ECOG-ACRIN cancer research group
Reshaping the future of patient care

Operations Office

August 19, 2020

[redacted] MS RAC
[redacted]
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room [redacted]
Bethesda, MD 20892

Dear Ms. [redacted]:

Enclosed is Addendum #25 to EAY131-T, *GDC-0449 (vismodegib) in Patients with Tumors (except basal cell skin carcinoma) with Smoothened (SMO) or Patched 1 (PTCH1) Mutation*

This addendum is in response to Dr. [redacted] Amendment Request for updates to specific protocol language for GDC-0449 (vismodegib) dated June 5, 2020.

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

This addendum has been reviewed and approved by the Central IRB, which is the sole IRB of record for this study. Local IRB review and approval is unnecessary.

Implementation of this addendum must occur on the activation date. Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

The following revisions to EAY131-T protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated version date and addendum number.
2.	Appendix III	Updated patient drug information template format.

The following revisions to EAY131-T Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated version date.

If you have any questions regarding this addendum, please contact [redacted] or 857-504-2900.

We request review and approval of this addendum to EAY131-T so ECOG-ACRIN may activate it promptly.

Thank you.

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

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Sincerely,

[redacted]

[redacted]

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Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol T: GDC-0449 (vismodegib) in Patients with Tumors (except basal cell skin carcinoma) with Smoothened (SMO) or Patched 1 (PTCH1) Mutations

GDC-0449 (VISMODEGIB) TREATMENT ARM CHAIR: [redacted], MD
GDC-0449 (VISMODEGIB) TREATMENT ARM CO-CHAIR: [redacted], MD
GDC-0449 (VISMODEGIB) TRANSLATIONAL CHAIR: [redacted], MD

Version Date: August 19, 2020

NOTE: This subprotocol (EAY131-T) should be used in conjunction with the MATCH Master Protocol (EAY131)

Rev. Add13 **NOTE: As of 11/17, all protocol changes will be noted by addendum number. Please reference the activation memo for the addendum activation date.**

SUBPROTOCOL ACTIVATION DATE

February 25, 2016 (Incorporated in Addendum #2)
Addendum #3 – 5/16
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #10 – 5/17
Addendum #13
Addendum #21
Addendum #25

Agent	IND#	NSC#	Supply
GDC-0449 (vismodegib)	IND Sponsor: DCTD, NCI IND#: [redacted]	747691	NCI Supplied

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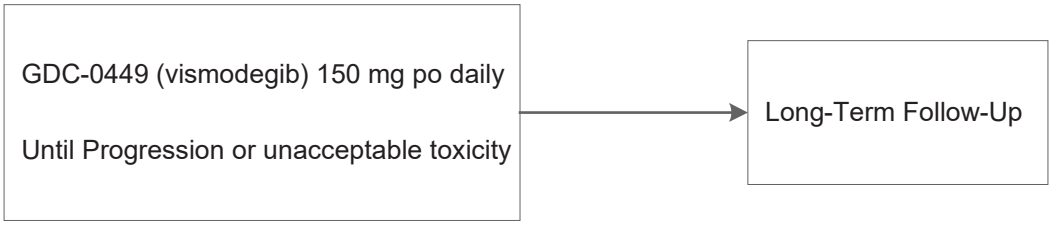
Schema



Cycle = 28 days
Accrual Goal: 35

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1. Introduction

1.1 Patched-1 (PTCH1) and Smoothened (SMO) genes and pathway

The Sonic hedgehog pathway is controlled at the cell surface by two transmembrane proteins, the tumor suppressor Patched-1 (*PTCH1*) in addition to the above discussed oncoprotein Smoothened (Smo). In the absence of the ligand Shh, Ptch maintains Smo in an inactive state. In the presence of Shh ligands (Sonic, Indian or Desert SHh), inhibition of Smo by *PTCH1* is relieved and signaling is transduced, leading to activation and nuclear translocation of Gli 1, 2 and 3 transcription factors[1]. The involvement of Gli1 activation in familial tumors came from the discovery that *PTCH1* on chromosome 9q22.3, which inhibits Gli activation, is mutated in basal-cell nevus syndrome (Gorlin's syndrome) – an autosomal dominant disorder where patients inherit a germline mutation in a *PTCH1* that causes hereditary predisposition to basal-cell carcinomas, medulloblastomas and other tumor types.[2,3] Inactivation of *PTCH1* results in constitutive activation of Smo and overexpression of full-length activated Gli1, underscoring the potential of this pathway as a therapeutic target. Inactivating, acquired PTCH1 mutations have been found in patients with sporadic basal cell carcinoma in approximately one third of cases, in patients with basal cell carcinomas related to xeroderma pigmentosum and in some sporadic of cases of medulloblastoma.[4,5]

Smoothened (SMO) is a 7 membrane spanning receptor involved in the hedgehog signaling pathway.[6] The SMO gene maps to the 7q31-q32 region. In the absence of Patched (PTCH) inhibition, SMO will accumulate, interact with Suppressor of fused (SUFU), and activate Gli family transcription factors with nuclear translocation. The Gli proteins have several functions, Gli1 and 2 are strong activators of transcription, whereas Gli3 is primarily inhibitory. Once the hedgehog pathway is activated, Gli3 is released from SUFU and undergoes proteasome inhibition, while Gli1 and 2 are translocated preferentially to the nucleus for transactivation activity.[6]

SMO has been identified as an oncogene; activating mutations in sporadic and germline basal cell carcinomas[6] and medulloblastomas[7] have been reported (Table 1). A hot spot for mutation has been identified at codon 535; codon 535 exon 9 changes tryptophan to leucine and codon 562 exon 10 changes arginine to glutamine.[6,8] Oral SMO inhibitors, such as GDC-0449 (vismodegib), have documented successful anti-tumor activity in basal cell carcinomas (BCC) with hedgehog pathway mutations (SMO, PTCH1).[9,10] The use of SMO inhibitors in medulloblastoma is more complex, and reports are indicating variable sensitivity depending on the mutation.[7]

Of importance to note, certain SMO mutations (codon D473H Asp to His) have been reported to confer disease resistance to GDC-0449 (vismodegib) (Erivedge, Genentech, San Francisco, CA), an oral SMO inhibitor.[11] This mutation was not believed to be an activating oncogenic mutation, but one that was relevant in the absence of PTCH1 inhibition. It is believed that D473H prevents GDC-0449 (vismodegib) binding to mutant SMO. Asp-473 lies along the SMO extracellular lip of the cavity for the G-protein coupled receptor, along the c-terminal end of the 6th transmembrane segment. Also, SMO mutations in gastric cancer have been reported, but are not considered to be oncogenic drivers.[12]

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1.1.1 SMO mutations in NSCLC

Although SMO mutations have been identified in basal cell carcinoma, medulloblastoma, and gastric cancers, they have only recently been reported in non-small cell lung cancer (NSCLC).[13] At M.D. Anderson Cancer Center (MDACC), 2 datasets were interrogated for SMO mutations and hedgehog pathway dysregulation in NSCLC, the MDACC Molecular Diagnostic Lab (MDL) and The Cancer Genome Atlas (TCGA) databases for lung adenocarcinoma (n=230) and squamous cell carcinoma (n=178). Mutations were determined by whole exome sequencing and copy number was assessed by GISTIC 2.0 (scores of 2 considered high level amplification). Mutations in hotspot regions of 46 cancer related genes including SMO was performed as part of clinical diagnostic evaluation (Ion AmpliSeq Cancer Panel; Life Technologies, CA). At MDACC, approximately 243 sequential patients were evaluated and 3 had SMO mutations, *for an incidence of 1.2%*.[14] This project is still ongoing.

In TCGA lung adenocarcinoma studies, alterations in SMO (mutation, amplification, or mRNA overexpression) were observed in 12.2% of tumors. The *incidence of SMO mutations was 2.6%* and SMO gene amplifications 5%. SMO mutations and amplifications strongly correlated with sonic hedgehog gene dysregulation ($p<0.0001$). In the TCGA squamous cell lung cancer study, SMO was altered in 10.1% of tumors, primarily via mRNA upregulation. Only 1 SMO missense mutation was identified in the Lung SCC cohort (D209Y).

At MDACC thoracic center, 3 patients with metastatic NSCLC were identified with SMO mutations by the MDACC MDL 46-gene panel. None of the 3 SMO mutations were known activating mutations and subsequent analysis has identified additional thoracic patients with SMO mutations (Table 2). The initial 3 SMO mutant patients were treated with GDC-0449 (vismodegib) with different clinical response outcomes. Patient [redacted] had a significant reduction in tumor burden with close to 6 months duration of benefit. Patient [redacted] with the SMO M525L mutation did not respond to GDC-0449 (vismodegib) therapy, whereas patient [redacted] had disease stabilization. Patient [redacted] was unable to tolerate GDC-0449 (vismodegib) due to nausea and stopped treatment after 14 weeks. His disease rapidly recurred after cessation of GDC-0449 (vismodegib).

SMO mutations and pathway alterations occur in NSCLC and may be an actionable target with hedgehog inhibitors. There is enough evidence that suggests NSCLC SMO mutant patients may benefit from GDC-0449 (vismodegib) therapy. However, additional correlative analysis is clearly needed. The preliminary clinical results indicate differential sensitivity to GDC-0449 (vismodegib), depending on the SMO mutation. Also, in the MDACC study, almost all of the patients carried concomitant p53 mutations in their tumors (Table 2). There have been preclinical reports suggesting that gain of function SMO mutations can inhibit p53 accumulation via MDM2 activation and ubiquitination.[15] In the TCGA data set, 4 of 6 SMO mutated lung adenocarcinomas and the one lung SCC SMO mutated patient had concomitant p53 mutations. It is plausible that some SMO mutations

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in NSCLC are not constitutively activating mutations but require potentiation with expression of mutant p53 in order to lead to oncogenesis.

1.2 GDC-0449 (vismodegib)

Inhibitors of this pathway have entered clinical development in the last several years. Cyclopamine, a plant derived steroidal alkaloid that directly binds to and inactivates Smo, thereby blocking activation of Gli1-mediated transcription [16,17], has been used mostly in laboratory studies. GDC-0449 (vismodegib) is an inhibitor of Smo similar to cyclopamine but with more favorable pharmacologic properties with respect to potency, selectivity, solubility, pharmacokinetics and bioavailability. Treatment of basal cell carcinoma using GDC-0449 (vismodegib) has been extraordinarily successful, providing proof of concept that targeting the Shh pathway in the appropriate tumor types is highly effective. An open-label, multicenter, two-stage phase I trial to evaluate the safety and tolerability of GDC-0449 (vismodegib) in patients with a variety of solid tumors refractory to standard therapy was conducted[9,18]. Of 68 patients enrolled at 3 centers, 33 had advanced basal cell carcinoma; 18 of these patients showed evidence of objective response, and 11 showed stable disease. Eight grade 3 adverse events, including fatigue, hyponatremia, muscle spasm and atrial fibrillation, were deemed possibly related to study drug and no dose-limiting toxic effects were observed. The recommended phase II dose was 150 mg per day, as pharmacokinetic analyses indicated that doses greater than this did not result in higher plasma concentrations of the drug. In this study, skin biopsies and hair follicles were analyzed for *Gli1* mRNA expression. Down-modulation of *Gli 1* transcription factor was observed in skin punch biopsy samples after treatment in all patients, suggesting that this is a valid pharmacodynamic marker [9,18].

1.2.1 GDC-0449 (vismodegib) FDA approval in BCC

Following this phase I study a multicenter, international trial enrolled 33 patients with metastatic basal cell carcinoma who exhibited 30% response rate as well as 63 patients with locally advanced disease not amenable to surgery or radiation who exhibited an overall 43% response rate anda 21% complete response rate. The median response duration was 7.6 months and the median progression-free survival was 9.5 months in both groups, and many of the complete responses were durable[19]. An expanded access program enrolled 119 similar patients; objective responses were seen in 46.4% of patients with locally advanced BCC and 30.8% of patients with metastatic BCC. Mean follow-up for safety was 6.5 months, with muscle spasms (70.6%), dysgeusia (70.6%), alopecia (58.0%), and diarrhea (25.2%) as the most common adverse events.[20]

1.2.2 GDC-0449 (vismodegib) is currently under evaluation in ongoing studies in patients with solid tumors. To date, no new safety signals have been reported.

1.2.3 GDC-0449 (vismodegib) benefit in preclinical models, dosing, administration

In vitro cell-based potency assays involving luciferase reporter genes under the control the Gli transcription factor promoter demonstrate that GDC-0449 (vismodegib) potently inhibits Hh signaling in human

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and mouse cell lines with an IC_{50} of 2.8 nM-13 nM (Investigator's Brochure, Version 8, January 2013). GDC-0449 (vismodegib) has been tested in a number of different *in vivo* model systems, including murine allograft, cell line xenograft, and patient-derived xenograft (PDX) models. In the mutation-driven *Ptch+/-* medulloblastoma allograft model, GDC-0449 (vismodegib) induces tumor regressions; in ligand-driven colorectal carcinoma (CRC) cell line xenografts (involving a "paracrine" mechanism of Hh pathway activation driven by tumor-produced ligand activation of Hh in the surrounding stroma that in turn promotes tumor growth), GDC-0449 (vismodegib) instead induces tumor growth inhibition[25].

Integrated pharmacodynamic modeling of the concentration-response relationship in the *Ptch1+/-* medulloblastoma allograft and colorectal carcinoma (CRC) xenograft models revealed that 50% of the maximal anti-tumor effect achieved correlated to approximately 82% pathway inhibition (as measured by drug-mediated decrease in *Gli1* transcript levels)[25]. The correlation between the suppression of *Gli1* transcript levels and tumor growth inhibition/regression is characterized by a steep Hill slope, implying that a modest change in pathway inhibition translates to a disproportionately significant impact upon the therapeutic efficacy achieved. This is consistent with the general principle that efficacy with molecularly targeted agents directed at oncogenic driver pathways requires both potent and durable target inhibition that in many cases can only be achieved within a narrow pharmacokinetic window[26,27].

1.2.4 Clinical Pharmacology

1.2.4.1 Mechanism of Action

GDC-0449 (vismodegib) is an inhibitor of the Hedgehog pathway. GDC-0449 (vismodegib) binds to and inhibits Smoothened, a transmembrane protein involved in Hedgehog signal transduction.

1.2.4.2 Pharmocokinetics

Absorption

GDC-0449 (vismodegib) is a compound with low aqueous solubility (BCS Class 2). The single dose absolute bioavailability of GDC-0449 (vismodegib) is 31.8%. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg or 540 mg GDC-0449 (vismodegib). GDC-0449 (vismodegib) capsule may be taken without regard to meals because the systemic exposure of GDC-0449 (vismodegib) at steady state is not affected by food.

Distribution

The volume of distribution of GDC-0449 (vismodegib) ranges from 16.4 to 26.6 L. GDC-0449 (vismodegib) plasma protein binding in patients is greater than 99%. GDC-0449 (vismodegib) binds to both human serum

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albumin and alpha-1-acid glycoprotein (AAG) and binding to AAG is saturable.

Metabolism

Greater than 98% of the total circulating drug-related components are the parent drug. Metabolic pathways of GDC-0449 (vismodegib) in humans include oxidation, glucuronidation, and pyridine ring cleavage. The two most abundant oxidative metabolites recovered in feces are produced in vitro by recombinant CYP2C9 and CYP3A4/5.

Elimination

GDC-0449 (vismodegib) and its metabolites are eliminated primarily by the hepatic route with 82% of the administered dose recovered in the feces and 4.4% recovered in urine. The estimated elimination half-life (t1/2) of GDC-0449 (vismodegib) is 4 days after continuous once-daily dosing and 12 days after a single dose.

Pharmacokinetics in Specific Populations

Hepatic Impairment: The effect of hepatic impairment on the systemic exposure of GDC-0449 (vismodegib) has not been studied.

Renal Impairment: The effect of renal impairment on the systemic exposure of GDC-0449 (vismodegib) has not been studied.

Population pharmacokinetic analyses showed that weight (range: 41-140 kg), age (range: 26-89 years), creatinine clearance (range: 30 to 80 mL/min), and sex do not have a clinically meaningful influence on the systemic exposure of GDC-0449 (vismodegib).

1.2.4.3 Cardiac Electrophysiology

In a thorough QTc study in 60 healthy subjects, there was no effect of therapeutic doses of ERIVEDGE on the QTc interval.

1.3 Proposed mechanisms of resistance to SMO inhibitors

Several mechanisms of resistance to GDC-0449 (vismodegib) have been proposed and discovered. The most striking example comes from the clinical case report of a patient with metastatic, *Ptch1* mutant medulloblastoma in whom GDC-0449 (vismodegib) produced a remarkable clinical response, only for progressive disease to develop 3 months into treatment[21]. Analysis of a progressive tumor revealed the acquisition of the *SMO* mutation *D473H*, which *in vitro* studies demonstrated confers drug resistance by disrupting GDC-0449 (vismodegib) binding to SMO[11]. A chemical screen of Hh pathway inhibitors (HPIs) successfully identified alternate compound antagonists that could inhibit this *SMO* mutation, a proof-of-principle that resistance mediated by such alterations can be overcome by distinct hedgehog pathway inhibitors [22]. Alternatively, *SUFU* mutations, *Gli2* amplification, *cyclin* D1 amplification, and *MYCN* amplification are all mechanisms of Hh pathway activation downstream of

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SMO which can circumvent GDC-0449 (vismodegib) action to potentially mediate drug resistance.[7,22,23]

Apart from alterations arising within components of the Hh pathway itself, activation of the phosphatidylinositol 3-kinase (PI3k)/Akt pathway has also been implicated as a mechanism of GDC-0449 (vismodegib) resistance. Pathway gene expression signatures of medulloblastoma tumors derived from *Ptch+/-/p53-/-* mice resistant to the SMO inhibitor LDE225 (Novartis) revealed enrichment of PI3k pathway genes relative to drug-sensitive tumors[23]. Activation of PI3k/Akt pathway indeed has been identified in Hh-driven medulloblastoma human tumor samples[7], and the addition of PI3k pathway inhibitors to Hh pathway inhibitors have been shown to augment the anti-tumor effect achieved in medulloblastoma mouse models[22-24]. However, with the exception of the *SMO (D473H)* example, all of these potential mechanisms of resistance to SMO inhibition have been described primarily in preclinical models and have yet to be clinically validated.

1.4 Scientific Rationale to study GDC-0449 (vismodegib) in SMO and PTCH mutant tumors

GDC-0449 (vismodegib) has been FDA approved for use in metastatic basal cell carcinoma and has a well-known safety and tolerability profile.[10] Identifying additional tumor types that derive benefit from GDC-0449 (vismodegib) should be a clinical research priority; as there is ample evidence that the hedgehog pathway is dysregulated in several different solid tumor types, the most well-established in medulloblastoma and more recently, in NSCLC.[7,13] Targeting the hedgehog pathway makes scientific sense, as this pathway has been shown to induce solid tumor carcinogenesis by ligand overexpression[28] or activating mutations in SMO and PTCH.[6] Additional clinical studies are needed with correlative science to clarify mutation sensitivity to SMO inhibitors, given that activating, non-activating, and GDC-0449 (vismodegib)-resistant SMO mutations have all been reported throughout various solid tumors.[7,11-13]

Table 1. Table of Reported incidence rates in the literature and known potential activating mutations.

Oncologic disease	%SMO	%PTCH mutation	Possible activating mutation
Basal cell carcinoma	10%	90%	SMO - Codon 535 hot spot[6,8] PTCH-D362Y, D513Y
Medulloblastoma	rare	rare	SMO - D473H - resistant[11] PTCH1 - W844C[11]
NSCLC	2.6% TCGA adenocarcinomas[13] 1.2% all histologies MDACC[14]	rare	SMO – 641A[13], D209*, other mutations listed in Table 2 are unknown significance.
Gastric cancer	10%[12]	PTCH 4%, 13%[12]	PTCH1: D362Y, D513Y, 392I*, R1307fs*, P1315L* SMO[12]: R547H*, R726Q*, 17insL*, D25G*, V270I*, R726Q*, R168H*

*unknown significance

Table 2. Concomitant SMO and p53 mutations in NSCLC tumors and radiographic RECIST response to GDC-0449 (vismodegib) therapy.

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Patient and site of tumor profiled	SMO mutation	RECIST Response to GDC-0449 (vismodegib)
[redacted] NSCLC lung tumor	NM_005631.4(SMO):c.1921C > G p.P641A NM_000546.5(TP53):c.574C > T p.Q192*	PR
[redacted] skin lesion	NM_005631.4(SMO):c.1921C > G p.P641A NM_000546.5(TP53):c.832_833delCCinsTT p.P278F	CR
[redacted] NSCLC lung tumor	NM_005631.4(SMO):c.1573A > T p.M525L NM_000546.5(TP53):c.1024C > T p.R342*	PD
[redacted] NSCLC lung tumor	NM_005631.4(SMO):c.1921C > G p.P641A NM_000546.5(TP53):c.722C > T p.S241F	SD
[redacted] NSCLC lung tumor	NM_005631.4(SMO):c.572G > Tp.G191V NM_000546.5(TP53):c.734del p.G245fs	Not treated yet
[redacted] NSCLC lung tumor	NM_005631.4(SMO):c.622G > A p.E208K NM_000546.5(TP53):c.814G > A p.V272M	Not treated yet
[redacted] NSCLC lung tumor	NM_005631.4(SMO):c.640G > A p.G214S P53 wildtype	Not treated yet
[redacted] lung tumor	NM_005631.4(SMO):c.1921C > G p.P641A NM_000546.5(TP53):c.818G > A p.R273H	Not treated yet

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2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the MATCH Master Protocol, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: All patients must have signed the relevant treatment consent form

2.1 Eligibility Criteria

_____ 2.1.1 Patients must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master Protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

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_____ 2.1.2 Patients must have activating mutations of Smoothened (SMO) or deleterious Patched 1 (PTCH1) as determined via the MATCH Master Protocol and described in Appendix II. See Appendix II for information on the Smoothened (SMO) or Patched 1 (PTCH1) mutations and corresponding Levels of Evidence.

_____ 2.1.3 Patient must not have basal cell carcinoma.

_____ 2.1.4 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have NONE of the following cardiac criteria:

- No clinically unstable abnormalities in rhythm, conduction or morphology of resting ECG e.g. complete left bundle branch block, third degree heart block.
- No factors that increase the risk of QTc prolongation or risk of arrhythmic events such as congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age

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Date of ECG: _____

_____ 2.1.5 Patients with known left ventricular dysfunction must have ECHO or nuclear study (MUGA or First Pass) within 4 weeks prior to registration to treatment and must not have left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN). If the LLN is not defined at a site, the LVEF must be > 50% for the patient to be eligible.

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_____ 2.1.6 Patients must not have known hypersensitivity to GDC-0449 (vismodegib) or compounds of similar chemical or biologic composition.

Date of ECHO/Nuclear Study: _____

_____ 2.1.7 Patient must not have had any of the prior therapies: GDC-0449 (vismodegib)

_____ 2.1.8 Women of childbearing potential and men who are sexually active must agree to use adequate contraception defined as appropriate double barrier method of birth control (such as female use of a diaphragm, intrauterine device (IUD), sponge and spermicide, in addition to the male use of a condom or involve female use of prescribed "birth control pills" or a prescribed birth control implant). Both double barrier contraception and birth control pills or implants must be used for at least one week prior to the start of the study and continue for 24 months after completion of study for women, and 3 months after completion of study for men.

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_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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3. GDC-0449 (vismodegib) Treatment Plan

3.1 Administration Schedule

GDC-0449 (vismodegib) will be administered as a flat dose and will not be based on ideal or actual body weight. GDC-0449 (vismodegib) will be administered as 150 mg po daily dose on a continual daily schedule.

One cycle of treatment will be 28 days. Tumor measurements will be conducted every other cycle or 8 weeks.

Patients will continue GDC-0449 (vismodegib) 150 mg po daily until disease progression, unacceptable toxicity or withdrawal of consent.

If a patient misses a dose of GDC-0449 (vismodegib), they should not take the missed capsule, but resume with the next scheduled dose. GDC-0449 (vismodegib) may be taken with or without food.

3.2 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 subprotocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

3.2.1 Additional instructions, requirements and exceptions for protocol EAY131 – Subprotocol T

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

EAY131 – Subprotocol T specific expedited reporting requirements:

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while a female patient is on GDC-0449 (Vismodegib), or within 24 months of the female patient's last dose of GDC-0449 (Vismodegib), are considered immediately reportable events. A female partner of a male patient who becomes pregnant within 3 months of the male's last dose of GDC-0449 (Vismodegib) is also considered a reportable event. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master Protocol for

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detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

NOTE: The timeframes and requriements stated here for reporting a pregnancy are different on this protocol than what is outlined in Appendix VIII of the MATCH Master Protocol. Please adhere to the timeframes and requirements listed here.

EAY131 – Subprotocol T specific expedited reporting exceptions:

For Subprotocol T, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

3.2.2 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.

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4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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3.3 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 2197 patients*. Below is the CAEPR for GDC-0449 (Vismodegib).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Version 2.6, April 23, 2019[1]

Adverse Events with Possible Relationship to GDC-0449 (Vismodegib) (CTCAE 5.0 Term) [n= 2197]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
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			
	Aspartate aminotransferase increased		
	CPK increased		
	GGT increased		
Weight loss			***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
Muscle cramp			***Muscle cramp (Gr 2)***

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Adverse Events with Possible Relationship to GDC-0449 (Vismodegib) (CTCAE 5.0 Term) [n= 2197]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Musculoskeletal and connective tissue disorder - Other (premature epiphyseal closure)	
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Irregular menstruation[2]			***Irregular menstruation[2] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Pruritus		

[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 - Febrile neutropenia; Thrombotic thrombocytopenic purpura

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

EYE DISORDERS - Blurred vision; Keratitis; Retinal vascular disorder

EAR AND LABYRINTH DISORDERS - Vertigo

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

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Facial pain; Fever; Flu like symptoms; General disorders and administration site

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conditions - Other (general physical health deterioration); 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; Fall; Hip fracture

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

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

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle tightness/stiffness); 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; Dysesthesia; 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; Oropharyngeal pain; Pleural effusion; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (COPD); Sneezing; Sore throat

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Eczema; Hair color changes; Hyperhidrosis; Nail ridging; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (actinic keratosis); 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.

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3.4 Dose Modifications

3.4.1 Dose Reductions

Dose reduction of GDC-0449 (vismodegib) is not permitted as there is only a 150-mg capsule strength available. Capsules must not be opened or crushed. If a patient misses a dose of GDC-0449 (vismodegib), they should not take the missed capsule, but resume with the next scheduled dose. GDC-0449 (vismodegib) may be taken with or without food.

If a treatment interruption occurs, and it is determined that GDC-0449 (vismodegib) will be re-started, the original dose of 150 mg daily dose will be maintained

GDC-0449 (vismodegib) dose reduction and schedule modifications during the study are not recommended due to the pharmacokinetic characteristics of the drug (see GDC-0449 (vismodegib) Investigator Brochure v8). Briefly, GDC-0449 (vismodegib)'s pharmacokinetic profile is a result of high affinity, reversible binding to Alpha-1 acid Glycoprotein (AAG) and binding to albumin, in addition to solubility limited absorption and slow metabolic elimination properties (Graham 2011). Initiation of less frequent administration schedules than the approved dose and schedule of GDC-0449 (vismodegib) of 150 mg orally once daily,(i.e. 150 mg three times weekly or 150 mg once weekly dosing), was associated with marked decrease in the pharmacologically active unbound fraction.

Unbound steady-state GDC-0449 (vismodegib) concentrations were 60% and 85% lower for the TIW and QW dose groups, respectively, relative to the QD dose group. Such decreases may be associated with loss of GDC-0449 (vismodegib) activity based on findings from nonclinical models. Integrated PK/PD modeling of GDC-0449 (vismodegib) in xenograft models has revealed a steep relationship between pathway modulation (GLI1 inhibition) and anti-tumor effect, suggesting that even small reductions in exposure could lead to dramatic loss in GDC-0449 (vismodegib) activity (see GDC-0449 (vismodegib) Investigator Brochure v8)

3.4.2 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Dose modification guidelines below apply only to toxicities judged to be related to GDC-0449 (vismodegib).

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 website (http://ctep.cancer.gov).

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Nausea	Management/Next Dose for GDC-0449 (vismodegib)
≤ Grade 1	No change in dose
Grade 2	May continue dosing while managing with anti-emetics. If occurs despite optimal management, hold until ≤ Grade 1**. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 4	Off protocol therapy
*Patients requiring a delay of > 2 weeks should go off protocol therapy.	
Recommended management: antiemetics.	

Vomiting	Management/Next Dose for GDC-0449 (vismodegib)
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at same dose level.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: antiemetics, IV fluid hydration if indicated.	

Diarrhea	Management/Next Dose for GDC-0449 (vismodegib)
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at same dose level.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

For any other non-hematologic grade 3 toxicity that is deemed to be related to GDC-0449 (vismodegib), the study drug GDC-0449 (vismodegib) can be held for up to 2 weeks until the toxicity resolves to ≤ grade 1. GDC-0449 (vismodegib) will be restarted at 150 mg daily dosing.

Neutropenia	Management/Next Dose for GDC-0449 (vismodegib)
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold* until < Grade 2. Resume at same dose level.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: Consider growth factor support if neutropenia lasts over 1 week after holding GDC-0449 (vismodegib).	

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Thrombocytopenia	Management/Next Dose for GDC-0449 (vismodegib)
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at same dose level.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

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3.5 Supportive Care

The following guidelines should be used for patients enrolling onto EAY131-T:

- 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.
- 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 patients 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 must not breastfeed a baby while on this study and should not breastfeed for 24 months after last dose of study medication.
- Female patients must NEVER donate ova while being treated with GDC-0449.
- All sexually active male subjects (including those who have undergone vasectomy) must 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 must 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.

All supportive measures consistent with optimal patient care will be given throughout the study.

3.6 Duration of Agent-specific treatment

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

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- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression

3.7 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

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4. Study Parameters

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4.1 Therapeutic Parameters for GDC-0449 (vismodegib) Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving GDC-0449 (vismodegib) treatment.

NOTE: All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation and electrocardiogram (ECG).

Test/Assessment	Prior to Registration to Treatment	Treatment		End of Treatment	Follow Up[F]
		Cycles 1-5 and then every other cycle thereafter	After Cycle 2, 4 and then after every 2 cycles thereafter		
H&P, Weight, Vital signs[A]	X	X[J]			X
Performance status	X	X[J]			X
CBC w/diff, plts[B]	X	X[J]			X
Serum chemistry[B]	X	X[J]			X
Radiologic evaluation[D]	X		X[D]		X[F]
β-HCG[C]	X	X[C]			
Toxicity Assessment[G]		X[J]		X	X[F]
Pill Count/Diary[H]		X[J]		X	
ECG[K]	X				
Echocardiogram or Nuclear Study	X[I]				
Tumor biopsy and blood sample for MATCH Master Protocol[E]			X	X	

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of cycles 1-5 and then every other cycle thereafter (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

C. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. For women of childbearing potential, a negative pregnancy test within 7 days prior to commencement of dosing is required. Urine pregnancy tests will be

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performed before every cycle for women who are capable of becoming pregnant. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[D.] Disease measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

[E.] Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

[F.] Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

[G.] Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person. The Toxicity Assessment is not required prior to Cycle 1, but is required every subsequent cycle.

[H.] The pill calendar will be collected at the end of every cycle. The Pill Count/Diary is not required prior to Cycle 1, but is required every subsequent cycle.

[I.] As clinically indicated.

[J.] For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this timepoint: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications.

[K.] Within 8 weeks of treatment assignment.

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5. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment arm prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug 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 – see general information) The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, 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.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an “active” account status, a “current” password, and an active person registration status.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator.

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Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

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5.1 GDC-0449 (NSC 747691)

5.1.1 Other Names

vismodegib, Erivedge

5.1.2 Classification

Hedgehog Pathway Antagonist

5.1.3 Mode of Action

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GDC-0449 provides anticancer responses by inhibiting the hedgehog pathway. GDC-0449 binds to and inhibits SMO, whose only established function is to transmit the Hedgehog signal. 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.

5.1.4 Storage and Stability

Storage: Do note store above 30°C (85ºF).

Stability: Stability testing is ongoing.

5.1.5 Dose Specifics

Patients will be initiated at 150 mg po daily dose.

If a patient misses a dose of GDC-0449 (vismodegib), they should not take the missed capsule, but resume with the next scheduled dose.

GDC-0449 (vismodegib) may be taken with or without food.

The capsules must be swallowed whole. Do not open or crush the capsules.

5.1.6 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 vismodegib, microcrystalline cellulose PH101, lactose monohydrate, sodium lauryl sulfate, povidone K29/32, talc, sodium starch glycolate, and magnesium stearate and purified water. The capsule shell consists of gelatin, red iron oxide, black iron oxide, and titanium dioxide. A compendial-grade black printing ink may be used. Each bottle contains 32 capsules.

5.1.7 Route of Administration

Oral.

5.1.8 Incompatibilities

Clinically significant PK interactions between vismodegib and CYP450 inhibitors are not expected. GDC-0449 is not a potent inhibitor of P450 isoforms 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 No clinically significant PK interaction between vismodegib and fluconazole (a moderate CYP2C9 inhibitor) or itraconazole (a strong CYP3A4 inhibitor) were seen in healthy volunteers (Genentech study GP28465). Inducers of CYP3A4 are not predicted to alter vismodegib

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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).

Clinically significant PK interactions between vismodegib and P-gp inhibitors are not expected. No clinically significant PK interaction between vismodegib and itraconazole (a strong P-glycoprotein inhibitor) were seen in healthy volunteers (Genentech study GD28465).

GDC-0449 inhibited OATP1B1, OATP1B3, and BCRP, but the likelihood of GDC-0449 being a clinically relevant inhibitor of OATP1B1, OATP1B3, and BCRP is low. It is unlikely that there will be an interaction between GDC-0449 and UGT substrates.

Clinically significant PK interactions between vismodegib and pH elevating agents are not considered clinically meaningful. Co-administration of the PPI rabeprazole with GDC-0449 resulted in a slight decrease of approximately 14% in GDC-0449 steady state exposure compared with administration of GDC-0449 alone.

Clinically significant PK interactions between vismodegib and CYP450 substrates are not expected. No clinically significant PK interaction between vismodegib and rosiglitazone (a CYP2C8 substrate) or oral contraceptives ethinyl estradiol and norethindrone (Genentech study SHH4593g). Clinically significant PK interactions between vismodegib and BCRP substrates are not expected. In vitro data indicate that vismodegib is an inhibitor of the BCRP transporter; however, the in vitro concentrations at which inhibition occurred are significantly greater than the unbound vismodegib concentrations observed in patients.

5.1.9 Side Effects

See Section 3.3 for side effects.

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5.1.10 Nursing/Patient Implications

The terminal half-life of GDC-0449 is approximately 9-12 days.

Vismodegib capsules contain lactose monohydrate. Patients with the rare hereditary problems of galactose intolerance, primary hypolactasia, or glucose-galactose malabsorption should not take this medicine.

Reproductive Risks:

- Women of child bearing potential should continue contraceptive measures for 24 months after the last dose of GDC-0449.
- Male patients should maintain adequate contraception methods for 3 months

Patients should not donate blood or blood products during the study and for 24 months after discontinuation.

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6. Translational Studies

Please refer to the MATCH Master Protocol for information on the Translational Studies.

7. References

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Appendix I

Patient Pill Calendar

Storage: Store at Room Temperature

Pill Calendar Directions

1. Take your scheduled dose of one capsule each day.
2. If you forget, the missed capsules will not be taken made up. You should resume taking one capsule daily.
3. Please bring the empty bottle or any leftover capsules and your pill calendar to your next clinic visit.
4. GDC-0449 (vismodegib) should be taken at approximately the same time each day and may be taken with or without food.
5. Swallow capsules whole, do not crush, chew or open capsules.

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Patient Pill Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused capsules and your completed pill calendar to your doctor's visits.

GDC-0449 (vismodegib)

DAY	Date			Time capsules taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year		
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 Signature: _____ Date: _____

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Appendix II

Actionable Mutations for Sub-Protocol EAY131-T

A. Inclusion variants

MATCHBOX also was implemented with a function to identify any deleterious mutations in PTCH1 not listed in the table below as inclusion variants (LOE code =3). Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
SMO	COSM216037	SNV	2	p.L412F
SMO	MCH10	SNV	2	p.P641A
PTCH1	COSM96909	SNV	3	p.W844C
SMO	COSM13144	SNV	3	p.S533N

B. Exclusion variants

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
SMO	MCH19	SNV	3	p.M525L
SMO	COSM3942015	SNV	2	p.V321M
SMO	MCH7	SNV	2	p.I408V
SMO	MCH5	SNV	3	p.N219D
SMO	MCH6	SNV	3	p.L221R
SMO	MCH8	SNV	3	p.E518K
SMO	MCH9	SNV	3	p.E518A

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Molecular Analysis for Therapy Choice (MATCH)
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Appendix III

PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:
Diagnosis:
Study Doctor:
Study Doctor Phone #:
NCI Trial #:
Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

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