immunopathology of chronic GVHD (T cells, B cells, and monocytes/dendritic cells) and correlate findings with the clinical outcome. . Analyses will utilize multicolor flow cytometry to profile helper and regulatory $CD4^+$ T cells, effector $CD8^+$ T cells, circulating monocytes, and B cells and define impact of GDC-0449..

Regulatory T cell analyses ($CD3^+$ $CD4^+$ $CD25^+$ $Foxp3^+$) will focus on markers of their suppressive potential with likely functional impact in chronic GVHD (such as Helios and CTLA-[53-57]. Th1/Th2/Th17 polarization among helper T cells will be analyzed by flow cytometry, evaluating canonical transcription factors Tbet, GATA3, and RORγ and cytokine production in re-stimulated T cells. In addition, sort purified $CD4^+$ and $CD8^+$ T cells will be transcriptionally profiled for broader cytokine production and changes that occur under GDC-0449.

B cells are well documented mediators of chronic GVHD and represent an intermediary step in triggering fibrotic tissue response. We will provide immunophenotypic analyses and focus on characterization of GDC-0449 impact on defined subsets with pathogenic relevance in chronic GVHD, including “autoreactive” $CD27^{neg}CD21^{low}$, pre-germinal center $CD27^+IgD^+CD38^{hi}$, and plasmablast-like $CD27^+IgD^{low}CD38^{hi}$ B cells in peripheral blood. In addition, B cells will be sort purified to evaluate transcriptionally impact of GDC-0449 on Hh target genes.

Emerging evidence supports key role for alternative macrophage activation and polarization in fibrotic tissue remodeling in chronic GVHD, and pre-clinical studies have identified early monocyte polarization is essential for fibrotic GVHD onset. We will profile impact of GDC-0449 on subsets of patrolling ($CX3CR1^{high}CD14^{dim}CD16^+$) and classical ($CCR2^{high}CD14^+CD16^-$) monocytes by flow cytometry. In addition, we will sort purify bulk monocytes and transcriptionally analyze for regulation of Hh target genes and classicall vs

alternative polarization towards macrophages.

The effect of GDC-0449 on immune subsets remains uncharacterized aside for pre-clinical reports of no impact on leukocyte tissue infiltration in models of chronic fibrotic GVHD. Pre-clinical data suggest impact of Hh signaling on innate immunity, thus, if clinical benefit is documented, we hypothesize biggest differences will be seen in the pool of peripheral blood monocytes. While Hh pathway has been shown to play a role in T cell development its impact on mature T cell responses remains undefined. We postulate that Hh will not influence T cell polarization or function, nor B cell responses directly, and possible clinical benefits will be largely derived through its impact on myeloid regulation and/or terminal tissue remodeling functions. Importantly, our studies will document the effects of GDC-0449 on adaptive immunity and thus inform of the possible immunosuppressive effects of this therapy that could pose further risks to patients with chronic GVHD.

Flow Cytometry panels:

Panel 1: Treg	**Panel 2: T helper**	**Panel 3: B cells / Monocytes**	**Panel 4: Sort**
41BB	IL-17	CD3	CD3
CD4	CD4	CCR2	CD4
CD127			
ICOS	IFNg	CD14	CD14
FoxP3	RORc	CD64	CD64
PD-1		CD20	CD20
Helios	GATA3	CD38	
OX40	IL-4	CD16	CD16
		IgD	
CD25	Tbet	CX3CR1	
CD3	CD3		
CTLA-4		CD27	
CD8		CD21	CD8
Viability	Viability	Viability	Viability

13.1.2.2 Platelet Function Assay

Assay description	Proposed candidates
Whole blood flow cytometric assay for platelet activation	CD41, P-selectin, PAC-1, CD154 (CD40L).
Isolated platelets flow cytometric assay for platelet apoptosis and immune functions	Annexin V, Caspase-3, Bcl-2, MHC class I, CXCR4, CCL5 (RANTES), PDGF, PF4(CXCL4), TGF-β, TNF-α.
Ex vivo stimulated platelets flow cytometric assay for platelet activation and immune functions	CD41, P-selectin, PAC-1, CD154 (CD40L), CXCR4, CCL5, PDGF, VEGF, PF4, TGF-β, TNF-α.
ELISA for the quantification of platelet released cytokine and growth factors upon stimulation ex vivo	VEGF, PDGF, TGF-β, TNF-α, IL-1, IL-6, serotonin.
Western immunoblotting of isolated platelet lysates and ex vivo stimulated platelet lysates for the characterization of Wnt/Shh signaling pathway	Wnt, β-Catenin and phospho-β-Catenin.
RNA sequencing of platelets	Global genetic signature characterization of platelets.
Validation at protein level of candidates screemed from RNA sequencing data	Dependent on the RNA sequencing data.

Abbreviations:

CCL5: Chemokine ligand 5
CXCR4: C-X-C chemokine receptor type 4
ELISA: Enzyme-linked immunosorbent assay
PDGF: Platelet derived growth factor
PF4: Platelet factor 4
TGF-β: Transforming growth factor-beta
TNF-α: Tumur necrosis factor
VEGF: Vascular endothelial growth factor

Whole blood will be drawn from consenting patients and controls using sterile, ACD-containing, BD vacutainer tubes. We will draw approximately 40mLs of whole blood from each patient or control at each time point. Blood will be used immediately for real-time assays (e.g. whole blood flow cytometry and platelet stimulation assays) and cells and plasma components will also be isolated (e.g. platelets, PBMCs, plasma, plasma-derived microparticles) for studies performed in batches to minimize variability. Table 1 is a proposed list of assays and target candidates. These candidates include canonical indices of platelet activation (e.g. P-selectin, PAC-1), immune and inflammatory molecules expressed by or secreted from platelets (e.g. TNF, CD154, MHC Class I, CCL5), apoptosis markers (e.g. Annexin V), and growth factors (e.g. VEGF). We will also interrogate candidates involved in the hedgehog pathway including Wnt and beta-catenin (both unphosphorylated and phosphorylated forms). Other assays may be included as new targets are identified. Next-generation RNA-sequencing will be done on a subset of patients and controls (n=5-10/group) as a discovery tool to interrogate other genes differentially expressed in patients with GHVD.

13.1.3 Skin Biopsies:

Four mm punch biopsies will be collected at baseline and 6 months from patients enrolled in the study. Biopsies will be cut in half and one half will be fixed and embedded in paraffin for immunohistochemistry studies for the HH stabilized transcription factors GLI-1 and GLI-2. The other half will be used to obtain RNA to test for mRNA expression of SHH, GLI-1, GLI-2,

PTCH 1 and PTCH-2. Samples will be stored in HCI's Biorepository and Molecular Pathology (BMP) storage facility.

Biological parameters will be correlated with clinical markers of disease severity in exploratory longitudinal analyses.

The logistics for obtaining the samples required for the correlative studies are summarized on the Table below:

	Whole Blood	Plasma	Tissue
Collection Timepoints	Baseline, 3, 6, 9, 12 months Collect pre-dose	Baseline, 3, 6, 9, 12 months One time pre-dose	Baseline, 6 months Optional for 1st patient
Specimen Type/ Amount	(3) Green Top Sodium Heparin 10 ml tubes	(1) Purple Top EDTA 3 ml tube	4 mm Skin Punch Biospy
Processing Instructions	Whole blood will be sent ambient to BMP who will process cells and freeze.	Centrifuge tubes at standard speed and time. Pour off plasma into aliquot tube and freeze.	4 mm bx divided: ½ formalin fixed paraffin embedded, ½ snap frozen in liquid nitrogen.
Storage	BMP until ready to ship	BMP until ready to ship	BMP until ready to ship
Shipping Instructions *e-mail lab prior to shipment to notify of arrival.	Batch ship as directed by the PI	Batch ship as directed by the PI	Batch ship as directed by the PI
Laboratory Location	University of Utah George and Dolores Eccles Institute of Human Genetics 15 N 2030 E Salt Lake City, UT 84112	Rondina Lab University of Utah Eccles Institute of Human Genetics 15 N 2030 E Salt Lake City, UT 84112	

13.1.4 Investigators

The investigators performing the proposed assays are:

Matthew Rondina, MD., MS., has been a University of Utah Department of Medicine faculty member since 2006. His clinical practice is focused on preventing thrombotic disorders, specifically examining platelet and megakaryocyte functions in infectious and inflammatory disorders where thrombosis is common. The majority of his laboratory research is housed in the Molecular Medicine Program in the Eccles Institute of Human Genetics and is

NIH funded. His lab has contributed a novel understanding of platelets, magakaryocytes, and platelet-leukocyte interactions during health and disease. Whole blood and plasma samples will be analyzed in the University of Utah Molecular Medicine Program in the Rondina Lab at the Eccles Institute of Human Genetics.

13.1.5 Overall Anticipated Results, Interpretations and Pitfalls:

In all analyses, each patient will serve as their own control by comparing baseline measures with longitudinal results post-treatment. GDC-0449 may have little impact on inflammatory cell numbers in the peripheral blood or IHC specimens based on previous murine results [34]. Whether GDC-0449 will alter T cell cytokine profiles in circulation or in skin is unknown. Patients responding well to this SMO inhibitor may show reduced IL-17 and IFNγ in circulation as these cytokines have been associated with cutaneous manifestations of cGVHD [47]. These same studies showed Th2 cytokines (IL-4/13) were associated with aGVHD. If therapy fails to mediate clinical improvement, it may be due to an inability to inhibit these T cell responses. If GDC-0449 is effective, we anticipate reduced expression of GLI-1, GLI-2, PTCH-1 and PTCH-2 in skin. Because GLI-1 can activate IL-6 and IL-8 [63], these cytokines may be reduced in plasma post-GDC-0449 treatment and this may offer an assay to look for HH activity indirectly. Patients who do not respond may show no reductions in HH signaling (e.g. GLI-1) and this may indicate that drug levels were insufficient. It is also possible that patients may acquire SMO mutations that make them resistant to GDC-0449 [64, 65]. This could be determined by sequence analysis of SMO in those patients. We believe systemic markers of ECM synthesis, turnover and degradation will also be altered by GDC-0449 treatment in patients showing signs of clinical efficacy. We realize that these analyses are exploratory in nature given the relatively small sample size (n=12) for which CTEP agreed to provide study drug. However, these studies are highly significant as they are likely to identify relevant biomarkers that correlate with clinical efficacy or that may explain therapeutic futility. These will be critical insights into designing larger future trials.

14 ADVERSE EVENTS

14.1 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for AE and SAE reporting. An electronic copy of the CTCAE Version 4.0 can be downloaded from: **http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx**

14.1.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical

conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The collection of adverse events will begin after the first dose of study treatment and end 30 days post the last dose of study treatment.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade based on CTCAE v.4 (grade 1-5)
2. its relationship to the study drugs (definite, probable, possible, unlikely, not related)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 6 for guidance). Once an adverse event is detected, it should be followed until its resolution, or until the end of the follow-up period (6 months after removal from study treatment or until death, whichever occurs first) and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug is described in the Drug Information (section 3) and the most recent Investigator Brochure. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

14.1.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. Refer to section 14.3 for NCI serious adverse event guidelines.

14.2 Huntsman Cancer Institute SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and the NCI, according to the requirements described below:

A CTEP-AERS form must be completed per NCI guidelines listed in section 14.3. At the completion of the online submission, the SAE report should be exported to a PDF and printed. The PI should sign and date the report which will then be submitted to compliance@hci.utah.edu as soon as possible, but no later than 10 days of first knowledge or notification of event (5 days for fatal or life threatening event).

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the CTEP-AERS form to the proper DSMC member as necessary for each individual study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

IRB Notification:

- Events meeting the University of Utah IRB reporting requirements (http://www.research.utah.edu/irb/) will be submitted through the IRB's electronic reporting system within 10 working days.

14.3 CTEP Notification and Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

14.3.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

Comprehensive Adverse Events and Potential Risks list (CAEPR) for GDC-0449 (Vismodegib, NSC 747691)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1893 patients.* Below is the CAEPR for GDC-0449 (Vismodegib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational

agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, December 22, 2016[1]

Adverse Events with Possible Relationship to GDC-0449 (Vismodegib) (CTCAE 4.0 Term) [n= 1893]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
	Diarrhea		***Diarrhea (Gr 2)***
	Dyspepsia		
	Nausea		***Nausea (Gr 3)***
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
INVESTIGATIONS			
	CPK increased		
Weight loss			***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia	Dehydration		***Anorexia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
Musculoskeletal and connective tissue disorder - Other (muscle spasms/twitching)			***Musculoskeletal and connective tissue disorder - Other (muscle spasms/twitching) (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (premature epiphyseal closure)	
NERVOUS SYSTEM DISORDERS			
Dysgeusia			***Dysgeusia (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Irregular menstruation[2]			***Irregular menstruation[2] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Irregular menstruation was observed in 30% (3 of 10) women of child bearing age and/or in 28% (18 of 64) women who had menses at baseline who were enrolled in studies of advanced BCC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on GDC-0449 (Vismodegib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that GDC-0449 (Vismodegib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Febrile neutropenia; Thrombotic thrombocytopenic purpura

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Heart failure; Myocardial infarction; Pericardial tamponade; Sinus bradycardia

EYE DISORDERS - Keratitis; Retinal vascular disorder

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dry mouth; Dysphagia; Esophageal pain; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (thrush); Gastrointestinal hemorrhage[3]; Gastrointestinal pain; Ileus; Mucositis oral; Pancreatitis; Stomach pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Facial pain; Fever; Injection site reaction; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Portal hypertension

INFECTIONS AND INFESTATIONS - Infection[4]

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Hip fracture

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cholesterol high; Creatinine increased; GGT increased; INR increased; Investigations - Other (brain natriuretic peptide increased); Investigations - Other (elevated LDH); Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle tightness/stiffness); Myalgia; Neck pain; Pain in extremity; Trismus

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dizziness; Dysesthesia; Headache; Intracranial hemorrhage; Movements involuntary; Nervous system disorders - Other (amimia); Olfactory nerve disorder; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Tremor

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Hallucinations; Insomnia; Psychosis

RENAL AND URINARY DISORDERS - Acute kidney injury; Renal hemorrhage

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Cough; Dyspnea; Epistaxis; Hiccups; Hypoxia; Pleural effusion; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (COPD); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Sneezing; Sore throat

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Nail ridging; Pruritus; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (hair color changes); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (skin exfoliation); Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event; Vasculitis

Note: GDC-0449 (Vismodegib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Additional Adverse Events

Serious or Life-threatening Birth Defect Effects of GDC-0449
Studies have demonstrated that inhibition of the Hh pathway in embryos results in brain, facial, and other midline defects, including holoprosencephaly or microencephaly, cyclopia, absent nose, cleft palate, tooth abnormalities, and bone development abnormalities (Bale, 2002). While the effects of GDC-0449 on the developing human fetus at the recommended therapeutic dose are unknown, women of childbearing potential and men must agree to use two methods of contraception (i.e., barrier contraception and another method of contraception) prior to study entry, for the duration of study participation, and for 24 months following treatment.

Women of childbearing potential are defined as follows:

- Patients with regular menses

- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 12 months in a woman > 45 years old.

Women of childbearing potential are required to use two forms of acceptable contraception (refer to Appendix B), including one barrier method during participation in the study and for the 24 months following the last dose. All patients should receive contraceptive counseling either by the investigator or by an OB/gynecologist or other physician who is qualified in this area of expertise. If a woman of childbearing potential believes that her contraceptive method has failed, emergency contraception should be considered.

If a patient is suspected to be pregnant, GDC-0449 should be IMMEDIATELY discontinued and the study physician contacted. A positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing with GDC-0449.

If a female patient becomes pregnant during therapy or within 24 months after the last dose of GDC-0449, or if the female partner of a male patient exposed to the drug becomes pregnant while the male patient is receiving GDC-0449 or within 3 months after the last dose of GDC-0449, the investigator must be notified in order to facilitate outcome follow-up.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any congenital anomaly/birth defect in a child conceived during the study or within 24 months after the last dose of GDC-0449 to a female patient or to a female partner of a male patient exposed to the agent during treatment or within 3 months after the last dose of GDC-0449 should be recorded and reported as an SAE.

In addition, it is not known whether GDC-0449 that may be present in seminal fluid would cause serious or life-threatening birth defects in a fetus born to the female partner of a male subject. Sexually active male subjects should utilize a barrier form of contraception, even those who have had a vasectomy, during study treatment and for 3 months after the last dose. Male patients should advise their partners to use an additional method of contraception during the study and for at least 3 months after discontinuation of GDC-0449. Male subjects should also not donate sperm during treatment or up to 12 months after the last dose.

Risk of Male Germ Cell Degeneration

[redacted]

[redacted]

14.3.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** 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.

- **For expedited reporting purposes only:**
  -AEs for the agent that are **bold and italicized** in the CAEPR (i.e., those listed in the SPEER column, should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
  - Possible – The AE may be related to the study treatment.
  - Unlikely – The AE is doubtfully related to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

14.4 Expedited Adverse Event Reporting

14.4.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity

is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

14.4.2 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported **as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions."** Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5

		Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

14.4.3 Expedited Adverse Event Reporting for Suspected Exposure to Agent that May Cause Serious or Life-threatening Birth Defects for Patients Receiving GDC-0449

- CTEP considers **any possible prenatal exposure to GDC-0449**, a reportable expedited adverse event that should be reported to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days.

- Any patient suspected of being pregnant or fathering a child, (i.e. any female patient or female partner of a male patient, respectively), or should any lapse in contraception occur, should stop taking GDC-0449 until it is confirmed that pregnancy has not occurred.

- Pregnancies that occur up to 24 months after the last dose of GDC-0449 will be followed until the outcome of the pregnancy is known.

- The adverse event (pregnancy) should be reported as a Grade 4 event using CTCAE 4.0 as follows:
  - Endocrine disorders- Other (Prenatal exposure to a possible teratogen)
  - A completed "Possible Prenatal Exposure to Teratogen Report" Form (Appendix C) should be attached to the complete CTEP-AERS Report. This form may also be faxed to CTEP along with any relevant supporting medical information at 301-230-0159 (alternative FAX Number: 301-897-7404).
  - This form should be submitted for any female patient or any female partner of a male patient who becomes pregnant during therapy or up to 12 months after the last dose of GDC-0449.

- Any congenital anomaly/birth defect in a child conceived to a female patient or to a female partner of a male patient exposed to GDC-0449 during treatment or within 24 months after the last dose of GDC-0449 should be reported as an expedited adverse event to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days.

- Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any abortion occurring during the study or within 24 months after the last dose of GDC-0449 to a female patient or to a female partner of a male patient exposed to the agent during treatment or within 24 months after the last dose of GDC-0449 should be reported as an expedited adverse event to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days.

14.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

14.6 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

14.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

15.2 Institutional Review

Study will be approved by the Institutional Review Board of University of Utah.

15.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This study will be reviewed by the full committee at each quarterly DSMC meeting. This includes a review of all serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates as well as all grade 3 or greater toxicities for patients on treatment and within 30 days follow-up window (only if possibly, probably or definitely related).

15.4 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

15.5 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also

undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

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17 APPENDIX

Refer to pages 69 – 82 for Appendices

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
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	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
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	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL AND ACCEPTABLE AND UNACCEPTABLE FORMS OF CONTRACEPTION

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 12 months in a woman >45 years old.

Determine pregnancy status within 10-14 days prior to initiation of treatment in females of reproductive potential. For females with a negative pregnancy test, initiate a highly effective form of contraception (failure rate of less than 1%) 4 weeks prior to the first dose. Continue highly effective contraception during therapy and for 24 months after the last dose of GDC-0449

The following are acceptable forms of barrier contraception:

- Latex condom (always used with spermicide)
- Diaphragm (always used with spermicide)
- Cervical cap (always used with spermicide)

The following are acceptable forms of secondary contraception, when used with a barrier method:

- Tubal ligation
- Partner's vasectomy
- Hormonal contraception including birth control pills, patches, rings, or injections, *with the exception of the progesterone-only "mini pill"*
- Intrauterine device (non–progesterone T)
- Vaginal sponge (containing spermicide)

In addition, 100% commitment to abstinence is considered an acceptable form of contraception.

The following are **unacceptable** forms of contraception for women of childbearing potential:

- IUD progesterone T
- *Progesterone-only "mini pill"*
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

APPENDIX C POSSIBLE PRENATAL EXPOSURE TO TERATOGEN REPORT

ATTACH TO CTEP-AERS 5-DAY REPORT

Possible Prenatal Exposure to Teratogen Report
AdEERS Ticket Number:_____

Study #:
SAE FAX NO: (301) 230-0159
Alternate FAX NO: (301) 897-7404

Initial Report Date: DD - MMM - YY	Follow-up Report Date: DD - MMM - YY
Principal Investigator:	Reporter:
Reporter Telephone #:	Reporter FAX #:

Investigator Number | Subject Number

Complete all of the investigator and subject number boxes provided. Use leading zeros, when necessary, to complete all expected boxes.

Example: Investigator #407 would be filled in as: 0 0 4 0 7

Subject Initials

Record the first letter of the subject's first, middle and last name, in that sequence. If the subject has no middle name, enter a dash.

Example: A - C

Subject's Sex: ☐ Female ☐ Male	Subject's Weight: _____ kg	Subject's Date of Birth: DD - MMM - YYYY

Subject's Ethnicity (check one only): ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not Available

Subject's Race (check all that apply): ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Not Available

Study Drug: **GDC-0449**	Study Drug Start Date: DD - MMM - YY Study Drug Stop Date: DD - MMM - YY OR ☐ Study Drug Continuing		
Dose:	Route: **ORAL**	Frequency: **QD**	Kit #:

First Day of Last Menstrual Period: DD - MMM - YY Estimated Date of Delivery: DD - MMM - YY

Method of Contraception (check all that apply):
☐ Oral Contraceptive Pills ☐ Condoms ☐ Periodic Abstinence ☐ Progestin Injection or Implants ☐ Spermacide
☐ Diaphragm ☐ Intrauterine Device (IUD) ☐ Tubal Ligation ☐ Other, specify:_____

Reproductive History: ☐ Gravida _____ ☐ Para _____

Tests performed during pregnancy: ☐ None ☐ Unknown
☐ CVS Results: ☐ Normal ☐ Abnormal
☐ Amniocentesis Results: ☐ Normal ☐ Abnormal
☐ Ultrasound Results: ☐ Normal ☐ Abnormal

Pregnancy Outcome
Was pregnancy interrupted? ☐ Yes ☐ No
If yes, specify: ☐ Elective Termination ☐ Spontaneous Abortion ☐ Ectopic
Date of Termination: DD - MMM - YY
If pregnancy was **not** terminated, specify pregnancy outcome (and provide infant outcome information)
☐ Vaginal Birth: ☐ Premature ☐ Term OR ☐ C-Section: ☐ Scheduled ☐ Emergency Date of Delivery: DD - MMM - YY
Infant outcome information: ☐ Normal ☐ Abnormal

Additional Case Details (if needed):

Note: Report possible teratogen exposure to AdEERS within 24 hours. See Protocol Section 11.3.1 for instructions. Attach this form to the complete 5-day AdEERS report.

APPENDIX D PATIENT'S MEDICATION DIARY

CTEP-assigned Protocol #_____

Local Protocol # _____

PATIENT'S MEDICATION DIARY

Today's date _____ **Agent: GDC-0449**

Patient Name (*initials acceptable)* **Patient Study ID**

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take **GDC-0449** capsules once daily. You should take the capsules at approximately the same time each day.
   Dose: take ___ 150 mg capsules.
3. If you have any comments or notice any side effects, please record them in the Comments column.
4. Please bring this form and your bottles of **GDC-0449** capsules when you return for each appointment.

Day	Date	Time of dose	# of capsules taken	Comments
			150 mg	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study_____
3. Total number of capsules taken this month _____
4. Physician/Nurse/Data Manager's Signature _____

APPENDIX E INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The patient _____ is enrolled on a clinical trial using the experimental agent GDC-0449. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times.

GDC-0449 interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the counter remedy), or anything that you buy from the health food store or grocery store (herbal supplement).

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you**. These are the thing that you and they need to know:

- GDC-0449 is a CYP3A4/5 and CYP2C9 substrate. GDC-0449 also inhibits CYP2C8, CYP2C9, and CYP2C19. These CYPs are enzymes in your liver. GDC-0449 must be used very carefully with other medicines that need certain liver enzymes to be effective or to be cleared from your system.
  - The specific enzymes are CYP3A4/5, CYP2C9, CYP2C8, and CYP2C19.
  - You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
  - Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of CYP3A4/5, CYP2C9, CYP2C8, or CYP2C19."
  - Your regular prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.asp to see if any medicine they want to prescribe is on a list of drugs to avoid.
  - Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and printed on the ingredient list. Find the generic name (your pharmacist can help) and look at the table on the back of this page. Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you take herbal medicine regularly. You should not take St. John's wort while you are taking GDC-0449.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent **GDC-0449.** This clinical trial is sponsored by the NCI. **GDC-0449** interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**GDC-0449** interacts with specific liver enzymes named **CYP3A4/5, CYP2C9, CYP2C8,** and **CYP2C19**, and must be used very carefully with other medicines that interact with these enzymes. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP_____**." ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX F GVHD CHRONIC FLOWSHEET

Chronic GVHD Flowsheet GDC-0449, IRB 84584

MOUTH		0=None	1= Mild	2= Moderate	3=Severe
	Erythema				
	Licheniods				
	Ulcers				
	Mucosal Changes				
GI-ESOPHAGEAL					
	Dysphagia				
	Odynophagia				
GI-UPPER GI					
	Early Satiety				
	Anorexia				
	Nausea/Vomiting				
GI-LOWER GI					
	Diarrhea				
SKIN					
	Maculopapular Rash/Erythema				
	Lichen Planus Features				
	Sclerotic Features				
	Papulosquamous Lesions				
	Ichthyosis				
	Karatosis Pilaris-like				
	Non-GVHD Abnormality Present				
EYES					
	Eyes				
	Non-GVHD Abnormality Present				
LUNGS					
	FEF 1				
	Lungs				
	Non-GVHD Abnormality Present				
JOINTS/ FASCIA					
	Joints and Fascia				
	Non-GVHD Abnormality Present				
	Shoulder - Right				
	Shoulder - Left				

	Elbow – Right				
	Elbow - Left				
	Wrist/Fingers – Right				
	Wrist/Fingers – Left				
	Ankle – Right				
	Ankle – Left				
GRADE					
	Health Care Provider Global Rating				
	Overall Severity Chronic GVHD				