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

Operations Office

January 25, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #18 to EAY131-I, *Molecular Analysis for Therapy Choice (MATCH): MATCH Treatment Subprotocol I: GDC-0032 (taselisib) in Patients with Tumors (other than breast cancer) with PIK3CA Mutation but without KRAS Mutation or PTEN Loss.*

This addendum is in response to Dr. L. Austin Doyle's January 22, 2019 Request for Rapid Amendment for GDC-0032.

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

	Section	**Change**
1.	Cover Page	Updated Version Date.
2.	Section 3.3	Updated the GDC-0032 CAEPR list with version 2.2, October 11, 2018.

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

	Section	**Change**
1.	Page 1	Updated Version Date.
2.	What possible risks can I expect from taking part in this study?	Updated the GDC-0032 risk list with version 2.2, October 11, 2018.

If you have any questions regarding this addendum, please contact kpollard@ecog-acrin.org or 857-504-2900.

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

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

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EAY131-I

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol I: GDC-0032 (taselisib) in Patients with Tumors (other than breast cancer) with PIK3CA Mutation but without KRAS Mutation or PTEN Loss

GDC-0032 (TASELISIB) TREATMENT SUBPROTOCOL CHAIR: Ian Krop, M.D., Ph.D.

GDC-0032 (TASELISIB) TREATMENT SUBPROTOCOL CO-CHAIR: Juneko Grilley-Olson, M.D.

GDC-0032 (TASELISIB) TRANSLATIONAL CHAIR: Josh Lauring, M.D., Ph.D.

Version Date: January 25, 2019

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

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

SUBPROTOCOL ACTIVATION DATE

February 25, 2016 (Incorporated in Addendum #2)
Addendum #3 – 5/16
Addendum #4 – 7/16
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #13
Addendum #18

Agent	IND#	NSC#	Supply
GDC-0032 (taselisib)			NCI Supplied

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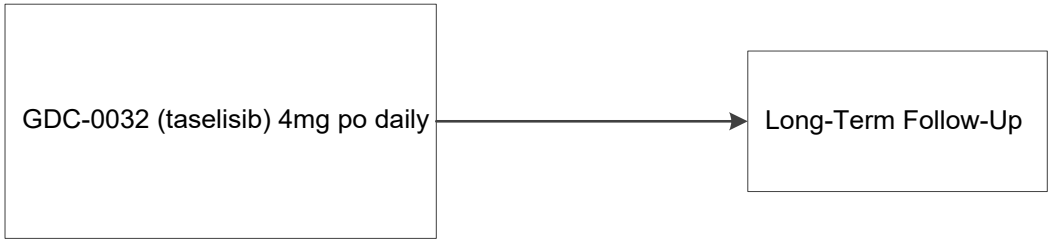
Rev. 3/17

Schema



Cycle = 28 days
Accrual Goal: 70

1. Introduction

1.1 GDC-0032 (taselisib)

GDC-0032 (taselisib) is a potent, selective inhibitor of Class I phosphoinositide 3-kinase (PI3K) alpha, delta, and gamma isoforms, with approximately 30-fold less inhibition of the p110 beta isoform.

1.2 Supporting Preliminary Data

Rationale:

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/mammalian target of rapamycin (mTOR) pathway[1,2]. Activating and transforming mutations of the gene encoding the p110 alpha subunit of PI3K (*PIK3CA*) are commonly found in solid and hematological tumors[1,3-5]. For example, *PIK3CA* mutations were found in 17-18% of 6234 tumors listed on cBioPortal (http://www.cbioportal.org/public-portal/). In addition, the PI3K/Akt pathway is activated in numerous types of cancer by receptor tyrosine kinase (RTK) signaling, loss of the phosphatase and tensin homolog (PTEN), or rat sarcoma (RAS) mutations. In nonclinical studies, pan-class I PI3K inhibitors and alpha isoform selective PI3K inhibitors show greater potency against cell lines with *PIK3CA* mutations. Janku et al analyzed characteristics and outcome of over 1600 patients with diverse advanced tumors and *PIK3CA* mutations. Of 160 patients found to have *PIK3CA* mutations, the majority of the mutations occurred in three hotspots: E545K (1633G > A) in 32.5%; E542K (1624G > A) in 20% and H1047R (3140A > G) in 18%. These hotspot mutations in *PIK3CA*, in addition to a number of less frequent mutations (Appendix II), have been shown to increase the lipid kinase activity of PIK3CA and increase phosphorylation of downstream signaling targets[6-10]. There was an improved response rate in patients with *PIK3CA* mutations or PTEN loss who were treated with allosteric mTOR inhibitors, AKT inhibitors or PI3K inhibitors compared to similar patients treated with similar agents, but not having *PIK3CA* mutations or PTEN loss, and compared to patients with *PIK3CA* mutations or PTEN loss treated with agents that do not target the PI3K-AKT-mTOR pathway[11]. The PTEN protein is a tumor suppressor protein that negatively regulates the PI3K pathway thorough its lipid phosphatase activity, dephosphorylating PIP3 to PIP2. PTEN function can be reduced or abrogated in tumors by loss of expression resulting from either genetic or epigenetic causes. Protein loss can be detected by absence of staining using immunohistochemistry. Genetic causes of PTEN inactivation include heterozygous and homozygous gene deletion, frameshift, indel, and nonsense mutations causing protein truncation or nonsense mediated mRNA decay, as well as missense mutations that alter amino acids critical for PTEN's enzymatic activity (Appendix II)[12,13]. Several preclinical studies have shown that PTEN-deficient tumors preferentially depend on the beta isoform of PI3K for survival and respond to beta-specific, but not alpha-specific, inhibitors[14-16]. A clinical case report showed that PTEN mutations can be an acquired resistance mechanism to an alpha-specific PI3K inhibitor[17]. Additional studies have shown that RAS mutations, *KRAS* mutations in particular,

are associated with resistance to PI3K inhibitors, even in the context of a cell line with a *PIK3CA* mutation[18,19]. This effect of activating RAS mutations appears to be due to the activation of the mitogen activated protein kinase (MAPK) pathway, leading to preservation of phosphorylation of critical downstream substrates such as ribosomal protein S6 and EIF4EBP1, even in the face of PI3K inhibition[19]. The beta isoform of PI3K is involved in glucose metabolism as evidenced by increased glucose levels in conditional p110β knockout mice compared with wild-type mice following a glucose challenge test[15]. These data provide a strong rationale for developing beta isoform-sparing PI3K inhibitors that inhibit the PI3K pathway in human tumors while minimizing effects on glucose metabolism. In summary, use of a beta-isoform sparing PI3K inhibitor is predicted to have enhanced efficacy and tolerability against tumors harboring activating *PIK3CA* mutations, but without activating *KRAS* mutations or PTEN loss or loss-of-function mutations.

Nonclinical studies:

GDC-0032 (taselisib) is a potent inhibitor of Class I PI3K alpha, delta, and gamma isoforms (mean apparent Ki [Ki_{app}] values of 0.29 nM, 0.12 nM, and 0.97 nM, respectively), and approximately 30-fold less potent against the beta isoform (Ki 9.1 nM) compared to the alpha isoform. GDC-0032 (taselisib) has demonstrated activity in nonclinical models of PI3K-mutant tumor cells in vitro and in vivo. Studies of the mechanism of action indicate that downstream PI3K pathway components such as Akt, PRAS40, and S6 are inhibited, resulting in G_1 arrest and apoptosis. GDC-0032 (taselisib) has been proven to be potent in nonclinical xenograft models of PI3K-mutant breast tumors following PO daily (QD), as well as intermittent, dosing. Single-agent GDC-0032 (taselisib) resulted in 128% tumor growth inhibition (TGI) at a maximum tolerated dose (MTD) of 25 mg/kg QD (7 partial regressions [PRs] and 1 complete regression [CR] out of 8 animals) in the KPL-4 breast cancer xenograft model, which contains a *PIK3CA* mutation in the catalytic domain of p110 alpha (H1047R), in severe combined immunodeficient (SCID) beige mice; 105% TGI at an MTD of 22.5 mg/kg QD (6 PRs out of 8 animals) in the MCF7-neo/HER2 breast cancer xenograft model, which contains a *PIK3CA* mutation in the helical domain of p110 alpha (E545K), in nude mice; and 94% TGI at a dose of 20 mg/kg QD in the A549 NSCLC xenograft model, which contains a K-ras mutation, in nude mice. GDC-0032 (taselisib) is potent against a panel of human cell lines but significantly more potent against cell lines that contain PI3K mutations: mean IC_{50}s for the PI3K wild-type and PI3K mutant were 2.6 and 0.06 μM, respectively.

Clinical studies:

Study PMT4979g is an open-label, first-in-human, Phase I/II dose-escalation study designed to define the safety, tolerability, and PK and pharmacodynamic (PD) effects in patients with locally advanced or metastatic solid tumors. A dose-escalation stage evaluated the safety and pharmacokinetics of increasing doses of GDC-0032 (taselisib) administered once daily (QD) in a 28-day cycle. The single-agent expansion cohorts enrolled patients with *PIK3CA*-mutant breast cancer, *PIK3CA*-mutant solid tumors other than breast cancer, solid tumors, human epidermal growth factor receptor 2 (HER2)-positive breast cancers, *PIK3CA*-amplified solid tumors, and *PIK3CA*-mutant non-breast, non-colorectal solid tumors. Additional cohorts have enrolled patients with hormone receptor-positive breast cancer to receive GDC-0032 (taselisib) in combination with either

letrozole or fulvestrant. In the Phase II portion of the study, 60 postmenopausal patients with locally advanced or metastatic HER2-negative, hormone receptor–positive breast cancer have received combination treatment with fulvestrant and GDC-0032 (taselisib).

Study GO27802 is an open-label, multicenter, Phase Ib dose-escalation study designed to assess the safety, tolerability, and pharmacokinetics of oral GDC-0032 (taselisib) administered in combination with either docetaxel or paclitaxel in patients with HER2-negative locally recurrent or metastatic breast cancer or non-small-cell lung cancer (NSCLC). In studies PMT4979g and GO27802, as of 30 July 2014, a total of 246 patients have been treated with GDC-0032 (taselisib) either as a single agent (n = 115) or in combination with fulvestrant (n = 87), letrozole (n = 28), docetaxel (n = 4), or paclitaxel (n = 12).

Preliminary Pharmacokinetics

PK data are available from 30 patients treated with GDC-0032 (taselisib) at 3, 5, 8, 12, and 16 mg capsules in the ongoing Phase I clinical trial (Study PMT4979g). The cohort mean apparent clearance (CL/F) and the terminal half-life ($t_{1/2}$) following a single oral dose of GDC-0032 (taselisib) had a range of 4.77–9.17 L/hour and 37.2–43.8 hours, respectively. Following daily oral dosing for 8 days, there was a 2- to 4-fold accumulation of GDC-0032 (taselisib). The pharmacokinetics of GDC-0032 (taselisib) appear to be dose linear and time independent. Results from the mass balance study suggest that hepatic elimination of unchanged GDC-0032 (taselisib) represents the predominant pathway of elimination, with renal elimination a minor route of total clearance. No GDC-0032 (taselisib)-related metabolites were identified in systemic circulation. GDC-0032 (taselisib) was metabolized primarily by CYP3A4 in human liver microsomes and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 (taselisib) has low to moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg capsule dose of GDC-0032 (taselisib) daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC-0032 (taselisib) may be administered concomitantly with CYP3A4 substrates without the risk of a pharmacokinetic drug-drug interaction. Co-administration of taselisib with a strong CYP3A4 inhibitor, itraconazole, or a potent CYP3A4 inducer, rifampin, resulted in an approximate 49% increase and 23% decrease, respectively, in taselisib exposure (AUC). There was no apparent food effect on pharmacokinetics.

Preliminary Pharmacodynamics

Tumor biopsies were obtained from 2 NSCLC patients during screening (baseline biopsy) and once during Cycle 1 in Study PMT4979g (on-treatment biopsy). The on-treatment biopsy was obtained 1 to 4 hours after dosing at approximately Day 18 (between Days 15 and 21). Needle core biopsies were fixed in optimal cutting temperature compound and evaluated by reverse phase protein array for Akt pathway markers, including phospho-Akt. Decreases of > 60% in pAkt and pS6 (compared with baseline) were demonstrated in these patients who were treated with GDC-0032 (taselisib) at capsule doses of 3 mg and 16 mg QD.

Concentration QT/QTc Analysis

Preliminary C-QT analysis was conducted using 911 data points from 146 patients for QTcF and using 759 data points from 132 patients for QTcF CFB. The C-QT analysis showed a weak positive correlation between GDC-0032 (taselisib) plasma concentration and QTcF and QTcF CFB within the available exposure range of GDC-0032 (taselisib). Within the 6-mg exposure range, the upper level of the CI around the median profile of QTcF CFB reaches approximately 10 ms and excludes 20 ms (criteria suggested by FDA for oncology drugs).

Safety:

Ninety-six of the 115 patients (83%) treated with single-agent GDC-0032 (taselisib) experienced at least 1 adverse event that was assessed by the investigator as related to GDC-0032 (taselisib).

Adverse events that occurred in ≥ 10% of patients that were assessed by the investigator as related to GDC-0032 (taselisib) were diarrhea (52%), hyperglycemia (35%), nausea (35%), fatigue (31%), decreased appetite (25%), rash (18%), stomatitis (15%), vomiting (13%), and mucosal inflammation (12%).

Among the 115 patients treated with single-agent GDC-0032 (taselisib), at least one Grade 3 or higher adverse event was reported for 72 patients (63%). Events reported for more than 1 patient included hyperglycemia (14%), colitis (6%), diarrhea (5%), hypokalemia (5%), pneumonitis (5%), anemia (4%), fatigue (4%), rash (4%), abdominal pain (3%), increased ALT (3%), dyspnea (3%), hyponatremia (3%), hypophosphatemia (3%), increased lipase (3%), pneumonia (3%), UTI (3%), congestive cardiac failure (2%), Clostridium difficile infection (2%), hypoxia (2%), neutropenia (2%), pruritus (2%), respiratory failure (2%), and stomatitis (2%).

Efficacy:

Preliminary efficacy data as of 30 July 2014 for patients enrolled in the Phase I/II study PMT4979g with measurable disease at baseline and known *PIK3CA* mutation status show that treatment with GDC-0032 (taselisib) alone or in combination with fulvestrant or letrozole appears to result in more pronounced anti-tumor activity in patients with *PIK3CA*-mutant tumors compared to those without the mutation, including in patients with breast cancer. In the single-agent GDC-0032 (taselisib) group, 11 of 91 patients (12%) with measurable disease at baseline had a partial response as their best overall response, with 9 having confirmed partial responses per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. All 11 partial responses were observed in the 53 patients with *PIK3CA*-mutant positive tumors (21%), whereas none were seen in the 38 patients without detectable *PIK3CA* mutation. Thirty-four patients treated with single-agent GDC-0032 (taselisib) had been diagnosed with breast cancer, and among those, partial responses were observed in 7 patients (21%), all of whom had tumors harboring *PIK3CA* mutations. Six patients had confirmed partial responses per RECIST 1.1. The PR rate in breast cancer patients with *PIK3CA* mutations treated with single agent GDC-0032 (taselisib) was 7 out of 25 (28%). Stable disease as best overall response was observed in 34% of patients with *PIK3CA* mutant tumors and 39% of those with *PIK3CA* wild type tumors, for an overall SD rate of 36% across all tumor types.

In the 63 patients with measurable disease at baseline receiving GDC-0032 (taselisib) in combination with fulvestrant, 1 (2%) had a complete response and 19 (30%) had a partial response as their best overall response, with 14 having confirmed partial responses per RECIST 1.1. Twelve of the partial responses were observed in the 33 patients (36%) with *PIK3CA*-mutant positive tumors, whereas the remaining 7 were seen in the 30 patients (23%) without detectable *PIK3CA* mutation. The single complete response was observed in a patient without detectable *PIK3CA* mutation but was not confirmed. In the 20 patients with measurable disease at baseline receiving GDC-0032 (taselisib) in combination with letrozole, 5 (25%) had a partial response as their best overall response, with 4 being confirmed partial responses per RECIST 1.1. Four of the partial responses were observed in the 10 patients (40%) with *PIK3CA*-mutant positive tumors, whereas 1 was seen in the 10 patients (10%) without detectable *PIK3CA* mutation. In this early trial, nine (12%) of the 73 patients had a partial response as best response, of which 6 patients had a confirmed partial response. Twenty-eight patients (38%) had a best confirmed response of stable disease per RECIST.

Because GDC-0032 (taselisib) has demonstrated an objective response rate in patients with PIK3CA mutant breast cancer in excess of the primary endpoint of MATCH, patients with breast cancer will be excluded from this study. The effect of GDC-0032 (taselisib) on patients with PIK3CA mutant, but not amplified, squamous cell carcinoma of the lung is being evaluated in a separate basket study and therefore this PIK3CA patient population will also be excluded from the current study.

In summary, GDC-0032 (taselisib) is a potent inhibitor of class I PI3K isoforms alpha, gamma, and delta with less potency against the beta isoform, which has demonstrated an acceptable safety profile in clinical studies to date and has shown preliminary evidence of single agent efficacy against tumors of various types, with higher observed response rates against tumors with *PIK3CA* mutations. The recommended phase II dose is 9 mg (capsule form), equivalent to 4-6 mg (tablet form). The tablet formulation has been selected for further clinical development. For this study, the 4mg (tablet) once daily dosing will be used, since clinical activity has been observed at this dose level and this dose will maximize tolerability. Please refer to the GDC-0032 (taselisib) Investigator's Brochure for additional details.

2. Selection of Patients

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

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

ECOG-ACRIN Patient No. _____

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

Physician Signature and Date _____

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

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

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

2.1 Eligibility Criteria

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

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_____ 2.1.2 Patients must have a PIK3CA mutation as determined via the MATCH Master Protocol. See Appendix II for a list of the eligible PIK3CA alterations and corresponding Levels of Evidence.

_____ 2.1.3 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block).

Date of ECG: _____

_____ 2.1.4 Patients with known left ventricular dysfunction must have ECHO or MUGA within 4 weeks prior to registration to treatment and must not have left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN). If the LLN is not defined at a site, the LVEF must be > 50% for the patient to be eligible.

Date of ECHO/MUGA: _____

_____ 2.1.5 Patients must not have known hypersensitivity to GDC-0032 (taselisib) or compounds of similar chemical or biologic composition.

_____ 2.1.6 Patients must have a fasting glucose ≤ 125 mg/dL

NOTE: Please provide clear documentation that the glucose test was conducted at a fasting state.

_____ 2.1.7 Patients must not have breast cancer.

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_____ 2.1.8 Patients with squamous cell carcinoma of the lung who have PIK3CA mutations who have access to AND are eligible for Lung-MAP (S1400) are not eligible.

_____ 2.1.9 Patients must not have KRAS mutations, and/or PTEN mutation or loss, detected in the tumor sample as determined by the MATCH screening assessment. PTEN loss will be determined by immunohistochemistry. See Appendix II for a list of the exclusionary KRAS and PTEN alterations and corresponding Levels of Evidence.

_____ 2.1.10 Patients must not have had prior therapy with a PI3K inhibitor or PI3K/mTOR inhibitor. These include, but are not limited to: BEZ235, XL-765 (SAR245409), GDC-0980, PF-04691502, PF-05212384 (PKI-587), SF-1126, GSK 2126458, P-7170, BGT-226, LY3023414, GDC-0084, DS-7423, BKM-120 (buparlisib), PX-866, XL-147, GDC-0941 (pictilisib), VS-5584, BAY-80-6946, ZSTK-474, WX 037, AZD8835, GSK2636771, GS-9820, BYL719, MLN1117 (INK1117), Idelalisib, TGR1202, RP6530, duvelisib (IPI-145), CUDC-907. Prior GDC-0032 (taselisib) is not allowed.

_____ 2.1.11 Patients must not have had prior therapy with an Akt inhibitor. These include, but are not limited to: MK-2206, GSK690693, AZD5363, triciribine, perifosine, GSK2141795, GSK2110183, SR13668, BAY1125976, GDC-0068 (ipatasertib), LY2780301, ARQ092.

_____ 2.1.12 Patients with prior treatment with an mTOR inhibitor are acceptable. These include, but are not limited to: temsirolimus, everolimus, ridaforolimus, sirolimus, CC-223, MLN128 (INK128), DS-3078, CC-115, AZD-2014, AZD8055.

_____ 2.1.13 Patients must not have type 1 or 2 diabetes requiring anti-hyperglycemic medication (e.g. metformin, glipizide, insulin)

_____ 2.1.14 Patients must not have current dyspnea at rest or require any daily supplemental oxygen

_____ 2.1.15 Patients must not have history of inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) or active bowel inflammation (e.g. diverticulitis)

_____ _____

Physician Signature Date

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

3. GDC-0032 (taselisib) Treatment Plan

3.1 Dosage and Administration

The dose of GDC-0032 (taselisib) on this study will be 4 mg taken orally once a day (4 mg PO QD) on a 28 day cycle. GDC-0032 (taselisib) is formulated as 2 mg tablets, so patients will take two 2 mg tablets once daily to receive a 4 mg dose. Patients will repeat cycles until progression.

Patients should take the GDC-0032 (taselisib) dose at the same approximate time each day without regard to the timing of administration of food. If a dose is missed (not taken within 6 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Sections 3.4 and 3.6.

3.2 Adverse Event Reporting Requirements

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

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

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

Additional Instructions

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

EAY131 – Subprotocol I specific expedited reporting requirements:

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on GDC-0032 (taselisib), or within 28 days of the subject's last dose of GDC-0032 (taselisib), are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master Protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131 – Subprotocol I specific expedited reporting exceptions:

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

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

3.2.2 Second Primary Cancer Reporting Requirements

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

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

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

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

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be

submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

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

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3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for GDC-0032 (Taselisib, NSC 778795)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 910 patients*. Below is the CAEPR for GDC-0032 (taselisib).

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

Version 2.2, October 11, 2018[1]

Adverse Events with Possible Relationship to GDC-0032 (taselisib) (CTCAE 5.0 Term) [n= 910]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis		***Colitis (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		

Adverse Events with Possible Relationship to GDC-0032 (taselisib) (CTCAE 5.0 Term) [n= 910]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		
	Skin and subcutaneous tissue disorders - Other (rash)[3]		***Skin and subcutaneous tissue disorders - Other (rash)[3] (Gr 2)***

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

[2]Infections, including serious infections, includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Rash may include rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, and rash vesicular.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia

EAR AND LABYRINTH DISORDERS - Vertigo

GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Dysphagia; Enterocolitis; Gastrointestinal disorders - Other (Crohn's disease); Oral pain; Rectal fistula

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS – Death NOS

INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Cholesterol high; Lymphocyte count decreased; Neutrophil count decreased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypokalemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Muscle cramp; Myalgia

NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia; Headache; Nervous system disorders - Other (neuropathy peripheral); Stroke

PSYCHIATRIC DISORDERS - Psychiatric disorders - Other (mood altered)

RENAL AND URINARY DISORDERS - Acute kidney injury

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Erythroderma; Pruritus

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.

3.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

The side effects observed with GDC-0032 (taselisib) are consistent with those observed with other PI3K inhibitors. Selected toxicities of interest for GDC-0032 (taselisib) include gastrointestinal toxicities, pneumonitis, rash, stomatitis, and hyperglycemia and these are described in detail below. Certain adverse events (e.g., rash, colitis, and pneumonitis) may also occur within 4 weeks of holding or stopping GDC-0032 (taselisib).

The GDC-0032 (taselisib) dose reduction instructions provided in **Table 1** are intended to serve as recommended guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while monitoring patient safety. The investigator may temporarily suspend GDC-0032 (taselisib) dosing for up to 28 days from the last scheduled dose due to a GDC-0032 (taselisib)-related toxicity or an unanticipated medical event not associated with study treatment toxicity or with disease progression. Depending on the nature and the severity of the GDC-0032 (taselisib)-related toxicity, the investigator may resume GDC-0032 (taselisib) dosing in the patient at the same dose or at one dose level lower (as detailed in Tables 2−6).

Table 1 Overall Dose Modification Guideline for GDC-0032 (taselisib)-Related Adverse Events

	GDC-0032 (taselisib)
Starting dose	4 mg daily
First reduction	2 mg daily
Second reduction	2 mg every other day (QOD)

No dose reduction is allowed for patients treated at a dose of GDC-0032 (taselisib) of 2mg QOD – if there is an indication for further dose reduction, the patient must permanently discontinue GDC-0032 (taselisib). Dose re-escalation is not allowed after a dose reduction.

NOTE: Due to the approximately 40 hour half-life for GDC-0032 (taselisib), investigators should consider holding GDC-0032 (taselisib) for certain Grade 2 toxicities until the adverse events resolves to Grade ≤ 1 as discussed below (e.g., stomatitis/oral mucositis, rash, diarrhea). In addition, certain toxicities can occur or worsen within 1–2 weeks of holding or discontinuing GDC-0032 (taselisib) (e.g., pneumonitis, colitis, rash). Investigators should follow management guidelines for toxicities as described below including administration of topical or systemic corticosteroids as appropriate.

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 also cause diarrhea and can be poorly tolerated, other antihyperglycemic medications such as sulfonylureas (e.g., glimepiride, glipizide) can be used. Extra caution should 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. Management guidelines for fasting patients with hyperglycemia are listed below in Table 2

Table 2: Management of Hyperglycemia

Grade	Intervention	Dose Adjustment
1	Initiation of an oral anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring should be considered.	No change.
2	Initiation or increased dose of an oral anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring should be considered.	Dosing with GDC-0032 (taselisib) may either be held or continued per Investigator evaluation.
3, asymptomatic	Patient should be managed as per standard care, including implementation of additional glucose monitoring and initiation and/or increase of anti-hyperglycemic therapy (e.g., metformin).	Consideration should be given to suspending GDC-0032 (taselisib) dosing until the hyperglycemia resolves to Grade $\leq$ 2. Dosing with GDC-0032 (taselisib) may resume at the same dose level or at one dose level lower as outlined in Table 1 and after discussion with the Study Principal Investigator.
3, symptomatic (e.g., blurred vision, frequent urination, excessive thirst) or grade 4	Patient should be managed as per standard care, including implementation of additional glucose monitoring and initiation and/or increase of anti-hyperglycemic therapy	GDC-0032 (taselisib) dosing should be suspended until the hyperglycemia resolves to Grade $\leq$ 2. The patient will be discontinued from the study if such therapy fails to control their hyperglycemia. Dosing with GDC-0032 (taselisib) may otherwise resume at one dose level lower as outlined in Table 1.

*****Based on fasting glucose level

Management of Pneumonitis

Patients will be assessed for pulmonary signs and symptoms throughout the study (including physical examinations, pulse oximetry, and periodic CT scans). Oxygen saturation by pulse oximetry will be measured at every visit as part of the assessment of vital signs. Patients experiencing symptomatic or asymptomatic pneumonitis should be treated per standard of care and individual protocol guidelines adapted from recommendations by White et al. for the management of pneumonitis in cancer patients receiving everolimus[10]. Use of corticosteroids should be considered for symptomatic cases of noninfectious pneumonitis. Management guidelines for patients with possible pneumonitis are listed below in the Table 3

Table 3: Management of Pneumonitis

Grade	Intervention	Investigations	Dose Adjustment
1	No specific therapy required.	CT scan. Consider PFTs. Repeat CT scan every 6 to 9 weeks until return to baseline.	No change.
2	Symptomatic only. Prescribe corticosteroids[a] if cough is troublesome and infectious etiology is ruled out.	CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs and bronchoscopy.	Discontinue all study treatment until improvement to Grade ≤ 1. If pneumonitis improves to grade ≤1 and upon completion of any corticosteroids, resume GDC-0032 (taselisib) at one dose level lower Discontinue treatment if recovery to Grade ≤ 1 is not evident within 28 days.
3- 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 all study treatment regardless of the attribution.

Table modified from White et al[10].

[a] Suggested corticosteroids include methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg × 2 days, 40 mg × 2 days, 20 mg × 2 days, etc.).

CT = computed tomography; PFT = pulmonary function test

PFTs include tests for DLCO and room air oxygen saturation at rest (pulse oximetry).

Repeat CT scans should match schedule for re-staging exams if feasible.

Management of Rash

Treatment-related rash, including cases of Grade 3 rash, has occurred in patients who received GDC-0032 (taselisib) monotherapy or in combination with other anti-cancer drugs. This rash is commonly manifested as maculopapular type with or without pruritus, with some having developed desquamation. Rash and other dermatological events should be closely monitored. 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, hold all study treatment until Grade ≤ 1 (see Table 4 below), and patients should be treated with supportive therapy per standard of care. Use of topical antihistamine, as well as topical or systemic corticosteroids, may be considered

Table 4: Dose Delay and Modification Guidelines for Rash

Grade	Intervention	Dose Adjustment
Grade 1	Consider prescribing topical corticosteroids [a]	Continue dosing at current dose and monitor for change in severity.
Grade 2	Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]).	Consider holding GDC-0032 (taselisib) or reducing to the next lower dose if rash is troublesome.
Grade 3 or 4	Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]). Consider dermatological consultation. Consider obtaining photographs of rash if permitted by local regulations.	Hold all study treatment until Grade ≤ 1. Restart GDC-0032 (taselisib) at the next lower dose upon discussion with Overall Principal Investigator, or permanently discontinue.

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 × 2 days, 40 mg × 2 days, 20 mg × 2 days, etc.).

Management of Gastrointestinal Toxicity

Diarrhea

Patients should be closely monitored for gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, 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. Prompt management of diarrhea with antidiarrheal medications should be implemented. Because of the approximately 40 hour half-life of GDC-0032 (taselisib), investigators should hold GDC-0032 (taselisib) for Grade ≥ 2 diarrhea.

Steroid-responsive diarrhea and colitis have been difficult to distinguish in patients treated with taselisib. All cases of colitis have been reversible with corticosteroid treatment. Prompt initiation of corticosteroids for persistent diarrhea despite anti-diarrheal treatment can decrease the severity of the diarrhea and prevent the need for hospitalization. Patients who develop severe steroid-responsive diarrhea usually have been on GDC-0032 (taselisib) treatment for at least 2 months, with an average onset at 4 to 6 months of treatment. A stool culture is helpful in identifying concurrent infections, and patients have been successfully treated with concurrent steroids and appropriate antibiotics, if needed.

If a patient is being treated with corticosteroids, total parenteral nutrition is discouraged, as this increases the risk for severe hyperglycemia. Discontinuation of non-steroidal inflammatory medications or other medications that exacerbate colitis are also recommended during colitis episodes.

Specific dose modification and management guidelines for diarrhea and colitis are provided in Table 5.

Colitis

For persistent Grade 2 diarrhea that does not resolve or for Grade ≥ 3 diarrhea, further evaluation should include colitis in the differential diagnosis with the appropriate work-up (e.g., abdominal CT scan, endoscopy with biopsy, stool cultures for cytomegalovirus, Clostridium difficile, and parasites). Grade ≥ 2 colitis should be managed by interruption of all study treatment. In addition, discontinuation of nonsteroidal anti-inflammatory medications or any other medications known to exacerbate colitis symptoms should be considered. If noninfectious colitis is suspected, treatment with corticosteroids per institutional standard of care is recommended. It is suggested that prednisone (for oral administration) or solumedrol (for IV administration) are the corticosteroids of choice in the treatment of colitis. For severe symptoms, prednisone 60 mg or equivalent may be required to control initial symptoms, and the dose should be gradually tapered. Lower doses of prednisone, oral budesonide, or mesalamine (or other 5-aminosalicyclic acid derivatives) may be considered for less severe cases of colitis. It has been observed that patients that have developed colitis upon GDC-0032 (taselisib) treatment have improved with drug hold and coadministration of systemic steroids.

Specific dose modification and management guidelines for colitis are provided in Table 5.

Table 5: GDC-0032 (taselisib) Dose Modification and Management Guidelines for Diarrhea and Colitis

Grade of Diarrhea	Intervention	Dose Modification
Grade 1	Manage per institutional standard of care that includes antidiarrheals. [a] For persistent Grade 1 diarrhea occurring after Cycle 2, recommend evaluation for infectious causes via stool culture[b]. For non-infectious diarrhea, consider colonoscopy to evaluate for colitis.	Continue current dose.
Grade 2	Initially manage per institutional standard of care until Grade ≤ 1. These include antidiarrheals [a] Obtain stool culture for infectious workup [b] Infections (e.g. Clostridium dificile, enteric bacteria, CMV) should be treated with the appropriate antibiotic For persistent Grade 2 non-infectious diarrhea lasting longer than 48 hours despite treatment with antidiarrheals, treat with oral corticosteroids (20-40 mg prednisone QD starting dose with taper) or budesonide 9mg PO QD. If Grade 2 diarrhea does not improve after 48 hours of corticosteroid treatment, a colonoscopy is recommended to evaluate for other causes of diarrhea (e.g., CMV colitis)	Hold GDC-0032 (taselisib) and follow guidelines below: If Grade 2 diarrhea occurred before Cycle 2, did not require corticosteroid treatment, and was an initial episode, resume GDC-0032 (taselisib) treatment at the same dose upon improvement to Grade ≤ 1. If Grade 2 diarrhea occurred after Cycle 2, was a recurrent episode, or improved with corticosteroid treatment, resume GDC-0032 (taselisib) treatment at one dose level lower upon improvement to Grade ≤ 1 and after completion of corticosteroid treatment. For Grade 2 colitis, resume GDC-0032 (taselisib) treatment at one dose level lower upon improvement to Grade ≤ 1 and after completion of corticosteroid treatment.
Grade 3 (first episode)	Initially manage with antidiarrheals [a]. Obtain stool culture for infectious workup [b]. For Grade 3 diarrhea or colitis, treat with systemic corticosteroids (prednisone 60-80 mg QD equivalent or solumedrol 16-20 mg IV q 8 h to start). Can increase steroid dosage if diarrhea does not improve. Concurrent infections (e.g., Clostridium dificile, enteric bacteria, CMV) should be treated with the appropriate antibiotic. For patients that do not improve upon 48 hours of corticosteroid treatment, a colonoscopy is recommended to evaluate for other causes of diarrhea (e.g. CMV colitis)	Hold GDC-0032 (taselisib). If diarrhea or colitis improves to Grade ≤ 1 and upon completion of any steroid taper or antibiotic treatment, resume GDC-0032 (taselisib) treatment at one dose level lower.
Grade 3 (recurrent) or Grade 4	Work-up and treatment algorithm as for Grade 3 (first episode).	Permanently discontinue GDC-0032 (taselisib)

a Suggested antidiarrheals include the following: 1) loperamide (initial: 4 mg, followed by 2 mg after each lose stool, up to 16 mg/day); 2) diphenoxylate and atropine (diphenoxylate 5 mg, four times daily [QID], until control achieved (maximum: 20 mg/day), then reduce dose as needed; some patients may be controlled on doses of 5 mg/day; 3) tincture of opium (6 mg of undiluted opium tincture (10 mg/mL) QID.

b Non-infectious diarrhea can be diagnosed by stool culture with work-up for various enteric bacteria and C. difficile. Fecal calprotectin is a possible marker for bowel inflammation. Blood-based CMV PCR test can also be used to detect CMV infection.

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 6). 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 6: Dose Delay and Modification Guidelines for Stomatitis and Oral Mucositis

Grade of Stomatitis/Mucositis	Intervention	Dose Adjustment
Grade 1	Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) Diet management (e.g., avoidance of spicy foods)	Consider holding Taselisib until resolution before restarting at same dose.
Grade 2	Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) Diet management (e.g., avoidance of spicy foods)	Hold Taselisib and manage until Grade $\leq$ 1 then restart Taselisib at the same dose. If Grade 2 stomatitis/oral mucositis recurs, hold Taselisib until Grade $\leq$ 1 and restart Taselisib at the next lower dose.
Grade 3 or 4	Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) Diet management (e.g., avoidance of spicy foods)	Hold Taselisib and manage until Grade $\leq$ 1 then restart Taselisib at the next lower dose. For Grade 4 event, consider permanent discontinuation of Taselisib.

3.5 Supportive Care

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

3.6 Duration of Agent-specific treatment

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

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

3.7 Duration of Follow-Up

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

4. Study Parameters

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4.1 Therapeutic Parameters for GDC-0032 (taselisib) Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving GDC-0032 (taselisib) treatment.

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

Test/Assessment	Prior to Registration to Treatment	Treatment			End of Treatment	Follow Up[F]
		Every Cycle, prior to treatment	Cycle 1, Day 15	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X	X[J]				X
Performance status	X	X[J]				X
CBC w/diff, plts[B]	X	X[J]				X
Serum chemistry[B]	X	X[J]				X
Fasting blood glucose	X	X[J]	X[L]			
Radiologic evaluation[D]	X			X[D]		X[F]
β-HCG[C]	X					
Toxicity Assessment[G]		X			X	X[F]
Pill Count/Diary[H]		X			X	
ECG[K]	X	X[I]				
Tumor biopsy and blood sample for MATCH Master Protocol[E]				X	X	

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

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B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). CBC w/diff, platelets and serum chemistries should be performed fasting on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

C. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment.

D. Disease measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks

before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

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

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

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

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

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

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

I. As clinically indicated.

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

K. Within 8 weeks of treatment assignment.

L. Fasting glucose can be drawn day 15 ± 3 days and can be drawn at a local lab.

NOTE: Please provide clear documentation that the glucose test was conducted at a fasting state.

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5. Drug Formulation and Procurement

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

Availability

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

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

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

NCI Supplied Agent(s) – General Information

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

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

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

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

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5.1 GDC-0032 (NSC #778795)

5.1.1 Other Names

Taselisib, RG7606

5.1.2 Classification

PI3K inhibitor

5.1.3 Mode of Action

Inhibition of PI3K pathway components such as Akt, PRAS40, and S6, resulting in G1 arrest and apoptosis.

5.1.4 Storage and Stability

Storage: GDC-0032 tablets should not be stored above 25ºC.

Stability: Shelf-life surveillance of the intact bottles is ongoing.

If a storage temperature excursion is identified, promptly return GDC-0032 (taselisib) to ambient temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

5.1.5 Dose Specifics

Two 2-mg GDC-0032 tablets will be administered orally once a day on a continuous daily dosing schedule.

5.1.6 How Supplied

Genentech supplies and PMB, CTEP, DCTD distributes GDC-0032 as white, film-coated, immediate-release 2 mg tablets. The tablet formulation consists of GDC-0032 active, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and Opadry 2 white film-coating. The film-coating consists of polyvinyl alcohol-part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc. Each bottle contains 30 film-coated tablets.

5.1.7 Route of Administration

GDC-0032 is taken orally, and may be taken with or without food.

5.1.8 Method of Administration

GDC-0032 may be taken with or without food.

5.1.9 Incompatibilities

GDC-0032 is metabolized via CYP3A4/5. GDC-0032 should not be administered with strong CYP3A4/5 inhibitors/inducers and administered with caution when combined with moderate CYP3A4/5 inhibitors/inducers. No drug-drug interactions were observed in cancer patients with the following CYP3A4 substrates: midazolam, letrozole, or fulvestrant. Grapefruit and grapefruit juice should be avoided due to the risk of increased GDC-0032 exposure.

Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

In vitro studies showed that taselisib was a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In vitro testing also found GDC-0032 to be an inhibitor of OATP1B1, OATP1B3, OCT1, OCT2 and OAT3. GDC-0032 was also found to not be a potent inhibitor of CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 or transporters P-gp, BCRP or OAT1.

5.1.10 Side Effects

See Section 3.3 for side effects.

5.1.11 Nursing/Patient Implications

- Hyperglycemia (Grades 1-4) was reported in approximately 32% of the patients who received GDC-0032 as a single agent. Patients with diabetes mellitus requiring insulin therapy should be excluded from studies of GDC-0032. Glucose levels should be carefully monitored at baseline and during study per individual protocol guidelines. Patients should be instructed to report symptoms associated with hyperglycemia, such as thirst, frequent urination, and blurred vision. Anti-hyperglycemic agents should be used to control severe hyperglycemia per institutional standard of care.
- Non-infectious pneumonitis has been observed in patients treated with GDC-0032 QD, with onset at approximately Day 66-167 days post dosing. Patients who require any daily supplemental oxygen should not be recruited for the study.
- Reproductive Risks:
  - Women of child bearing potential and male patients should continue contraceptive measures for 4 months after the last dose of GDC-0032.

6. Translational Studies

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

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Rev. 12/16
Rev. 3/17

Appendix I

Patient Pill Calendar

Storage: Store at Room Temperature

Pill Calendar Directions

1. Take your scheduled dose of two 2-mg tablets, which will be administered orally once a day, at approximately the same time each day.
2. If you forget to take your dose at the scheduled time, you may take it within 6 hours after the usual time. If the dose is not taken within 6 hours of the usual time, the missed tablets will not be taken later. Instead, resume your dose the next day.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
4. Tablets will be taken once a day, at approximately the same time each day, with a full glass of water, with or without food.
5. Swallow tablets whole, do not crush or chew tablets.

Patient Pill Calendar

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

GDC-0032 (taselisib)

DAY	Date Month	Day	Year	Time tablets taken	Number of tablets taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
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25						
26						
27						
28						

Patient Signature: _____ Date: _____

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Appendix II

Rev. 5/16
Rev. Add13

Actionable Mutations for Sub-Protocol EAY131-I

Rev. 12/16 A. Inclusion variants

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
PIK3CA	COSM746	SNV	2	p.R88Q
PIK3CA	COSM754	SNV	2	p.N345K
PIK3CA	COSM757	SNV	3	p.C420R
PIK3CA	COSM759	SNV	3	p.P539R
PIK3CA	COSM760	SNV	3	p.E542K
PIK3CA	COSM763	SNV	3	p.E545K
PIK3CA	COSM764	SNV	3	p.E545G
PIK3CA	COSM765	SNV	2	p.E545D
PIK3CA	COSM767	SNV	3	p.Q546P
PIK3CA	COSM775	SNV	2	p.H1047R
PIK3CA	COSM776	SNV	3	p.H1047L
PIK3CA	COSM12458	SNV	3	p.E545A
PIK3CA	COSM766	SNV	3	p.Q546K
PIK3CA	COSM12590	SNV	3	p.T1025S
PIK3CA	COSM12591	SNV	3	p.M1043V
PIK3CA	COSM29313	SNV	3	p.M1043I
PIK3CA	COSM94984	SNV	3	p.M1043I
PIK3CA	COSM773	SNV	3	p.M1043I
PIK3CA	COSM774	SNV	3	p.H1047Y
PIK3CA	COSM27493	SNV	3	p.R93W
PIK3CA	COSM748	SNV	3	p.G106V
PIK3CA	COSM13570	SNV	3	p.K111E
PIK3CA	COSM751	SNV	3	p.G118D
PIK3CA	COSM94978	SNV	3	p.N345I
PIK3CA	COSM762	SNV	3	p.E542V
PIK3CA	COSM6147	SNV	3	p.Q546E
PIK3CA	COSM12459	SNV	3	p.Q546R
PIK3CA	COSM27504	SNV	3	p.N1044K

PIK3CA	COSM12592	SNV	3	p.N1044K
PIK3CA	COSM12597	SNV	3	p.G1049R
PIK3CA	COSM12584	SNV	3	p.E453K
PIK3CA	COSM27133	SNV	3	p.E545Q
PIK3CA	COSM27505	SNV	3	p.K111N
PIK3CA	COSM12580	SNV	3	p.K111N

B. Exclusion variants

MATCHBOX also was implemented with a function to identify any deleterious mutations in PTEN as exclusion variants (LOE code = 3).

Patients with negative PTEN IHC staining are not eligible (LOE code = 3).

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
PTEN	COSM86058	SNV	3	p.A34D
PTEN	COSM5223	SNV	3	p.M35R
PTEN	COSM5135	SNV	3	p.G36R
PTEN	OM1539	SNV	3	p.N48K
PTEN	MCH13	SNV	3	p.H61D
PTEN	MCH14	SNV	3	p.Y68D
PTEN	COSM5264	SNV	3	p.D92A
PTEN	COSM35759	SNV	3	p.D92E
PTEN	COSM125653	SNV	3	p.D92E
PTEN	COSM5099	SNV	3	p.D92G
PTEN	COSM23566	SNV	3	p.D92H
PTEN	COSM5236	SNV	3	p.D92V
PTEN	COSM5283	SNV	3	p.H93D
PTEN	COSM5043	SNV	3	p.H93Y
PTEN	COSM5265	SNV	3	p.P96Q
PTEN	COSM5273	SNV	3	p.A121E
PTEN	COSM5234	SNV	3	p.I122S
PTEN	COSM921088	SNV	3	p.H123D
PTEN	COSM5082	SNV	3	p.K125E
PTEN	COSM5041	SNV	3	p.A126V
PTEN	COSM5143	SNV	3	p.G127E
PTEN	COSM28917	SNV	3	p.G129E
PTEN	COSM5276	SNV	3	p.G129V
PTEN	COSM246853	SNV	3	p.G129R
PTEN	COSM5104	SNV	3	p.T131I
PTEN	COSM5144	SNV	3	p.Y155C
PTEN	COSM5114	SNV	3	p.G165E
PTEN	COSM249877	SNV	3	p.G165V

PTEN	MCH20	SNV	3	p.S170R
PTEN	MCH17	SNV	3	p.L181P
PTEN	MCH18	SNV	3	p.V343E
PTEN	COSM5133	SNV	3	p.Y16C
PTEN	COSM5247	SNV	3	p.Y27S
PTEN	COSM5042	SNV	3	p.H61R
PTEN	COSM5036	SNV	3	p.Y68H
PTEN	COSM5102	SNV	3	p.C71Y
PTEN	COSM5266	SNV	3	p.C105F
PTEN	COSM5212	SNV	3	p.D107Y
PTEN	COSM5106	SNV	3	p.L112P
PTEN	MCH15	SNV	3	p.L112R
PTEN	COSM5214	SNV	3	p.A121P
PTEN	COSM921089	SNV	3	p.C124R
PTEN	COSM5224	SNV	3	p.C124S
PTEN	COSM5219	SNV	3	p.R130G
PTEN	COSM5033	SNV	3	p.R130Q
PTEN	COSM5216	SNV	3	p.R130L
PTEN	COSM5044	SNV	3	p.V133I
PTEN	COSM12734	SNV	3	p.C136Y
PTEN	COSM5091	SNV	3	p.G165R
PTEN	COSM5045	SNV	3	p.S170N
PTEN	COSM5089	SNV	3	p.R173C
PTEN	COSM5039	SNV	3	p.R173H
PTEN	MCH16	SNV	3	p.R173P
PTEN	COSM5221	SNV	3	p.Y174N
PTEN	COSM5220	SNV	3	p.G251C
PTEN	COSM5255	SNV	3	p.F341V
PTEN	COSM5213	SNV	3	p.L345Q
PTEN	MCH21	SNV	3	p.S170R
PTEN	MCH22	SNV	3	p.S170R
KRAS	COSM555	SNV	2	p.Q61H
KRAS	COSM554	SNV	2	p.Q61H
KRAS	COSM553	SNV	2	p.Q61L
KRAS	COSM552	SNV	2	p.Q61R
KRAS	COSM551	SNV	2	p.Q61P
KRAS	COSM550	SNV	2	p.Q61E
KRAS	COSM549	SNV	2	p.Q61K
KRAS	COSM539	SNV	2	p.G15D
KRAS	COSM538	SNV	2	p.G15S
KRAS	COSM30567	SNV	2	p.G13E
KRAS	COSM87280	SNV	2	p.G13E
KRAS	COSM534	SNV	2	p.G13V
KRAS	COSM533	SNV	2	p.G13A

KRAS	COSM532	SNV	2	p.G13D
KRAS	COSM527	SNV	2	p.G13C
KRAS	COSM529	SNV	2	p.G13R
KRAS	COSM528	SNV	2	p.G13S
KRAS	COSM512	SNV	2	p.G12F
KRAS	COSM514	SNV	2	p.G12L
KRAS	COSM13643	SNV	2	p.G12N
KRAS	COSM520	SNV	2	p.G12V
KRAS	COSM522	SNV	2	p.G12A
KRAS	COSM521	SNV	2	p.G12D
KRAS	COSM516	SNV	2	p.G12C
KRAS	COSM518	SNV	2	p.G12R
KRAS	COSM517	SNV	2	p.G12S
KRAS	COSM19404	SNV	3	p. A146T

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol I: GDC-0032 (taselisib)

Appendix III

Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **GDC-0032 (taselisib)**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

GDC-0032 (taselisib) interacts with a certain specific enzymesenzyme in your liver* and certain transport proteins that help move drugs in and out of cells.**

- * The enzyme in question is **CYP3A4.** GDC-0032 (taselisib) is metabolized by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.
- **The proteins in question are P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). GDC-0032 (taselisib) is a substrate of these transporters and is moved in and out of cells/organs by these transport proteins. GDC-0032 (taselisib) is an inhibitor of OAT1B1, OAT1B3, OCT1, OCT2, and OAT3 and may affect transport of other drugs in and out of cells.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

GDC-0032 (taselisib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

GDC-0032 (taselisib) must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A4, P-gp or BCRP.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Do not drink or eat grapefruit, grapefruit /juice andor Seville oranges

- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
- Your study doctor's name is

  _____ and he or she can be contacted at

  _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **GDC-0032 (taselisib)**. This clinical trial is sponsored by the NCI. **GDC-0032 (taselisib)** may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Do not drink or eat grapefruit/juice or Seville oranges.

GDC-0032 (taselisib) interacts with a specific liver enzyme called CYP3A4/5, transport proteins P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2 and OAT3and must be used very carefully with other medicines that interact with these enzymes and transporters.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A4/5 or transporters P-gp and BCRP. GDC-0032 (taselisib) can inhibit transporters OATP1B1, OATP1B3, OCT1, OCT2 and OAT3 that may affect other drugs.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is

  _____ and can be contacted at

  _____.