

Cover Page for Clinical Trials Document posting

Official Title: S1400B, "A PHASE II STUDY OF GDC-0032 (TASELISIB) FOR PREVIOUSLY TREATED PI3K POSITIVE PATIENTS WITH STAGE IV SQUAMOUS CELL LUNG CANCER (LUNG-MAP SUB-STUDY)"

NCT Number: 02785913

Version Date: 9/1/2017

Description:

S1400 [NCT 02154490] is the parent study to **S1400B** [NCT 02785913].

The **S1400** Lung-MAP study is considered one study under one IND consisting of:

- S1400 Version Control Protocol
- S1400 Main Screening Protocol Component
- Multiple Sub-Studies (or sub-protocols) Components

Each component is contained in its own separate document.

S1400B is one of these components. Each "component" consists of the protocol document and its associated informed consent document(s). Since each screening and sub-study component operates independently from the other components contained in Lung-MAP, each has its own version date and NCT number. This is due to the complexity of the study and how it must be entered into different computer programs.

S1400B: PI3K – GDC-0032

A BIOMARKER-DRIVEN MASTER PROTOCOL FOR PREVIOUSLY TREATED
SQUAMOUS CELL LUNG CANCER

A PHASE II STUDY OF GDC-0032 (TASELISIB) FOR PREVIOUSLY TREATED
PI3K POSITIVE PATIENTS WITH STAGE IV SQUAMOUS CELL LUNG CANCER
(LUNG-MAP SUB-STUDY)

NCT #02154490

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Available from Pharmaceutical Collaborators:
GDC-0032 (Taselisib) (NSC 778795)
(IND-119672)

Available from Commercial Sources:
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* Docetaxel is not a current study agent effective 12/18/2015.

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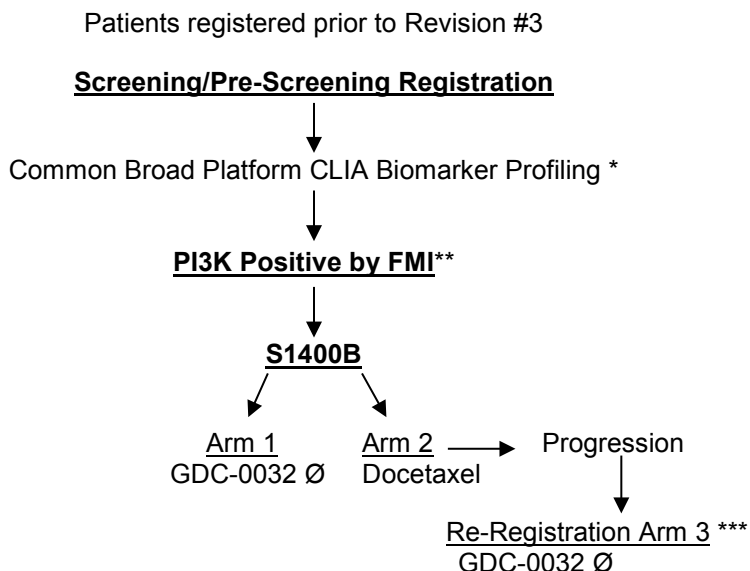
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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

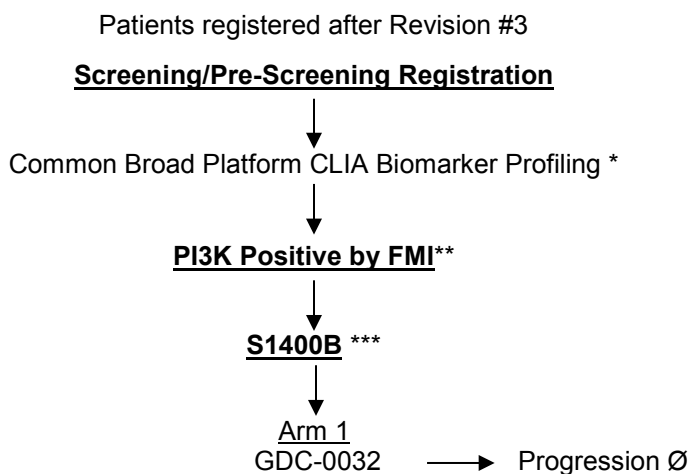
To submit site registration documents:	For patient enrollments:	Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103</p> <p>Fax: 215-569-0206</p> <p>Email: CTSURegulatory@ctsu.coccg.org</p> <p>For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.</p>	<p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</p> <p><u>Other Tools and Reports:</u> Institutions participating through the CTSU continue to have access to other tools and reports available to the SWOG Workbench. Access this by using your active CTEP-IAM USER ID and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx.</p>
<p>The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.</p> <p>CTSU sites should follow procedures outlined in the protocol for site registration, Patient Enrollment Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.</p>		
<p><u>For patient eligibility questions</u> contact the SWOG Data Operations Center by phone or email:</p> <p>206-652-2267 S1400question@crab.org</p> <p><u>For treatment or toxicity related questions</u> contact S1400BMedicalquery@swog.org.</p>		
<p><u>For questions unrelated to patient eligibility, treatment, or data submission</u> contact the CTSU Help Desk by phone or e-mail:</p> <p>CTSU General Information Line: 888-823-5923 ctsucontact@westat.com</p> <p>All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>The CTSU Web site is located at https://www.ctsu.org</p>		

SCHEMA
OLD SCHEMA



- * Archival formalin-fixed paraffin-embedded (FFPE) tumor, fresh core needle biopsy if needed
- ** Notification of sub-study assignment will be provided by the SWOG statistical center (see Section 11.0 in **S1400** for details).
- *** Optional re-registration to Arm 3- GDC-0032, (patients must have progressed as defined in Section 10.2d of **S1400**).
- ∅ Upon progression (as defined in Section 10.2d in **S1400**), patients may be eligible for another sub-study. The new sub-study assignment will be determined by the SWOG Statistical Center (see [Section 14.4](#)).

NEW SCHEMA



- * Archival formalin-fixed paraffin-embedded (FFPE) tumor, fresh core needle biopsy if needed
- ** Notification of sub-study assignment will be provided by the SWOG statistical center (see Section 11.0 in **S1400** for details).
- *** Arm 2 Docetaxel has been removed from the main schema as it is closed to accrual per Revision #3, Version Date 11/18/15.
- ∅ Upon progression (as defined in Section 10.2d in **S1400**), patients may be eligible for another sub-study. The new sub-study assignment will be determined by the SWOG Statistical Center (see [Section 14.4](#)).

1.0 OBJECTIVES

Included here are the objectives related to the single arm Phase II portion of Design #2 (Sequential Phase II to Phase III) as described in **S1400**

The objective of **S1400B** is to evaluate GDC-0032 (Taselisib), a phosphoinositide 3-kinase (PI3K) inhibitor, in PI3K-positive patients. **S1400B** will utilize a broad definition of PI3K-positivity for eligibility (Foundation Medicine [FMI] criteria as defined in [Section 5.0](#) and [11.1](#)). However, the primary analyses will be performed first using a more restricted definition of PI3K-positivity (Genentech [GNE] criteria as defined in [Section 11.1](#) of **S1400B**), followed by an evaluation using the more broad FMI criteria if the first analysis meets the pre-specified efficacy endpoints.

1.1 Primary Objectives

a. Phase II Component

The primary objective within the Phase II component of **S1400B** is to evaluate if there is sufficient evidence to continue to the Phase III component by evaluating the objective response rate (ORR) for PI3K GNE-positive patients registered to **S1400B** treated with GDC-0032.

b. Phase III Component

If the study meets the criteria specified in **S1400** Section 11.2a, the study will be amended to include a follow-on randomized Phase III trial.

1.2 Secondary Objectives

a. Phase II Component

1. To evaluate investigator-assessed progression free survival (IA-PFS) and overall survival (OS) in both the subset of patients defined to be PI3K GNE-positive and in the entire **S1400B** (PI3K FMI positive) study population treated with GDC-0032
2. To evaluate ORR in the entire **S1400B** (PI3K FMI positive) study population treated with GDC-0032 to evaluate the Duration of Response (DoR) both in GNE positive and FMI positive.
3. To evaluate the duration of response (DoR) both in the entire **S1400B** PI3K FMI positive study population and in GNE positive patients treated with GDC-0032 who achieve a CR or PR (confirmed and unconfirmed) by RECIST 1.1.
4. To evaluate the frequency and severity of toxicities associated with GDC-0032

1.3 Translational Medicine Objectives

- a. To identify additional predictive tumor/blood biomarkers that may modify response or define resistance to the GDC-0032 beyond the chosen biomarker for biomarker-driven sub-studies.
- b. To identify potential resistance biomarkers at disease progression.
- c. To establish a tissue/ blood repository from patients with refractory squamous cell carcinoma (SCCA) of the lung.

2.0 BACKGROUND

The Phosphoinositide 3-Kinase Pathway

Phosphoinositide 3-kinase (PI3K) is a lipid kinase involved in tumor cell proliferation, survival, and migration upon activation by growth factor receptors and integrins. PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3), a second messenger involved in the phosphorylation of AKT and associated proteins in the AKT-mTOR pathway. (1, 2) Activating and transforming mutations, as well as amplification, in the p110 α subunit of PI3K are commonly found in solid and hematological tumors. In addition, the PI3K-AKT pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling, the loss of the phosphatase tensin homolog (PTEN), or RAS mutations. (3, 4, 5, 6)

GDC-0032 (Taselisib) is a potent, selective small molecule inhibitor of Class 1 PI3K that is being developed by Genentech, Inc. as an anti-cancer therapeutic agent. PI3K-AKT pathway activation has been implicated in several types of cancer. (7, 8, 9) Activating and transforming mutations in the p110 α subunit of PI3K are commonly found in tumors. (10, 11, 12) The beta isoform of PI3K is involved in glucose metabolism as evidenced by increased glucose levels in conditional p110 β knockout mice compared with wild-type mice following a glucose challenge test. (13) GDC-0032 (GDC-0032) has approximately 30-fold biochemical selectivity of the alpha isoform relative to the beta isoform and has been shown to be a potent inhibitor of growth in nonclinical models of PI3K-mutant tumors.

GDC-0032 (Taselisib) Clinical Data

The currently ongoing and planned studies are described below.

Study PMT4979g

Study PMT4979g is an open-label, Phase I/II study evaluating the safety and tolerability of GDC-0032 in patients with locally advanced or metastatic solid tumors. Patients have been enrolled in three parts: a dose-escalation part (Stage 1) and an expansion part (Stage 2) and a Phase 2 part. The dose-escalation stage evaluated the safety and pharmacokinetics of increasing doses of single-agent GDC-0032 administered QD in a 28-day cycle. Stage 2 includes expansion cohorts with single-agent GDC-0032 and in combination with either letrozole or fulvestrant in a Ph1b setting for breast cancer patients. The Phase 2 portion consists of GDC-0032 and fulvestrant in a less heavily pretreated breast cancer patient population.

As of 10-31-13, single-agent GDC-0032 dose escalation had been completed with 34 patients enrolled at doses with a range of 3-16 mg. GDC-0032 was well tolerated in the first three cohorts (3, 5, and 8 mg), with no patients experiencing a dose limiting toxicity (DLT). At the 16-mg dose level, 2 of the 11 safety evaluable patients experienced a DLT (Grade 4 hyperglycemia and Grade 3 fatigue). At the 12-mg dose level, 1 of the 10 safety evaluable patients experienced a DLT of Grade 3 acute renal failure. Although the single agent GDC-0032 maximum tolerated dose (MTD) was not exceeded at the 16-mg dose level, the recommended GDC-0032 dose and schedule for the single agent expansion cohorts was 9 mg daily on the basis of long-term safety data through multiple treatment cycles.

Confirmed partial responses have been observed in dose escalation in patients with PIK3CA mutant tumors only. This includes a confirmed partial response observed in a PIK3CA-mutant NSCLC patient treated at the 3 mg QD dose level. Other partial responses have been observed in PIK3CA-mutant breast cancer patients at the 5-12mg QD dose levels.

Clinical pharmacodynamic data with single-agent GDC-0032 suggests promising pharmacodynamic knockdown of the PI3K signaling pathway beginning at 3 mg QD. Pharmacodynamic knockdown of the PI3K pathway based upon reverse phase protein array analysis of paired tumor biopsies (pre-treatment and during GDC-0032 treatment) has been observed in at the lowest dose tested of single agent 3 mg QD in a NSCLC patient. Decreases in mean SUV uptake via FDG-PET analysis that correlate with inhibited glucose uptake are another pharmacodynamics marker of PI3K pathway inhibition. Such decreases have also been observed beginning at the lowest dose tested of 3 mg QD with single-agent GDC-0032

64 patients have been enrolled in the single-agent expansion cohorts at 9mg QD. The adverse events observed at the 9 mg QD dose level are expected toxicities that have been observed with GDC-0032 at higher dose levels.

Dose escalation of GDC-0032 in combination with either fulvestrant or letrozole has been completed. No dose limiting toxicities were observed at either the 6 mg or 9 mg dose levels of GDC-0032 when combined with either letrozole (n = 28) or fulvestrant (n = 27). The 6mg dose level was chosen for the Phase II portion of the study (GDC-0032 with fulvestrant), and enrollment is ongoing (n = 22).

Study GO27802

Study GO27802 is a Phase Ib study that is examining the safety, tolerability of GDC-0032 in combination with either paclitaxel or docetaxel in patients with advanced HER2-negative breast cancer. Dose escalation has begun recently with 8 patients treated.

Rationale for GDC-0032 (Taselisib) - Dose Selection for **S1400B**

GDC-0032 4 mg PO QD in the 2 mg tablet formulation has been selected as the dosing regimen for this 2 mg sub-study based on both safety and efficacy considerations with the goal of maximizing drug exposure while maintaining long-term tolerability. This dose is equivalent to 6 mg PO QD in the capsule formulation. First, pharmacodynamic knockdown of the PI3K pathway has been observed beginning at the 3 mg cohort in the capsule formulation in NSCLC patients by tumor biopsies and FDG-PET. This dose is equivalent to 2 mg in the tablet formulation. Second, anti-tumor activity has been observed in patients with PIK3CA-mutant tumors, with a confirmed partial response in a PIK3CA-mutant NSCLC patient at the 3 mg dose level in the capsule formulation and a confirmed partial response in a PIK3CA-mutant breast cancer patient at the 5 mg dose level with the capsule formulation. These doses are equivalent to 2 mg and 3.3 mg in the tablet formulation, respectively. Third, although the 9 mg PO QD dose in the capsule formulation (equivalent to 6 mg in the tablet formulation) has been tolerated in the single agent expansion cohorts, we believe that for this trial and this squamous NSCLC patient population with their various comorbidities, the 4 mg PO QD in the 2 mg tablet formulation (equivalent to 6 mg in the capsule formulation) offers an optimal balance between efficacy and safety considerations.

3.0 DRUG INFORMATION

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, GDC-0032 is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Taselisib (GDC-0032) (NSC 778795) (IND-119672)

a. PHARMACOLOGY

Mechanism of Action: GDC-0032 is an inhibitor of Class I phosphoinositide 3-kinase (PI3K) that belongs to a benzoxepin class and is being developed as an anti-cancer agent. GDC-0032 is a potent, selective inhibitor of Class I PI3K alpha, delta and gamma p110- isoforms, with approximately 30-fold less inhibition of the p110-beta isoform. Nonclinical studies with GDC-0032 demonstrate that GDC-0032 treatment results in a substantial reduction of PI3K pathway markers, including phosphorylated Akt (pAkt), phosphorylated PRAS40 (pPRAS40), and phosphorylated S6 (pS6, also known as PS6RP). As a result of robust PI3K pathway suppression, GDC-0032 inhibits proliferation of human cancer cell lines, particularly breast cancer cell lines harboring p110 α -mutations in vitro and in tumor xenograft models. GDC-0032 has an in vitro and nonclinical in vivo absorption, distribution, metabolism, and elimination profile, characteristic of an orally administered compound that can achieve clinical exposure consistent with nonclinical efficacy findings described below. The results of the nonclinical toxicology program for GDC-0032 support the evaluation of GDC-0032 as a potential therapeutic agent for cancer.

b. PHARMACOKINETICS

1. Absorption: GDC-0032 was moderately-to-well absorbed following oral administration, with absolute bioavailability of 57% in humans. Median time to maximum concentration was approximately 3 hours. Administration of GDC-0032 with a high-fat meal had minimal effect on exposure.

2. Distribution: The plasma protein binding of GDC-0032 ranged from 70.7% to 97.6% bound in mouse, rat, rabbit, dog, monkey, and human. Binding to 40 mg/mL human serum albumin ranged from 64.7% to 67.3% and appeared to be independent of the concentration of GDC-0032 tested. Binding to 1 mg/mL of human alpha-1 acid glycoprotein ranged from 45.0% to 58.3% and was approximately 23% lower at 20 μ M than at 0.5 μ M GDC-0032.

GDC-0032 had a moderate volume of distribution relative to total body water across all nonclinical species.

3. Metabolism: No human-specific metabolites were observed in plasma from the comparison of metabolites from [14 C] in vivo studies in rat and human. Oxidation and to a lesser extent hydrolysis appear to be the major metabolism pathways in rats. CYP3A4 is the primary CYP isoform responsible for the oxidative metabolism of GDC-0032.

4. Elimination: The major route of excretion in rats and dogs was via the bile (approximately 20% and 69% of the dose in rats and dogs, respectively). Renal elimination was minor in both species, corresponding to less than 6% of the dose. Plasma half-life ranged from 37 to 44 hours.

c. ADVERSE EFFECTS

1. Adverse Events: 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. 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 425 patients.* Below is the CAEPR for GDC-0032.

Version 2.1, January 24, 2016¹

Adverse Events with Possible Relationship to GDC-0032 (CTCAE 4.0 Term) [n= 425]		
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis	
Diarrhea		
	Dry mouth	
	Dyspepsia	
	Mucositis oral	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Neutrophil count decreased	
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
Hyperglycemia		
NERVOUS SYSTEM DISORDERS		
	Dysgeusia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
	Pruritus	
	Skin and subcutaneous tissue disorders (rash) 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 Rash may include Rash, Rash maculo-papular, Rash erythematous, Rash follicular, Rash generalized, Dermatitis exfoliative, Rash macular, Rash maculovesicular, Rash popular, Rash pustular, Rash pruritus, Rash morbilliform, Rash papulosquamous, and Rash vesicular.

Adverse events reported on GDC-0032 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that GDC-0032 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia
GASTROINTESTINAL DISORDERS - Constipation; Oral pain
INFECTIONS AND INFESTATIONS - Sepsis
INVESTIGATIONS - Cholesterol high; Lymphocyte count decreased; White blood cell decreased
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia
NERVOUS SYSTEM DISORDERS – Dizziness; Peripheral sensory neuropathy
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS – Respiratory failure

Note: GDC-0032 (taselisib) 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.

2. Pregnancy and Lactation: GDC-0032 is known to cross the placenta and may cause harm to the fetus or affect reproductive capacity when given to pregnant women. GDC-0032 should not be administered to pregnant women. Women of childbearing potential and male partners of women of childbearing potential should take necessary precautions to avoid pregnancy while receiving GDC-0032 during the protocol and for 30 days for women and 90 days for males following the last dose. It is not known whether GDC-0032 is excreted in human breast milk. GDC-0032 should not be administered to nursing mothers.
3. Drug Interactions: GDC-0032 is metabolized by CYP3A4 and metabolism may be affected by strong inhibitors and inducers of CYP3A4. GDC-0032 displays weak time-dependent inhibition of CYP3A4 and has the potential to induce CYP3A4/5. In vitro studies showed that GDC-0032 was a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) but not a substrate of OATP1B1 and OATP1B3. GDC-0032 has the potential to inhibit the transport of substrates of OCT1 and OCT2.

Due to potential drug interactions, a complete patient medication list, including GDC-0032, should be screened prior to initiation of and during treatment with GDC-0032. See **S1400B** [Section 8.0](#) Toxicities to be Monitored and Dosage Modifications.

d. **DOSING & ADMINISTRATION**

1. Dosing: See **S1400B** [Section 7.0](#), Treatment Plan.

2. Administration Instructions: GDC-0032 should be administered orally at the same time of day +/- 2 hours regardless of meals, unless otherwise instructed. The GDC-0032 administration is 4 mg (2 mg tablets x 2) PO daily. If patient vomits dose, dose should not be retaken. Avoid grapefruit or grapefruit juice.

e. HOW SUPPLIED

1. GDC-0032 will be supplied by Genentech, Inc., and distributed by the CTEP, DCTD, NCI.
2. GDC-0032 will be supplied as 2 mg tablets as a white to off-white, film-coated tablet. Inert ingredients include: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry 2. Each bottle contains 30 tablets.

f. STORAGE, PREPARATION & STABILITY

1. GDC-0032 tablets should be stored at room temperature not to exceed 25°C.
2. Sites and subjects are advised to keep GDC-0032 in its original packaging.
3. Stability studies demonstrate that temperature excursions of up to 40°C for up to 6 months have no impact on product quality.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug Ordering: Study specific supplies will be provided to sites once a patient has been randomized. Starter supplies will not be provided. 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 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). The CTEP assigned protocol number (**S1400B**) 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 and a CV. 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.jsp> >. 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.

2. Drug Handling and Accountability

- a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the mandatory Oral NCI Drug Accountability Record Form DARF available on the NCI home page (<http://ctep.cancer.gov>).
- b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug Return and/or Disposition Instruction

- a. 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>).
- b. Drug expiration: Stability testing is ongoing. PMB will send a stock recovery letter when notified that the agent is no longer suitable for use.

4. Contact 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.

4.0 STAGING CRITERIA

See Section 4.0 of **S1400** for staging criteria.

5.0 ELIGIBILITY CRITERIA

Patient must meet the eligibility criteria in [Section 5.0](#) of **S1400B** to be eligible for **S1400B**. If the patient does not meet the sub-study specific eligibility criteria listed in [Section 5.1](#) and [Section 5.2](#) of **S1400B**, but meets the common sub-study criteria listed in [Section 5.3](#) of **S1400B**, submit the **S1400** Request for Sub-Study Reassignment Form for sub-study reassignment. Patients on Arm2, docetaxel, that have progressed and are proceeding to Re-Registration must meet the eligibility criteria in [Section 5.4](#) of **S1400B** to be eligible. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at S1400question@crab.org prior to registration.

5.1 Disease Related Criteria

- a. Patients must be assigned to **S1400B**. **S1400B** biomarker eligibility defined as PI3K Positive is as follows:

Gene	Alteration type	Eligible alteration
PIK3CA	Substitution	R38C, R38H, E81K, R88Q, R93Q, R93W, P104L, P104R, G106V, G106R, P104_G106>R, R108H, E110del, E110K,

		K111E, K111N, K111del, G118D, V344G, V344M, N345K, N345I, E365K, C378F, E418K, C420R, E453K, E453Q, P539R, E542K, E542A, E542V, E542G, E542Q, E545A, E545G, E545K, E545Q, E545D, Q546E, Q546H, Q546K, Q546L, Q546P, Q546R, E726K, G1007R, D1017H, Y1021C, Y1021H, T1025A, A1035V, A1035T, M1043I, M1043L, M1043V, H1047L, H1047R, H1047Y, H1047N, H1047Q, G1049R, G1049S, I1058L
	Fusion	None
	Amplification	None

5.2 Clinical Laboratory Criteria

- a. Patients must have a HbA1c < 7% and fasting glucose < 125 mg/dL obtained within 28 days prior to sub-study registration.
- b. Patients must not have Type I or II diabetes that requires anti-hyperglycemic medication.
- c. Patients must not have active or a history of small or large intestine inflammation such as Crohn's disease or ulcerative colitis.
- d. Patients must not require daily supplemental oxygen.
- e. Patients must be able to take oral medications. Patients may not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of GDC-0032 (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- f. Patients must not be taking, nor plan to take while on protocol treatment and for 14 days post the last dose of study treatment, drugs, herbal supplements or foods that are known to be strong/moderate CYP3A4 substrates. A list of these medications can be found in [Section 7.4](#) of this sub-study.
- g. Patients must have a Lipase and Amylase performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar.
- h. Patients must also be offered participation in banking for future use of specimens as described in [Section 15.0](#).

5.3 Common Eligibility Criteria for all Sub-Studies

The **S1400** Common Eligibility Criteria have been incorporated into Section 5.0 of each sub-study for ease of reference.

- a. Patients whose biomarker profiling results indicate the presence of an EGFR mutation or EML4/ALK fusion are not eligible. Due to existence of approved therapies the biomarker exclusion rules are as follows:

Gene	Alteration type	Ineligible Alteration
EGFR	Substitution	L858R, T790M, A289V, G719A, S768I, G719C, R108K, G598V, R222C, L62R, L861Q, P596L, V774M
	Indel	non-frame shifting insertions or deletions between amino acids 740 and 780, in exons 19 and 20, transcript NM_005228
	Fusion	None
	Amplification	None
ALK	Substitution	None
	Indel	None
	Fusion	EML4-ALK, CLIP4-ALK, CLTC-ALK, KIF5B-ALK, NPM1-ALK, RANB2-ALK, STRN-ALK, TFG-ALK
	Amplification	None

- b. Patients must have progressed (in the opinion of the treating physician) following the most recent line of therapy.
- c. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study registration. Patients must have recovered (\leq Grade 1) from any side effects of prior therapy. Patients must not have received any radiation therapy within 14 days prior to sub-study registration. (See [5.3e](#) for criteria regarding therapy for CNS metastases).
- d. Patients must have measurable disease (see [Section 10.1](#)) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in [Section 10.1c](#). Measurable disease must be assessed within 28 days prior to sub-study registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to sub-study registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to registration. See [Sections 15.0](#) and [18.1c](#) for guidelines and submission instructions for required central radiology review.
- e. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment and prior to registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.

- f. Patient must have fully recovered from the effects of surgery at least 14 days prior to sub-study registration.
- g. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
- h. Patients must have an ANC $\geq 1,500/\text{mcl}$, platelet count $\geq 100,000 \text{ mcl}$, and hemoglobin $\geq 9 \text{ g/dL}$ obtained within 28 days prior to sub-study registration.
- i. Patients must have adequate hepatic function as defined by serum bilirubin \leq Institutional Upper Limit of Normal (IULN) and either ALT or AST $\leq 2 \times$ IULN within 28 days prior to sub-study registration (if both ALT and AST are done, both must be ≤ 2 IULN). For patients with liver metastases, bilirubin and either ALT or AST must be $\leq 5 \times$ IULN (if both ALT and AST are done, both must be $\leq 5 \times$ IULN).
- j. Patients must have a serum creatinine \leq the IULN OR measured or calculated creatinine clearance $\geq 50 \text{ mL/min}$ using the following Cockcroft-Gault Formula:
- $$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{actual body weight in kg}) \dagger}{72 \times \text{serum creatinine}}$$
- Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 28 days prior to sub-study registration.
- †The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
- *Actual lab serum creatinine value with a minimum of 0.8 mg/dL.
- k. Patients must have Zubrod performance status of 0-1 (see [Section 10.4](#)) documented within 28 days prior to sub-study registration.
- l. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see [Section 18.1b](#)).
- m. Patients must not have documented evidence of acute hepatitis or have an active or uncontrolled infection.
- n. Patients with a known history of HIV seropositivity:
1. Must have undetectable viral load using standard HIV assays in clinical practice.
 2. Must have CD4 count $\geq 400/\text{mcl}$.
 3. Must not require prophylaxis for any opportunistic infections (i.e., fungal, MAC, or PCP prophylaxis).
 4. Must not be newly diagnosed within 12 months prior to sub-study registration.

- o. Prestudy history and physical exam must be obtained within 28 days prior to sub-study registration.
- p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.
- q. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.
- r. As a part of the OPEN registration process (see [Section 13.4](#) for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.
- s. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).
- t. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

5.4 Step 2 GDC-0032 Re-Registration

- a. Patients must have progressed (as defined in Section 10.2d in **S1400**) on Arm 2 (docetaxel) of this sub-study.
- b. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to Step 2 re-registration. Patients must have recovered (\leq Grade 1) from any side effects of prior therapy.
- c. Patients must have measurable disease (see [Section 10.1](#)) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in [Section 10.1c](#). Measurable disease must be assessed within 28 days prior to Step 2 re-registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to Step 2 re-registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior

to registration. See [Sections 15.0](#) and [18.1c](#) for guidelines and submission instructions for required central radiology review.

- d. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to Step 2 Re-Registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment and prior to re-registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to re-registration.
- e. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
- f. Patients must have an ANC $\geq 1,500/\text{mcl}$, platelet count $\geq 100,000 \text{ mcl}$, and hemoglobin $\geq 9 \text{ g/dL}$ obtained within 28 days prior to Step 2 Re-Registration.
- g. Patients must have adequate hepatic function as defined by serum bilirubin \leq Institutional Upper Limit of Normal (IULN) and either ALT or AST $\leq 2 \times$ IULN within 28 days prior to Step 2 Re-Registration (if both ALT and AST are done, both must be ≤ 2 IULN). For patients with liver metastases, bilirubin and either ALT or AST must be $\leq 5 \times$ IULN (if both ALT and AST are done, both must be $\leq 5 \times$ IULN).
- h. Patients must have a HbA1c $< 7\%$ and fasting glucose $< 125 \text{ mg/dL}$ obtained within 28 days prior to Step 2 Re-Registration.
- i. Patients must have a serum creatinine \leq the IULN OR measured or calculated creatinine clearance $\geq 50 \text{ mL/min}$ using the following Cockcroft-Gault Formula:
$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{actual body weight in kg})^\dagger}{72 \times \text{serum creatinine}^*}$$

Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 28 days prior to Step 2 Re-Registration.

† The kilogram weight is the patient weight with an upper limit of 140% of the IBW.

 - Actual lab serum creatinine value with a minimum of 0.8 mg/dL.
- j. Patients must have a Lipase and Amylase performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar.
- k. Patients must have Zubrod performance status of 0-1 (see [Section 10.4](#)) documented within 28 days prior to Step 2 Re-Registration.
- l. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see [Section 18.1b](#)).

- m. Patients must not have documented evidence of acute hepatitis or have an active or uncontrolled infection.
- n. Patients with a known history of HIV seropositivity:
 1. Must have undetectable viral load using standard HIV assays in clinical practice.
 2. Must have CD4 count \geq 400/mcL.
 3. Must not require prophylaxis for any opportunistic infections (i.e., fungal, mAC, or PCP prophylaxis).
 4. Must not be newly diagnosed within 12 months prior to re-registration.
- o. Prestudy history and physical exam must be obtained within 28 days prior to re-registration.
- p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.
- q. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.
- r. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.
- s. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).
- t. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

6.0 STRATIFICATION FACTORS

Prior to Revision #3, (Version Date 11/18/15) patients were stratified as follows below. As the Phase II trial has been modified to a single arm study design, the following randomization and stratification applied to the randomized Phase II/III are no longer required. However, patients will continue to be stratified by PIK3CA mutation status per Genentech (GNE) criteria (positive vs negative as defined in [Section 11.1](#)).

- 6.1 Patients were randomized between GDC-0032 and docetaxel using block randomization.
- 6.2 Randomization will be stratified by:
 - a. Zubrod Performance Status (0- vs. 2)
 - b. Gender (male vs. female)
 - c. Number of prior therapies (1 vs. 2 or more)
 - d. PIK3CA mutation status per Genentech (GNE) criteria (positive vs negative as defined in [Section 11.1](#)).

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Drs. Corey J. Langer and James L. Wade III at S1400BMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at <http://swog.org> (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication and Supportive Care

Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

Patients randomized to docetaxel should pre-medicate with dexamethasone beginning 24 hours prior to docetaxel administration. Dexamethasone may be administered per local institutional guidelines. Recommended dose listed below.

7.2 Treatment – **S1400B**

Prior to Revision #3, (Version Date 11/18/15) patients were randomized into one of two treatment arms. As the design and objectives have been modified to a Single arm Phase II, followed by a Randomized Phase III, all patients will be placed into Arm 1: GDC-0032 (Taselisib) for the Phase II portion. This section will be amended should the trial continue with the Randomized Phase III portion. The information regarding the docetaxel treatment plan will remain within the section for the patients continuing to receive treatment per protocol. Patients currently on Arm 2, docetaxel will be given the option to re-register to Arm 3, GCD-0032 after progressing as defined **S1400** Section 10.2d.

a. **Arm 1: GDC-0032 (Taselisib)**

Agent	Dose	Route	Day	Schedule*
GDC-0032 (Taselisib)	4 mg	PO	Daily	Continuous

* NOTE: A cycle of treatment is 21 days. Disease assessment must occur every 6 weeks. Treatment will continue until any of the criteria in [Section 7.5](#) is met.

Patients must take the GDC-0032 at the same time of day \pm 2 hours, unless otherwise instructed and regardless of meals.

b. **Arm 2: Docetaxel** (Closed to accrual per Revision #3)

Agent	Dose	Route	Day	Schedule*
Dexamethasone	8 mg BID **	Oral, beginning 24 hours Prior to docetaxel	0-2	Q 21 days
Docetaxel	75 mg/m ²	IV	1	Q 21 days

* NOTE: A cycle of treatment is 21 days. Disease assessment must occur every 6 weeks. Treatment will continue until any criteria in [Section 7.5](#) is met.

** Dexamethasone may be administered per local institutional guidelines. Recommended dose listed above.

c. **Arm 3: Re-Registration Treatment with GDC-0032 (Taselisib)**

Upon progression (see Section 10.2d in **S1400**), patients in Arm 2 may be eligible for Re-Registration to receive GDC-0032 as follows

Agent	Dose	Route	Day	Schedule*
GDC-0032 (Taselisib)	4 mg	PO	Daily	Continuous

* NOTE: A cycle of treatment is 21 days. Disease assessment must occur every 6 weeks. Treatment will continue until any of the criteria in [Section 7.5](#) is met.

Patients must take the GDC-0032 at the same time of day \pm 2 hours, unless otherwise instructed and regardless of meals.

7.3 Drug Compliance Documentation

Drug compliance for GDC-0032 will be recorded by patients on the Intake Calendar (see the **S1400** abstract page at www.swog.org). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.4 Concomitant Medications to Avoid

Based on in vitro data suggesting that GDC-0032 is metabolized by CYP3A4 the following drugs should be avoided. If use of one of these drugs is necessary, the risks and benefits should be discussed with the Study Chair prior to its concomitant use with GDC-0032:

- Strong/moderate CYP3A4 inhibitors: atazanavir, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, telithromycin, erythromycin, troleandomycin, flutranazole, itraconazole, ketoconazole, voriconazole, posaconazole, aprepitant, conivaptan, fluvoxamine, diltiazem,

nefazodone, mibefradil, verapamil, and grapefruit juice or grapefruit supplements.

- Strong/moderate CYP3A4 inducers: rifampin, carbamazepine, phenytoin, oxcarbazepine, phenobarbital, efavirenz, nevirapine, etravirine, modafinil, hyperforin (St. Johns Wort), and cyproterone.
- Strong/moderate CYP2D6 inhibitors: bupropion, fluoxetine, paroxetine, quinidine, cinacalcet, duloxetine, and terbinafine

7.5 Criteria for Removal from Protocol Treatment

- a. Progression of disease or symptomatic deterioration (as defined in Sections 10.2d and 10.2e of **S1400**).

* Upon progression, the **S1400** Request for New Sub-Study Assignment Form may be submitted to receive a new sub-study assignment (see Section 14.0).

- b. Arm 2 (docetaxel) only: If patient has documented progression (as defined in Section 10.2d in **S1400**), patient may continue to Re-Registration to receive GDC-0032. Patient would then be removed from re-registration protocol treatment upon subsequent progression of disease or symptomatic deterioration (as defined in Section 10.2d or 10.2e in **S1400**).
- c. Unacceptable toxicity.
- d. Treatment delay for any reason > 28 days (or as noted in [Section 8.0](#)).
- e. The patient may withdraw from this study at any time for any reason.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.7 Follow-Up Period

Patients will be followed until death or 3 years after sub-study registration, whichever occurs first. Patients registered to Step 2 (Re-Registration) will be followed until death or 3 years after Step 2 re-registration.

Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

- a. Missed doses for the oral drugs are to be omitted rather than made up.
- b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.
- c. Reductions are based on the dose given in the preceding reporting period and are based on toxicities observed since the prior toxicity evaluation.
- d. Once dose is reduced, patients will continue at the new dose. No dose re-escalations are allowed.
- e. A maximum of two dose reductions are allowed.

8.3 Dose Modifications GDC-0032 (Taselisib)

DRUG	DOSE LEVEL	DOSE
GDC-0032 (Taselisib)	Full	4 mg tablet QD
	-1 Level	2 mg tablet QD
	-2 Level ^a	2 mg tablet QOD ^b

QD = once daily; QOD = every other day.

^a If the patient continues to experience specified drug related adverse events after dose reduction, patient must be removed from protocol therapy.

^b GDC-0032 will be administered on Days 1–21 of the 21-day cycle. For the second dose reduction, dosing will be converted to 2 mg tablet QOD, in which case GDC-0032 may be given on two consecutive days during the transition from one cycle to the next specifically on the last day of one cycle and the first day of the next cycle.

Management of Toxicities

The dose delay and reduction instructions provided in Tables 1–6 are intended to serve as recommended guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while ensuring patient safety.

Due to the approximately 40 hour half-life for GDC-0032, investigators should consider holding GDC-0032 for certain Grade 2 toxicities until the adverse events resolves to Grade ≤ 1 as discussed below (e.g., stomatitis/oral mucositis, rash, diarrhea). Certain toxicities have occurred within 1–2 weeks of holding or discontinuing GDC-0032 drug (e.g., pneumonitis, colitis, rash). In these cases, the adverse event eventually resolved. Investigators should follow management guidelines for toxicities as described below including administration of topical or systemic corticosteroids as appropriate.

a. Management of Hyperglycemia

Metformin is the first antihyperglycemic medication of choice because of the lower risk of hypoglycemia with this agent. Because metformin in some patients may cause diarrhea and not be well tolerated, other antihyperglycemic medications such as sulfonylureas (e.g., glimepiride, glipizide) can be used. Extra caution must be used with other drugs such

as sulfonylureas because of the increased risk for hypoglycemia with these agents. Consultation with an endocrinologist can be helpful in managing hyperglycemia.

Table 1. Dose Modification and Management Guidelines for Hyperglycemia

Dose Modification and Management Guidelines	
Eligibility and monitoring	<ul style="list-style-type: none"> Monitoring: fasting glucose and HbA1C at baseline and at certain intervals Instruct patients to report symptoms such as thirst, blurred vision and frequent urination Grade ≥ 3 hyperglycemia identified as adverse event of special interest (AESI) hence requiring expedited reporting from study sites regardless of regulatory seriousness
Grades 1 or 2	<ul style="list-style-type: none"> Initiation of or an increase in the dose of an anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring must be implemented. Dosing with GDC-0032 may either be held or continued per Investigator evaluation.

Dose Modification and Management Guidelines	
Grade 3 (asymptomatic)	<ul style="list-style-type: none"> GDC-0032 dosing must be held and the patient should be managed per institutional standard of care, including implementation of additional glucose monitoring and initiation of or an increase in the dose of an anti-hyperglycemic therapy (e.g., metformin). If the hyperglycemic event improves to Grade ≤ 1, GDC-0032 dosing may resume at one dose level lower.
Grade 3 (symptomatic)*, Grade 3 (requiring hospitalization), or Grade 4	<ul style="list-style-type: none"> GDC-0032 dosing must be held and the patient should be managed per institutional standard of care, including implementation of additional glucose monitoring and initiation of or an increase in the dose of anti-hyperglycemic therapy. If the hyperglycemic event improves to Grade ≤ 1, GDC-0032 dosing may resume at one dose level lower, For recurrent symptomatic Grade 3 or Grade 4 hyperglycemic event, GDC-0032 must be permanently discontinued and removed from protocol treatment.

* Symptoms of hyperglycemia include blurry vision, polydipsia, and polyuria.

b. Management of Pneumonitis

Patients must be assessed for pulmonary signs and symptoms throughout the study. Patients must also have CT scans of the chest at every tumor assessment. Oxygen saturation by pulse oximetry must be measured at every visit as part of the assessment of vital signs. Management guidelines for patients with possible pneumonitis are listed in [Table 2](#).

Table 2: Dose Modification and Management Guidelines for Pneumonitis

Grade	Intervention	Investigations	GDC-0032 Dose Adjustment
1	No specific therapy required.	CT scan. Consider PFTs. Repeat CT scan every 8 weeks until return to baseline.	No change.
2	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs and bronchoscopy.	Reduce dose until improvement to Grade \leq 1; consider interruption if symptoms are troublesome. Interrupt treatment as long as corticosteroids are being given. Restart GDC-0032 at the same dose if clinical benefit evident. Consider restarting at reduced dose if recurrent event or per discussion with Study Chair. Discontinue and remove from protocol treatment if recovery to Grade \leq 1 is not evident within 28 days.
3	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated.	CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs. Bronchoscopy is recommended.	Interrupt treatment until improvement to Grade \leq 1. Restart therapy within 28 days at a reduced dose if clinical benefit is evident. Interrupt treatment as long as corticosteroids are being given.

Grade	Intervention	Investigations	GDC-0032 Dose Adjustment
4	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated.	CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs. Bronchoscopy is recommended.	Discontinue and remove from protocol treatment.

Table modified from White et al. 2010.
 CT = computed tomography; PFT = pulmonary function test
 PFTs include tests for DL_{CO} and room air oxygen saturation at rest (pulse oximetry).
 PFTs may be useful to monitor the effect of interventions such as dose reduction/discontinuation and corticosteroids, in conjunction with imaging (White et al. 2010).

c. Management of Rash

Rash and other dermatological events should be closely monitored, and patients with severe rash should be monitored for associated signs and symptoms such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. For severe rash, dosing of GDC-0032 must be interrupted, and patients should be treated with supportive therapy per standard of care. Use of antihistamines, as well as topical or systemic corticosteroids, may be considered (see [Table 3](#)).

Table 3: Dose Modification and Management Guidelines for Rash

Grade of Rash	Dose Modification and Management Guidelines
Grade 1	<ul style="list-style-type: none"> Continue dosing at current dose and monitor for change in severity Consider prescribing topical corticosteroids ^a
Grade 2	<ul style="list-style-type: none"> Interrupt GDC-0032 treatment Treat rash with topical corticosteroids. ^a Consider treatment of rash with oral corticosteroids. ^b Interrupt GDC-0032 treatment as long as oral corticosteroids are being given If rash improves to Grade ≤ 1 and upon completion of any systemic corticosteroids, resume GDC-0032 treatment at the same dose. For recurrent Grade 2 rash, resume GDC-0032 treatment at one dose level lower.
Grade 3	<ul style="list-style-type: none"> Interrupt GDC-0032 treatment Treat rash with topical corticosteroids and/or systemic corticosteroids (oral or IV). Interrupt GDC-0032 treatment as long as systemic corticosteroids are being given Consider dermatological consultation and skin biopsy

Grade of Rash	Dose Modification and Management Guidelines
	<ul style="list-style-type: none"> Obtain photographs of rash if permitted by local regulations If rash improves to Grade ≤ 1 and upon completion of any systemic corticosteroids, resume GDC-0032 treatment at one dose level lower.

Grade of Rash	Dose Modification and Management Guidelines
Grade 4	<ul style="list-style-type: none"> Permanent discontinuation of GDC-0032 treatment and remove from protocol treatment. Treat with topical corticosteroids and/or systemic corticosteroids. Consider dermatological consultation and skin biopsy Obtain photographs of rash if permitted by local regulations
AE = adverse event. ^a Suggested topical steroids include, hydrocortisone 2.5% to face twice daily, triamcinolone 0.1% or fluocinonide 0.1% cream to body bid. ^b Suggested oral steroids include methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg for 2 days, 40 mg for 2 days, 20 mg for 2 days, etc.).	

d. Management of Gastrointestinal Toxicity

Management of Diarrhea and Colitis

Patients should be closely monitored for gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, colitis, abdominal pain, stomatitis, and changes in stool, including checking for blood in stool if clinically indicated). Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. Gastrointestinal symptoms should be managed per protocol guidelines and institutional standard of care. For example, prompt management of diarrhea with antidiarrheal medications must be implemented. Because of the approximately 40 hour half-life of GDC-0032, investigators must hold GDC-0032 for Grade ≥ 2 diarrhea until it improves to Grade ≤ 1 .

Specific dose modification and management guidelines for diarrhea and colitis are provided in Table 4.

Table 4: Dose Modification and Management Guidelines for Diarrhea or Colitis

Dose Modification and Management Guidelines	
Grade 1	<ul style="list-style-type: none"> Manage per institutional standard of care with antidiarrheals¹ For Grade 1 diarrhea occurring after Cycle 2 that persists > 5 days despite treatment with anti-diarrheal agents, obtain stool culture for infectious workup^b. Infections (e.g., <i>Clostridium difficile</i>, enteric bacteria, CMV) should be treated with the appropriate antibiotic.

Dose Modification and Management Guidelines	
	<ul style="list-style-type: none"> For non-infectious diarrhea, consider holding GDC-0032 and treating with a corticosteroid taper (20–40 mg prednisone PO QD starting dose) or budesonide 9 mg PO QD. Upon completion of corticosteroid treatment, resume GDC-0032 dosing at same dose or one dose level lower per investigator evaluation.
Dose Modification and Management Guidelines	
Grade 2	<ul style="list-style-type: none"> Hold GDC-0032 and initially manage with anti-diarrheal agents <ol style="list-style-type: none"> Obtain stool culture for infectious workup Infections (e.g., Clostridium difficile, enteric bacteria, CMV) should be treated with the appropriate antibiotic. For non-infectious Grade 2 diarrhea that has not improved to Grade ≤ 1 despite 48 hours of anti-diarrheal treatment or for Grade 2 colitis, treat with corticosteroid taper (20–40 mg prednisone PO QD starting dose) or budesonide 9 mg PO QD. Steroid dosage can be increased if diarrhea does not improve. If diarrhea or colitis does not improve after 48 hours of corticosteroid treatment, a colonoscopy should be considered to evaluate for other causes of diarrhea (e.g., CMV colitis). If Grade 2 diarrhea occurred after Cycle 2 or improved with corticosteroid treatment or for Grade 2 colitis, resume GDC-0032 dosing at one dose level lower upon improvement to Grade ≤ 1 and after completion of any corticosteroid taper. <ul style="list-style-type: none"> If Grade 2 diarrhea occurred before Cycle 2 and did not require corticosteroid treatment, resume GDC-0032 dosing at the same dose level or one dose level lower per investigator evaluation upon improvement to Grade ≤ 1. <p>For recurrent Grade 2 diarrhea, resume GDC-0032 dosing at one dose level lower upon improvement to Grade ≤ 1</p>
Grade 3	<ul style="list-style-type: none"> Hold GDC-0032 dosing and initially manage with anti-diarrheal agents <ol style="list-style-type: none"> Obtain stool culture for infectious workup Infections (e.g., Clostridium difficile, enteric bacteria, CMV) should be treated with the appropriate antibiotic. For non-infectious Grade 3 diarrhea, treat with systemic corticosteroids (IV solumedrol 16-20mg q8hr or Prednisone 60-80mg QD equivalent to start). Can increase steroid dosage if diarrhea does not improve.² For non-infectious Grade 3 diarrhea or colitis, treat with systemic corticosteroids (IV solumedrol 16–20 mg every 8 hours or prednisone 60–80 mg PO QD equivalent to start). Can increase steroid dosage if diarrhea does not improve. If diarrhea improves to Grade ≤ 1 and upon completion of any steroid taper, resume GDC-0032 treatment at one dose level lower. Consider colonoscopy as part of further gastrointestinal workup. If diarrhea does not improve after 48 hours of corticosteroid treatment, a colonoscopy should be considered to evaluate for other causes of diarrhea (e.g., CMV colitis). If diarrhea or colitis improves to Grade ≤ 1 and upon completion of any steroid taper, resume GDC-0032 dosing at one dose level lower.

Dose Modification and Management Guidelines	
	<ul style="list-style-type: none"> Patients with recurrent Grade 3 diarrhea or colitis must be permanently discontinued from GDC-0032 and removed from protocol therapy.
Dose Modification and Management Guidelines (contd)	
Grade 4	<ul style="list-style-type: none"> Permanent discontinuation of GDC-0032 treatment and remove from protocol therapy. Manage as per Grade 3 diarrhea guidelines.
¹	Suggested antidiarrheals include the following: <ol style="list-style-type: none"> loperamide (initial: 4 mg, followed by 2 mg after each loose stool, up to 16 mg/day) diphenoxylate and atropine (Diphenoxylate 5 mg 4 times/day until control achieved [maximum: 20 mg/day], then reduce dose as needed; some patients may be controlled on doses of 5 mg/day)
²	Non-infectious diarrhea can be diagnosed by stool culture with workup for various enteric bacteria, C. difficile, and CMV.

Management of Stomatitis and Oral Mucositis

Aggressive mouth care for oral mucositis and stomatitis with mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) may also be helpful in managing symptoms, and it is recommended that these are implemented with early signs of dry mouth, Grade 1 mucositis, or Grade 1 stomatitis (see [Table 5](#)). Examples of mouth care include rinsing with nonalcoholic mouthwash, flossing after each meal, using a mild toothpaste and soft-bristled toothbrush, and avoiding agents containing hydrogen peroxide, iodine, and thyme derivatives. It may also be helpful to advise patients to avoid foods that are spicy, acidic, or salty.

Table 5: Dose Modification and Management Guidelines for Stomatitis and Oral Mucositis

Grade of Stomatitis/Mucositis	Dose Modification and Management Guidelines
All grade	<ul style="list-style-type: none"> Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) may be implemented to help manage symptoms Diet management (e.g., avoidance of spicy foods)
Grade 1	<ul style="list-style-type: none"> Monitor symptoms and initiate management (see above). Re-evaluate within 48 to 72 hours.
Grade 2	<ul style="list-style-type: none"> Interrupt GDC-0032 treatment and manage until Grade \leq 1. If stomatitis/mucositis improves to Grade \leq 1, resume GDC-0032 at the same dose. For recurrent Grade 2 stomatitis or mucositis, resume GDC-0032 treatment at one dose level lower.
Grade 3	<ul style="list-style-type: none"> Interrupt GDC-0032 treatment and manage until Grade \leq 1. If stomatitis/mucositis improves to Grade \leq 1, resume GDC-0032 at one dose level lower.

Grade of Stomatitis/Mucositis	Dose Modification and Management Guidelines
Grade 4	<ul style="list-style-type: none"> Permanent discontinue GDC-0032 treatment and remove from protocol therapy.

e. Management of Asymptomatic Lipase and/or Amylase Elevations

Some patients treated with GDC-0032 have experienced asymptomatic lipase and/or amylase elevations in blood tests without any clinical or radiographic symptoms of pancreatitis or another clear etiology for the abnormal lab values. Upon discussion with Study Chair and after a risk-benefit assessment, investigators can consider continuing GDC-0032 therapy in such patients at the same dose or one dose level lower. Investigators will have a low threshold for interrupting GDC-0032 for any concerning clinical gastrointestinal toxicities.

f. Management of Other Clinically Significant Adverse Events

See [Table 6](#) for the dose modifications for other clinically significant adverse events.

Table 6: Dose Modification and Management Guidelines for Other Clinically Significant Adverse Events

Grade	GDC-0032
Grade 3: first event	Hold GDC-0032 until Grade \leq 1. Consider restarting at next lower dose.
Grade 3: recurrent Grade 4, non-life-threatening	Hold GDC-0032 until Grade \leq 1. Restart at next lower dose.
Grade 4, life-threatening	Permanently discontinue GDC-0032 and remove from protocol therapy.

8.4 Dose Modifications – Docetaxel (Closed to accrual per Revision #3)

DRUG	DOSE LEVEL*	DOSE
Docetaxel	Full	75 mg/m ²
	-1 Level	55 mg/m ²
	-2 Level	35 mg/m ²

* Only two docetaxel dose reductions are allowed.

Dose Modifications of Docetaxel

Hematological Toxicity	
Grade 4 Febrile Neutropenia	Hold docetaxel until recovery to \leq Grade 1. Then resume docetaxel administration with one dose level reduction.
Grade 4 Neutropenia	Must undergo a dose reduction for subsequent cycles regardless of the duration of the neutropenia with a maximum of two dose reductions.
Grade 4 Thrombocytopenia	Hold docetaxel until recovery to \leq Grade 1. Then resume docetaxel administration with one dose level reduction.
Hepatic Toxicity	

Grade \geq 3	Hold docetaxel up to two weeks. If recovered to \leq Grade 1, resume treatment at one level dose reduction. Otherwise, remove from protocol treatment.
Grade 2	Reduce docetaxel at a one level dose reduction.
Non-Hematological Toxicity	
Grade 4 Vomiting	If occurs despite antiemetic prophylaxis, restart treatment after recovery to \leq Grade 1 at a one level dose reduction.
Grade \geq 3 Diarrhea	If occurs despite antidiarrheal treatment, restart treatment after recovery to \leq Grade 1 at a one level dose reduction.
Grade 2 Peripheral Neuropathy	One dose level reduction.
Grade 3 Peripheral Neuropathy	Remove from protocol treatment.
Grade 3 Fluid Retention	Hold docetaxel until recovery to \leq Grade 1, then restart treatment at a one level dose reduction.
Grade \geq 3 Stomatitis	Hold docetaxel until recovery to \leq Grade 1, then restart treatment at a one level dose reduction.
For All Other Non-Hematological Toxicities	Actions
Grade \geq 3	Hold docetaxel until recovery to \leq Grade 1, then restart treatment at a one level dose reduction.

a. Hypersensitivity Reactions

No dose reductions will be made for any hypersensitivity reactions. If, despite dexamethasone pre-treatment, the patient experiences a hypersensitivity reaction, treatment should be as indicated in the following table.

Grade 1:	<ul style="list-style-type: none"> Consider decreasing the rate of infusion until recovery to < Grade 1. Then, resume infusion at the initial planned rate.
Grade 2:	<ul style="list-style-type: none"> Stop docetaxel infusion and give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV. Resume docetaxel infusion after recovery < Grade 1; depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate (e.g., infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, then finally, resume at the hour infusion rate). Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, (e.g., infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, and finally, administer at the 1-hour infusion rate)
Grade \geq 3	<ul style="list-style-type: none"> REMOVE FROM PROTOCOL TREATMENT

In case of late occurring hypersensitivity symptoms, e.g., appearance within 1 week of treatment of a localized or generalized pruritis, symptomatic treatment may be given (e.g., oral antihistamine). Additional

oral or IV premedication with antihistamine may also be given for the next cycle of treatment depending on the intensity of the reaction observed.

b. Fluid Retention

If symptomatic, patients developing fluid retention may be treated with diuretics at the treating investigator's discretion. Spironolactone at a starting dose of 25 mg TID plus furosemide 20-40 mg PRN is recommended.

c. Hepatic Dysfunction

Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Dose Modifications for Abnormal Liver Function

Bilirubin	Alkaline Phosphatase	AST or ALT	Action
> IULN or	> 2.5 x IULN or	> 1.5 x IULN	Wait ≤ 2 weeks. If recovered*, retreatment should be at one level dose reduction. If not, remove from protocol treatment.

* Bilirubin ≤ IULN AND alkaline phosphatase ≤ 2.5 x IULN, AND AST or ALT ≤ 1.5 x IULN.

Note: A maximum of two dose reductions per patient are allowed.
IULN = institutional upper limit of normal.

d. Stomatitis

If stomatitis is present on Day 1 of any cycle, treatment should be withheld until the stomatitis has resolved.

e. Other Non-hematological Toxicities

Manage toxicities ≤ Grade 2 symptomatically, if possible, and retreat without dose reduction.

If toxicities ≥ Grade 3, drug should be held until resolution to ≤ Grade 1, then reinstated, if medically appropriate, with a one level dose reduction.

Unacceptable toxicity from docetaxel is defined as one or more of the following:

Grade ≥ 3 nonhematologic toxicity (excluding nausea and vomiting) despite 2 prior dose reductions

Severe fluid retention not responsive to symptomatic therapy or dose reduction

Grade 4 vomiting despite antiemetics and dose reductions

Grade 4 hematologic toxicity despite two prior dose reductions. However, Grade 4 neutropenia must be either > 7 days in duration or must be accompanied by fever (single elevation in oral temperature > 38.5°C) requiring parenteral antibiotics or with documented infection to be considered an unacceptable toxicity (despite two prior dose reductions).

8.5 Dose Modification Contacts

For treatment or dose modification questions, please contact Drs. Corey J. Langer and James L. Wade III at **S1400B**MedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at <http://swog.org> (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Coordinator and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Arm 1 GDC-0032 (Taselisib)

REQUIRED STUDIES	PRE-STUDY	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β			At Off Tx	Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15			
PHYSICAL																			
History & Physical Exam	X				X			X			X			X			X	X	
Weight & Performance Status	X				X			X			X			X			X	X	
Disease Assessment Ω	X							XΩ						XΩ				XΩ	
Toxicity Notation					X			X			X			X			X	Xcb	Xcb
Smoking Status Assessment	X																X		
LABORATORY																			
CBC/Diff/Platelets/Hgb	X	X€			X			X			X			X			X	Xcb	Xcb
Serum Bilirubin	X	X€			X			X			X			X			X	Xcb	Xcb
ALT or AST	X	X€			X			X			X			X			X	Xcb	Xcb
Serum Creatinine/Calc CrCl	X	X€			X			X			X			X			X	Xcb	Xcb
HbA1c	X																X		
Fasting Glucose	X	X€			X			X			X			X			X	Xcb	Xcb
Lipase & Amylase	X	X€			X			X			X			X			X	Xcb	Xcb
LDH ¥	X																		
Albumin ¥	X																		
X-RAYS AND SCANS																			
CT or MRI for Disease Assessment Ω	X							XΩ						XΩ				XΩ	
Brain CT/MRI	X																		
Image Submission Σ	X							X						X				X	

Calendar continued on next page. [Click here for footnotes.](#)

REQUIRED STUDIES	PRE-STUDY	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β			At Off Tx	Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15			
SPECIMEN SUBMISSION																			
Tissue for Banking																			X§
Blood for Banking <i>f</i>	X				X			X				X							Xδ
TREATMENT																			
Arm 1: (21 day cycle)																			
GDC-0032 (Taselisib)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in [Section 14.0](#).

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in <https://swog.org/Visitors/QA/Documents/Best%20Practices%20update.pdf>.

Footnotes for Calendar 9.1 (GDC-0032):

- Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.2 of **S1400**) must be repeated every 6 weeks (± 7 day window) until disease progression.
- Σ Submit scans as outlined in [Section 14.0](#) and [Section 15.0](#) of **S1400B**.
- β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle, unless otherwise noted. Disease assessments are to take place every 6 weeks (± 7 days window). Treatment and evaluation will continue until any of the criteria in [Section 7.5](#) of **S1400B** is met.
- Δ After off treatment prior to progression, patients should be followed by repeating indicated laboratory tests every 3 months or more often as clinically indicated for the first year, then every 6 months for up to 3 years from date of sub-study registration. Disease assessment should continue every 6 weeks until progression.
- √ After off treatment and after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of year 3 from date of sub-study registration. Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study.
- § With patient's consent, an additional research biopsy within 1 month after the time of first progression among patients who had a response to GDC-0032 (in the opinion of the treating physician) must be collected (see [Section 15.0](#) of **S1400B**).
- f* With patient's consent additional research blood draws will be collected (see [Section 15.0](#) of **S1400B**).
- ¥ Results of these tests do not determine eligibility but are recommended prior to sub-study registration.
- € If the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated.
- δ Assessments should continue until resolution of all acute adverse events.
- δ Blood for Banking specimen must be collected at first progression after study treatment (see [Section 15.0](#) of **S1400B**).

9.2 Arm 2 Docetaxel

REQUIRED STUDIES	PRE-STUDY	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β			Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15		
PHYSICAL																		
History & Physical Exam	X				X			X			X			X			X	
Weight & Performance Status	X				X			X			X			X			X	
Disease Assessment Ω	X							X						X			X	
Toxicity Notation					X			X			X			X			X	
Smoking Status Assessment	X																X	
LABORATORY																		
CBC/Diff/Platelets/Hgb	X				X			X			X			X			X	
Serum Bilirubin	X				X			X			X			X			X	
ALT or AST	X				X			X			X			X			X	
Serum Creatinine/Calc CrCl	X				X			X			X			X			X	
HbA1C	X																X	
Fasting Glucose	X				X			X			X			X			X	
Lipase & Amylase	X				X			X			X			X			X	
LDH ‡	X																	
Albumin ‡	X																	
X-RAYS AND SCANS																		
CT or MRI for Disease Assessment Ω	X							X						X			X	
Brain CT/MRI	X																	
EKG	X																	
Image Submission Σ	X							X						X			X	
SPECIMEN SUBMISSION																		
Blood for Banking f	X				X			X			X							X

Calendar continued on next page. Click here for [footnotes](#).

REQUIRED STUDIES	PRE-STUDY	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β			Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog \checkmark
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15		
TREATMENT																		
Arm 2: (21 day cycle)																		
Docetaxel		X			X			X			X			X				
Dexamethasone		X			X			X			X			X				

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in [Section 14.0](#).

Footnotes for Calendar 9.2 (Docetaxel):

- Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.2 of **S1400**) must be repeated every 6 weeks (\pm 7 day window) until disease progression.
- Σ Submit scans as outlined in [Section 14.0](#) and [Section 15.0](#) of **S1400B**.
- β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle. Disease assessments are to take place every 6 weeks. Assessments will follow Best Practices for SWOG Studies: <http://swog.org/Visitors/QA/Documents/Best%20Practices%20update.pdf>, however the disease assessment window is \pm 7 days. Treatment and evaluation will continue until any of the criteria in [Section 7.5](#) is met.
- Δ After off treatment prior to progression, patients should be followed by repeating indicated tests every 3 months for the first year, then every 6 months for up to 3 years from date of sub-study registration.
- \checkmark After off treatment and after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of year 3 from date of sub-study registration.
- f* With patient's consent, an additional research blood draw must be collected See [Section 15.0](#) of **S1400B**.
- \yen Results of these tests do not determine eligibility but are recommended prior to sub-study registration.

9.3 Arm 3 Re-Registration – GDC-0032 (Taselisib)

REQUIRED STUDIES	Step 2 Re-Registration	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β			At Off Tx	Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15			
PHYSICAL																			
History & Physical Exam	X				X			X			X			X			X	X	
Weight & Performance Status	X				X			X			X			X			X	X	
Disease Assessment Ω	X							XΩ						XΩ				XΩ	
Toxicity Notation					X			X			X						X	Xcb	Xcb
Smoking Status Assessment	X																X		
LABORATORY																			
CBC/Diff/Platelets/Hgb	X	X€			X			X			X			X			X	Xcb	Xcb
Serum Bilirubin	X	X€			X			X			X			X			X	Xcb	Xcb
ALT or AST	X	X€			X			X			X			X			X	Xcb	Xcb
Serum Creatinine/Calc CrCl	X	X€			X			X			X			X			X	Xcb	Xcb
HbA1c	X																X		
Fasting Glucose	X	X€			X			X			X			X			X	Xcb	Xcb
Lipase & Amylase	X	X€			X			X			X			X			X	Xcb	Xcb
LDH ¥	X																		
Albumin ¥	X																		
X-RAYS AND SCANS																			
CT or MRI for Disease Assessment Ω	X							XΩ						XΩ				XΩ	
Brain CT/MRI	X																		

Calendar continued on next page. Click here for [footnotes](#).

REQUIRED STUDIES	Step 2 Re-Registration	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β			At Off Tx	Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15			
SPECIMEN SUBMISSION																			
Tissue for Banking																			X§
Blood for Banking f	X				X			X			X								Xδ
TREATMENT																			
Arm 3: (21 day cycle)																			
GDC-0032 (Taselisib)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in [Section 14.0](#).

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in <https://swog.org/Visitors/QA/Documents/Best%20Practices%20update.pdf>.

Footnotes for Calendar 9.3 (Re-Registration GDC-0032):

- Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.2 of **S1400**) must be repeated every 6 weeks (± 7 day window) until disease progression.
- Σ Submit scans as outlined in [Section 14.0](#) and [Section 15.0](#) of **S1400B**.
- β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle, unless otherwise noted. Disease assessments are to take place every 6 weeks. (± 7 days window).
Treatment and evaluation will continue until any of the criteria in [Section 7.5](#) is met.
- Δ After off treatment prior to progression, patients should be followed by repeating indicated tests every 3 months or more often as clinically indicated for the first year, then every 6 months for up to 3 years from date of re-registration. Disease assessment should continue every 6 weeks until progression.
- √ After off treatment and after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of year 3 from date of re-registration. Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study.
- § With patient's consent, an additional research biopsy within 1 month after the time of first progression among patients who had a response to GDC-0032 (in the opinion of the treating physician) must be collected (see [Section 15.0](#) of **S1400B**).
- f With patient's consent additional research blood draws will be collected (see [Section 15.0](#) of **S1400B**).
- ¥ Results of these tests do not determine eligibility but are recommended prior to re-registration.
- € If the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated
- cb Assessments should continue until resolution of all acute adverse events
- δ Blood for Banking specimen must be collected at first progression after study treatment (see [Section 15.0](#) of **S1400B**).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

See Section 10.0 of **S1400** for criteria for evaluation and endpoint analysis.

11.0 STATISTICAL CONSIDERATIONS

This study will employ Design #2 the Seamless Phase II followed by Phase III design as described in **S1400** Section 11.2a. A complete description of the statistical design and analysis plan is included in Section 11.0 of **S1400**. This section includes details specific to **S1400B**.

11.1 Primary Objective and Biomarker Prevalence

Eligibility for **S1400B** is defined as the presence of any of the following mutations (Foundation Medicine [FMI] criteria).

Gene	Alteration type	Eligible alteration (FMI criteria)
PIK3CA	Substitution	R38C, R38H, E81K, R88Q, R93Q, R93W, P104L, P104R, G106V, G106R, P104_G106>R, R108H, E110del, E110K, K111E, K111N, K111del, G118D, V344G, V344M, N345K, N345I, E365K, C378F, E418K, C420R, E453K, E453Q, P539R, E542K, E542A, E542V, E542G, E542Q, E545A, E545G, E545K, E545Q, E545D, Q546E, Q546H, Q546K, Q546L, Q546P, Q546R, E726K, G1007R, D1017H, Y1021C, Y1021H, T1025A, A1035V, A1035T, M1043I, M1043L, M1043V, H1047L, H1047R, H1047Y, H1047N, H1047Q, G1049R, G1049S, I1058L
	Fusion	None
	Amplification	None

The expected prevalence of these PI3K mutations is 9.4% and the expected frequency of the other sub-study biomarkers among PI3K positive patients is: 0.9% for FGFR, 1.9% for CDK, and 1.9% for MET. Based on simulation using the randomization ratios as defined in **S1400** Section 11.1, the expected frequency of patients assigned to **S1400B** is 8.0%.

- a. However, PI3K mutation positivity by Genentech [GNE] criteria (PI3K GNE positive) is defined by the presence of a subset of these mutations. Specifically, a patient's tumor is defined as PI3K-positive based on the presence of the following mutations:

Gene	Alteration type	GNE criteria
PIK3CA	Substitution	E542K, E545A, E545G, E545K, E545Q, H1047L, H1047R, H1047Y
	Fusion	None
	Amplification	None

The primary objectives within **S1400B** are to evaluate GDC-0032 among patients defined to be PI3K positive based on the GNE criteria and the FMI criteria. The study sample size and timing of analysis is based on the subset defined to be PI3K GNE positive.

11.2 Sample Size with Power Justification

Phase II Design: **S1400B** will follow the Phase II design from the Seamless Phase II followed by Phase III (see Section 11.2c of **S1400**) among patients defined to be PI3K GNE positive.

Assuming 72% of PI3K-eligible patients will be PI3K- positive per GNE criteria, the total number of patients accrued to **S1400B** to achieve 40 eligible GNE+ patients is 56 eligible patients. Assuming that 5% of patients will be ineligible, the total accrual goal to the Phase II study is 59 PI3K-positive patients per FMI criteria (PI3K FMI positive). The anticipated duration of accrual to the phase II is 41-51 months from study activation.

12.0 DISCIPLINE REVIEW

This section does not apply to this sub-study.

13.0 REGISTRATION GUIDELINES

See Section 13.0 of **S1400** for registration guidelines.

13.1 Registration Timing

Patients must plan to begin treatment within 7 working days after Step 1: sub-study registration and Step 2: re-registration.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see [Section 14.3](#) for details.

14.3 Data Submission Procedures

- a. All participating institutions must submit data electronically via the Web using Medidata Rave® at the following url:
<https://login.imedidata.com/selectlogin>
 1. If prompted, select the 'CTEP-IAM IdP' link.
 2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

- You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (<http://swog.org>) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

b. To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the [CTSU](#) Participation Table on Page 5 of **S1400**.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF SUB-STUDY REGISTRATION, SUBMIT:

S1400B Onstudy Form

Smoking Status Assessment Form

Baseline Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at baseline (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease at baseline as specified in [Section 15.3](#).

b. WITHIN 7 DAYS AFTER STEP 2 RE-REGISTRATION:

Submit the following:

S1400B Re-Registration Eligibility Verification Form

Baseline Tumor Assessment Form (RECIST 1.1)

Smoking Status Assessment Form

Radiology reports from all scans performed to assess disease at baseline (NOTE: Upload reports via the Source Documentation: Baseline form found in the Re-Registration folder form i in Rave)

c. IF PATIENT CONSENTS, SUBMIT SPECIMENS:

Specimens as specified in [Section 15.0](#) of **S1400B**.

d. IMMEDIATELY AFTER EACH CYCLE (CYCLE = 21 DAYS) OF TREATMENT (INCLUDING BOTH ON INITIAL TREATMENT ARM AND RE-REGISTRATION TREATMENT ARM) SUBMIT:

S1400B Treatment Form

S1400B Adverse Event Form

S1400B Laboratory Values Form

For Cycle 1 only: submit the **S1400B** Pre-Treatment Laboratory Values Form

e. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION) (see **S1400B** [Section 9.0](#) for Disease Assessment Schedule), SUBMIT:

Follow-Up Tumor Assessment Form (RECIST 1.1) documenting results of assessment

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in [Section 15.3](#).

f. WITHIN 7 DAYS OF DISCONTINUATION OF TREATMENT (INCLUDING BOTH ON INITIAL TREATMENT ARM AND RE-REGISTRATION TREATMENT), SUBMIT:

Off Treatment Notice documenting reasons for off treatment

Smoking Status Assessment Form

S1400B Treatment Form

S1400B Adverse Event Form

S1400B Laboratory Values Form

g. ONCE OFF TREATMENT SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1400B** REGISTRATION*, THEN AT THE END OF YEAR 3 FROM SUB-STUDY/RE-REGISTRATION * SUBMIT:

Advanced NSCLC Follow-Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient

experiences any severe [Grade \geq 3] long term toxicity that has not been previously reported).

*For patients registered to Step 2 (Re-Registration), the follow-up schedule is calculated from the date of Step 2 Re-Registration.

Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study (See [Section 14.4j](#)).

h. WITHIN 7 DAYS OF PROGRESSION/RELAPSE (BOTH ON INITIAL TREATMENT ARM AND RE-REGISTRATION TREATMENT ARM), SUBMIT:

Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in [Section 15.3](#).

i. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information. In addition, if the patient was still on protocol treatment, submit materials specified in [Section 14.4e](#) or if patient was no longer on treatment, submit a final Advanced NSCLC Follow-Up Form.

j. Data Submission FOR PATIENTS WHO HAVE PROGRESSED AND WISH TO REGISTER TO A NEW SUB-STUDY:

WITHIN 7 DAYS OF PROGRESSION/RELAPSE:

Submit the **S1400** Request for New Sub-Study Assignment Form under **S1400** in Rave® Continue follow-up on **S1400B** per [Sections 9](#) and [14.4g](#) until registration to a new sub-study. See Section 14.6 of **S1400** for additional data submission requirements following request for new sub-study assignment.

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

See Section **S1400** Section 15.1 for SWOG Specimen Tracking System (STS) instructions.

15.2 Correlative Studies and Banking (Optional for Patients)

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) are considered optional for the patient:

- a. With patient's consent, specimens must be collected and submitted as follows:

1. Peripheral Blood:

Specimens must be collected at the following times during both Step 1 and Step 2 (Re-Registration):

- Pre-study (see Section 15.3 of **S1400**)
Note: If a patient provided blood at pre-screening at the time of progression on current treatment or screening (see Section 15.3 of **S1400**) and registration to **S1400** was within 42 days from sub-study registration, then that blood specimen can count as pre-study blood
- Weeks 4, 7, 10 - Patients that go off treatment are not required to continue to submit specimens.
- First Progression after study treatment

Approximately 8-10 mL of blood must be collected in EDTA tubes. Blood should be processed within one hour after venipuncture. If immediate processing within this time frame is not possible, EDTA tubes that are not processed immediately should be refrigerated at 4°C. The approximate time from collection to processing should be recorded as part of the patient's source documentation. EDTA tubes must be centrifuged at 800 g for 10 minutes at 4°C for the collection of plasma. Plasma must be transferred to one 15 ml centrifuge tube and spun again at 800 g for an additional 10 minutes. Plasma must then be pipetted into 1 ml coded cryovials at 0.5 ml aliquots. Plasma must be clear before freezing; no cells or debris should be present. Each buffy coat layer (the gray-white layer at the interface of blood cells and plasma, approximately 1 ml) from the blood tube must each be transferred into appropriately labeled 2-ml cryovials. Samples must be placed immediately in a -80°C freezer to ensure long-term viability.

2. New Biopsy of Tumor at Time of Progression among responders to GDC-0032:

A new biopsy is strongly requested from patients who responded to protocol treatment (in the opinion of the treating physician) and then experienced disease progression. Biopsies will be used for molecular analysis of molecular characteristics associated with mechanisms of resistance. New biopsy should be either bronchoscopy/surgical biopsy or CT guided biopsy. The biopsy should be performed within one month after progression and should be processed as FFPE material. The minimum requirement is a block or 12 unstained sections.

b. Specimen Submission

Samples for multiple patients can be shipped in batches, at least every 3 months if not more frequently, to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201.

Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (<http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp>).

c. Specimen collection kits are not being provided for this submission; sites must use institutional supplies.

15.3 Radiology Review (Required)

CT, PET/CT, and/or MRI images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for central data collection and quality control (QC) check as well as retrospective central review.

a. CT, PET/CT, and/or MRI images must be submitted to IROC Ohio for central review at the following timepoints for both Step 1 and Step 2 (Re-Registration):

- Baseline
- Every 6 weeks until progression

All study participants must have a CT (or MR or PET/CT) exam prior to sub-study entry. Participants must then undergo additional imaging every 6 weeks until progression of disease. The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (see [Section 10.1c](#)). Each exam should be performed per [Section 18.1c](#). IROC will perform a QC of the imaging exams.

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinical appropriate considerations.

Central review of scans will not be triggered if the study will not be submitted to the FDA for FDA approval of the investigational therapy. Central review of scans will be triggered only if deemed necessary for FDA evaluation. A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions, can be found in [Section 18.1c](#).

b. TRIAD Digital Image Submission

TRIAD is the secure electronic image upload application utilized for IROC Services of this trial. TRIAD de-identifies and validates the images as they are transferred.

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Ohio. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account (see [Section 13.2](#)).
- To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

2. TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link <https://triadinstall.acr.org/triadclient/>

Questions regarding image submissions, including TRIAD, should be directed to SWOG1400@irocOhio.org or call IROC Ohio at 614-293-2929.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in [Section 14.0](#).) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at <http://ctep.cancer.gov>. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to [Table 16.1](#)) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808, or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in [Table 16.1](#) or [16.2](#), as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in [Table 16.1](#). The investigational agent used in Arm 1 and Arm 3 of this study is GDC-0032. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention¹ GDC-0032 Arm 1 or Re-Registration, Arm 3.

<p>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)</p> <p>An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for \geq 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). 		
<p>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.</p>		
Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization \geq 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization \geq 24 hrs	Not required	
<p>NOTE: Protocol specific exceptions to expedited reporting of serious adverse events (if applicable) are found in Section 16.1f.</p> <p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> ○ “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. 		
<p>¹Serious 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:</p> <p>Expedited 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 3, 4, and Grade 5 AEs <p>Expedited 10 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 AEs resulting in hospitalization or prolongation of hospitalization 		
<p>May 5, 2011</p>		

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1) **Group-specific instructions.**

Supporting Documentation Submission - Within 5 **calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- a. Printed copy of the first page of the CTEP-AERS report
- b. Copies of clinical source documentation of the event
- c. If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2) **The adverse events listed below are considered to be adverse events of special interest (AESIs) and require expedited reporting for this trial:**

- Grade \geq 3 symptomatic hyperglycemia
- Grade \geq 2 colitis or enterocolitis
- Grade \geq 2 diarrhea
- Grade \geq 3 rash
- Grade \geq 2 pneumonitis
- Grade \geq 3 stomatitis
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law
- Suspected transmission of an infectious agent by the study drug

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in [Table 16.2](#). The commercial agent used in Arm 2 of this study is docetaxel. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on study Arm 2 who have received the commercial drug listed in [Section 16.1g](#) above within 30 days of the last administration of the commercial agent.

Attribution	Grade 4		Grade 5 ^a	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			CTEP-AERS	CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS	CTEP-AERS
<p>CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event^b.</p> <p>^a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.</p> <p>^b Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.</p>				

h. Reporting Secondary Malignancy, including AML/ALL/MDS

1. 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.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to 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.

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.

For more information see:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 “Pregnancy, puerperium and perinatal conditions – Other (pregnancy)”** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as “A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation” should be reported expeditiously as **Grade 4 “pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)”** under the **Pregnancy, puerperium and perinatal conditions** SOC.
3. **Death Neonatal** Neonatal death, defined in CTCAE as “A disorder characterized by cessation of life occurring during the first 28 days of life” that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 “General disorders and administration – Other (neonatal loss)”** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for “Pregnancy”, “Pregnancy loss”, or “Neonatal loss”, the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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