February 6, 2017

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 #7 to EAY131-P, *Molecular Analysis for Therapy Choice (MATCH): MATCH Treatment Subprotocol P: Phase II Study of PI3K Beta Specific Inhibitor, GSK2636771, in Patients with Tumors with PTEN Loss by IHC.*

Please note, the following revisions to this subprotocol were not originally included in the submission of MATCH Addendum #7, which has since been reviewed by CTEP and the CIRB. Per discussions with PIO, changes to this subprotocol are now incorporated along with the resubmission of Addendum #7 to the CIRB. For any questions related to this submission plan, please contact Martha Kruhm at PIO and/or Amanda Putnick at the CIRB.

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

	Section	**Change**
1.	Cover Page	Updated Version Date and added "Addendum #7" to the activation date list
2.	4.1	Footnote E: Updated language for additional specimen collection parameters under the Master Protocol. Table updated with additional optional blood submission time point.
3.	5	Inserted "Investigator Brochure Availability" subsection, per CTEP request, for consistency across subprotocols.
4.	Appendix I	Added additional instructions to pill calendar directions for clarity.
5.	Addendum II	Removed duplicate variant in aMOI list (COSM180789)
6.	Addendum III	Updated "Patient Drug Information Handout and Wallet Card" appendix with new language provided by CTEP

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

	Section	**Change**
1.	Page 1	Updated Version Date
2.	"What are the study groups?"	Added additional dosing instructions for consistency with the subprotocol.
3.	"What are the study groups?"	The term "medication diary" has been replaced with the term "patient pill calendar" for consistency with the subprotocol.

4.	"What possible risks…?	Updated contraception use from "continuing for up to 16 weeks" to "continuing for 16 weeks" as contraception is required for all 16 weeks after treatment.
5.	Study Calendar	The term "medication diary" has been replaced with the term "patient pill calendar" throughout for consistency with the subprotocol.

If you have any questions regarding this addendum, please contact zhang.jeffrey@jimmy.harvard.edu or 857-504-2900.

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

Thank you.

Sincerely,

Pamela Cogliano

Director of Protocol Development

Enclosure

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

EAY131-P

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol P: Phase II Study of PI3K Beta Specific Inhibitor, GSK2636771, in Patients with Tumors with PTEN Loss by IHC

GSK2636771 TREATMENT SUBPROTOCOL CHAIR: Filip Janku, MD, PhD

GSK2636771 TREATMENT SUBPROTOCOL CO-CHAIR: Shannon Puhalla, MD

GSK2636771 TRANSLATIONAL CHAIR: Panagiotis Konstantinopoulos, MD, PhD

Version Date: February 6, 2017

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

SUBPROTOCOL ACTIVATION DATE

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

Agent	IND#	NSC#	Supply
GSK2636771			NCI Supplied

Table of Contents

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Schema

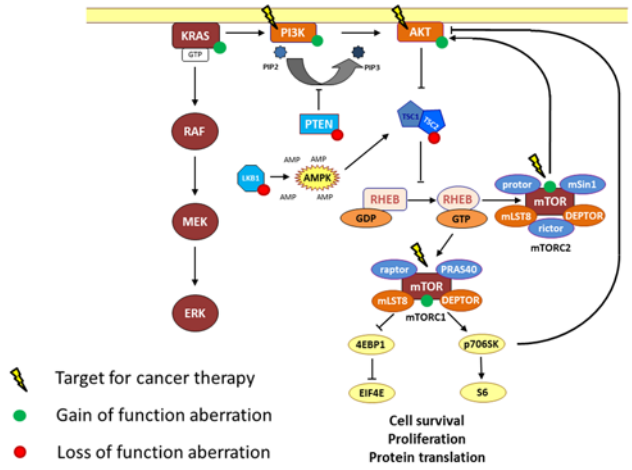
Cycle = 28 days
Accrual Goal: 35

1. Introduction

1.1 Background

The mechanisms underlying cancer are marked by complex aberrations that activate critical cellular signaling pathways in tumorigenesis. Identifying actionable molecular aberrations has been critical to several major therapeutic advances in cancer medicine. Examples include *BCR-ABL* fusion in chronic myeloid leukemia (CML), epidermal growth factor (*EGFR*) mutations and *EML4-ALK* fusion in non-small cell lung cancer, and *BRAF* mutations in melanoma.[1-4] The phosphatidylinositol 3-kinase/protein kinase-B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling cascade is one of the most important intracellular pathways, which is frequently activated in diverse cancers (Figure 1).[5,6] PI3K/AKT/mTOR signaling regulates cell proliferation, differentiation, cellular metabolism, and cytoskeletal reorganization leading to apoptosis and cancer cell survival. Activation of the PI3K/AKT/mTOR signaling pathway mediated through molecular aberrations such as loss of PTEN function is instrumental in promoting tumor development as well as resistance to anticancer therapies.[7,8] Preclinical models and early clinical data in several tumor types suggested that loss of PTEN function can result in increased sensitivity to therapies targeting the PI3K/AKT/mTOR signaling pathway.[5,9,10] It is conceivable that loss of PTEN function, which is a major negative regulator of the pathway, can be predictive, whereas simultaneous mutations in the mitogen-activated protein kinase (MAPK) or PI3K pathways may lead to therapeutic resistance.[5,8,11-13, 27-29]

Figure 1



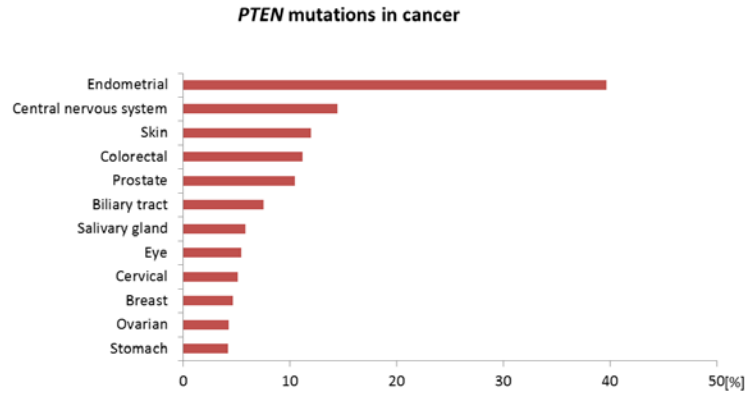
Polivka J, Janku F. Pharmacol Ther. 2014 May;142(2):164-75.

The tumor suppressor gene *PTEN* (also known as *MMAC*, mutated in multiple advanced cancers) was initially observed independently by two groups in 1997 on the 10q23 chromosomal region of *PTEN*, which was known to be deleted in many advanced cancers.[14,15] PTEN is a lipid phosphatase that catalyzes the conversion of the second messenger PIP3 to PIP2 and thus reverses PI3K functionality in signal propagation (Figure 1).[16] Moreover, it is now well established that PTEN has serine, threonine, and tyrosine phosphatase activity for several protein substrates, resulting in its complex functions in cellular

signaling.[17] PTEN protein consists of 403 amino acids divided into functional domains, the N-terminal PIP2-binding domain (PBD), phosphatase domain, C2 domain and C-terminal tail with two PEST (proline, glutamic acid, serine, threonine) domains, and a sequence governing protein-protein interactions (PDZ).[18] These different PTEN domains are relevant to its tumor suppressor function due to the large diversity of tumor-associated mutations observed across all of its domains.[19] The loss of PTEN function can be caused by various mechanisms including mutations, deletions, transcriptional silencing and epigenetic changes.[20] Transcriptional repression and epigenetic silencing of *PTEN* typically occurs via gene promoter hypermethylation.[21,22]

Mutations as well as loss of *PTEN* are found in various tumor types. The TCGA studies identified *PTEN* mutations in 63% of endometrial cancers, 30% of glioblastomas, 8% of cervical cancers, 7% of skin cancers as well as in other tumor types (cBioPortal for Cancer Genomics). The COSMIC database identified *PTEN* mutations in 39% of endometrial cancers, 14% of central nervous system tumors, 12% of skin cancers, 11% of colorectal cancers, 10% of prostate cancers, 5% of cervical cancers as well as in other tumor types (Figure 2) (COSMIC [Catalogue of Somatic Mutations in Cancer]). The complete loss of *PTEN* was also observed in a high number of cases of uterine (33%), renal (27%), salivary gland (20%), colorectal (18%), breast (13%), pancreatobiliary (13%) and prostate cancers (11%).[23] Because of the numerous mechanisms underlying *PTEN* inactivation on genetic and epigenetic levels, accurate assessment of *PTEN* status in individual tumor samples remains challenging.

Figure 2



Polivka J, Janku F. Pharmacol Ther. 2014 May;142(2):164-75.

Preclinical models demonstrated that *PTEN* function is an important regulator of G protein-coupled receptor signaling transmitted through *PIK3CB*. *PTEN*-deficient tumors are critically dependent on *PIK3CB* activity and tumors with *PIK3CB* activation are sensitive to *PIK3CB* inhibitors.[10,24] Notably, breast cancer cell lines with *PTEN* loss compared to those with *PIK3CA* mutations demonstrated resistance to treatment with mTOR complex 1 (mTORC1) targeted therapy.[9] A complete loss of PTEN expression was found in 10% of heavily pretreated patients with diverse advanced solid tumors, and 23% of them experienced a partial response or stable disease greater than or equal to 6 months when treated with a PI3K/AKT/mTOR axis inhibitors.[23] These findings

suggest that matching patients with inhibitors based on PTEN aberrations merits further exploration.[5]

GSK2636771 is a potent and selective inhibitor of phosphoinositide 3-kinase (PI3K) beta, which demonstrated activity in preclinical models with a loss of PTEN function.[25] In addition, the first-in-human dose escalation study has been completed.[25] Because PTEN function could be lost in various ways as noted above, MATCH will examine patients with complete PTEN loss of expression (by IHC) as well as those who retain PTEN expression by IHC but have a PTEN mutation or deletion by NGS. In the context of the NCI MATCH protocol, this is a phase II open label study for patients with PTEN deficient tumor (complete loss of staining on IHC with or without PTEN mutation or deletion). A separate MATCH subprotocol (EAY131-N) will investigate PTEN mutations without loss of IHC expression of PTEN.

1.2 GSK2636771

1.2.1 Non-clinical and clinical data

GSK2636771 has been assessed in primary and secondary pharmacodynamic studies, as well as safety, pharmacology and toxicology studies. A summary of the available relevant non-clinical data is provided below. Study details and additional information can be found in the Investigator Brochure.

1.2.2 Non-clinical pharmacology

GSK2636771 is a potent and selective inhibitor of phosphoinositide 3-kinase (PI3K) beta with an apparent Ki (Kiapp) value of 0.89 nM with selectivity > 900-fold over PI3K alpha and gamma with Kiapp values of 819 and > 5000 nM, respectively, and 10-fold over PI3K delta (Kiapp of 8.6 nM). Among the other members of the PI3K superfamily tested, GSK2636771 was not inhibitory at concentrations > 10uM and demonstrated less than 30% inhibition against 294 additional kinases. GSK2636771 is an ATP competitive inhibitor of PI3K beta that is rapidly reversible and not time dependent and has a similar potency (within 2-fold) against three PI3K beta orthologs; mouse, rat and dog as compared to human PI3K beta.

In phosphatase and tensin homolog (PTEN) mutant cell lines, but not wild-type PTEN lines, GSK2636771 inhibited cellular AKT phosphorylation in a concentration dependent manner. In the cell lines evaluated, the inhibition of AKT phosphorylation resulted in the inhibition of downstream PI3K/AKT signalling molecules in PTEN deficient, but not PTEN wild-type cell lines. GSK2636771 inhibited the anchorage independent cell growth of 87% of PTEN null tumor cell lines (13 out of 15 cell lines) but only 14% of PTEN wild-type (1 out of 7).

In mice bearing PC3 prostate carcinoma xenografts, single oral daily doses of GSK2636771 at 10, 30 and 100 mg/kg for 21 days resulted in stable disease with minimal tumor growth delay at 1 and 3 mg/kg. In mice bearing PC3 prostate carcinoma or HCC70 breast carcinoma xenografts, oral doses of 3 or 10 mg/kg (PC-3) or 10 or 30 mg/kg (HCC70) GSK2636771 inhibited AKT phosphorylation in both tumor

types (by up to 80%), in a dose-dependent manner. Inhibition of AKT phosphorylation was rapid and lasted for several hours after a single oral administration. In naïve mice, single oral daily doses of 100 mg/kg GSK2636771 for four consecutive days did not affect fasting blood glucose and insulin levels. GSK2636771 showed significant anti-tumor activities in a PDX model of gastric cancer when administered alone or in combination with trametinib (GSK1120212, a potent and selective MEK inhibitor). In a combined cardiovascular, respiratory and neurobehavioral study in dogs, a single oral dose of 300 mg/kg produced a reversible increase in mean arterial pressure (up to 11 mm Hg; up to 10%) from 2 to 8 hours post dose with a compensatory decrease in heart rate (up to 11 bpm; up to 12%) and decrease in cardiac contractility (up to 4.1% increase QA interval) during the same time period. The decrease in heart rate appears to be a baroreceptor-mediated reflex response to the increased arterial blood pressure, while the decrease in the measure of contractility may be attributed to the decrease in heart rate and a baroreceptor-mediated change in autonomic nervous input into the heart. Doses of 5 or 100 mg/kg did not produce any effect on arterial pressures or heart rate, and repeat doses up to 1000 mg/kg/day for 1 month did not produce any adverse effects on electrocardiogram (ECG) measurements. GSK2636771 did not produce acute neurobehavioral or respiratory effects in dogs following single doses up to 300 mg/kg. GSK2636771 minimally inhibited hERG tail current at the limit of solubility (20% inhibition at 70 ug/mL; 161 uM). In a rabbit left ventricular wedge assay, GSK2636771 exerted no torsadogenic potential up to the maximum concentration tested (13 ug/mL; 30 uM). Based on the weak hERG inhibition, absence of in vitro and in vivo effects on QTc and the high plasma protein binding in humans (99%), risk for QTc prolongation in humans is predicted to be low.

1.2.3 Non-clinical pharmacokinetics

The pharmacokinetics and metabolism of GSK2636771 have been evaluated both in vitro and in vivo in several preclinical species. GSK2636771 exhibited moderate blood clearance in the mouse and rat (32 and 47% liver blood flow, respectively), but low in the dog and monkey (9 and 2% liver blood flow, respectively). The steady state volume of distribution (Vdss) was approximately three to four times larger than total body water in rats and mice, suggesting the potential for tissue distribution. However, in dogs and monkeys, the Vdss was equivalent to, or less than total body water. The half-life (t1/2) ranged from 1.37 to 5.88 hours. The oral bioavailability of GSK2636771 was high (≥ 94%). Protein binding was species dependent with the highest free fraction in mouse (35%) and the lowest free fraction in human (1.3%). GSK2636771 has high passive membrane permeability and was not a substrate for P-glycoprotein (Pgp). GSK2636771 appeared to minimally distribute to the brain in the rat (brain concentration was 7% of blood concentration following a 1 hour intravenous infusion of 2 mg/kg).

GSK2363771 had low intrinsic clearance in hepatic microsomes and hepatocytes of all species evaluated (i.e. rat, dog and human). In vitro

and in vivo (rat), acyl glucuronidation was the major metabolic route for GSK2636771. However, GSK2636771 was the only detected component in rat blood. The major route of elimination in the rat was via the feces. The absorbed dose was eliminated primarily in the bile (the acyl glucuronide metabolite was the major component). GSK2636771 did not inhibit the major drug metabolizing cytochrome P450 (CYP450) enzymes including CYP3A4, and was not a time or metabolism dependent inhibitor of CYP3A4. GSK2636771 did not inhibit the drug transporters Pgp, breast cancer resistance protein (BCRP), organic anion transport polypeptide (OATP) 1B1 or OATP1B3. Therefore, the risk of GSK2636771 functioning as a perpetrator of drug interactions appears low.

1.2.4 Non-clinical toxicology and safety pharmacology

The systemic toxicity of GSK2636771 has been evaluated in rats and dogs. Genotoxicity studies have also been conducted. The principal dose-limiting toxicities seen in animal toxicology studies conducted with GSK2636771 were kidney and gastrointestinal effects. There was a dose dependent increase in kidney tubular basophilia at ≥100 mg/kg/day in rats with single cell and/or tubular necrosis in rats at 1000 mg/kg/day and tubular degeneration/regeneration in dogs at 1000 mg/kg/day. In rats, these findings correlated with increased mean kidney weights, decreased serum potassium, and increased mean serum urea. Urinary markers of kidney injury increased in rats and included KM1C, lipocalin-2, clusterin, RPAC at ≥100 mg/kg/day and urinary albumin, total protein, NAG, osteopontin, and alpha GST at 1000 mg/kg/day. Decreased body weight gain and food consumption and focal erosion and ulceration occurred in rat stomachs at 1000 mg/kg/day. The increased WBC counts in female rats at 1000 mg/kg/day is likely related to inflammation due to the kidney and gastrointestinal lesions. Increased heart weight and intramural coronary artery hypertrophy without ECG effects were observed in 1 male dog given 1000 mg/kg/day. A single dose of 300 mg/kg produced a reversible increase in mean arterial pressure, decreased heart rate and decreased cardiac contractility. Additional adverse findings in animals given 1000 mg/kg/day were present in liver, stomach, hematopoietic and reproductive systems. In dogs, there was minimal to mild single cell hepatocellular necrosis with increased serum ALT, GLDH and AST. Lymphoid necrosis occurred in spleen, lymph nodes, and GALT of dogs, and rats had decreased thymus weights. Spermatocyte depletion was observed in rats (also at 100 mg/kg/day) and dogs. In general, these findings were consistent with the expression and function of PI3 kinase. Based on the weak hERG inhibition, absence of in vitro and in vivo effects on QTc and the high plasma protein binding in humans (99%), the risk for QTc prolongation in humans is predicted to be low. In addition, GSK2636771 has a low genotoxic risk to humans. The kidney, gastrointestinal and liver effects are clinically monitorable and manageable, and generally recovered within 2 weeks off-treatment. In the 4 week rat study, the no observed adverse effect level (NOAEL) was 10 mg/kg/day [gender averaged AUC0-t 7.08 ug.h/mL, Cmax 1.83 ug/mL, Day 28 values]. The NOAEL in the 4 week dog study was

100 mg/kg/day [gender averaged AUC0-t 225 ug.h/mL, Cmax 38.8 ug/mL, Day 28 values].

1.3 Supporting Preliminary Data

1.3.1 Clinical Data

To date, the administration of GSK2636771 has been limited to 53 subjects with PTEN deficient tumors as determined by immunohistochemistry (IHC) analysis who were enrolled in the FIM study P3B115717.[25] The dose escalation part of the study has completed, and is now in an expansion phase enrolling patients with several tumor types with PTEN deficiency. Doses of GSK2636771 evaluated have ranged from 25 mg to 500 mg once daily. The maximum tolerated dose (MTD) has been defined as 400 mg orally once daily.

1.3.2 Safety

Dose limiting toxicities (DLTs) observed were hypophosphatemia and hypocalcemia. Dose-limiting toxicity (DLT) of hypophosphatemia was identified at 500 mg daily dose level, occurring in 3 of 4 subjects, and resulting in dose reductions and or discontinuations. Hypophosphatemia improved upon discontinuation of GSK2636771. The mechanism(s) of hypophosphatemia is under investigation. The most frequent adverse events (AEs) with GSK2636771 were Grade 1 or Grade 2 gastrointestinal (GI) toxicities, with the most frequently reported AEs being diarrhea (43%), nausea (43%), fatigue (28%), vomiting (34%), abdominal pain (26%), decreased appetite (23%), anemia (23%), constipation (19%), headache (17%), hypokalemia (15%), Rash (15%), cough (13%), dyspnea (11%), edema peripheral (13%), hypocalcemia (13%), hypophosphatemia (11%), and urinary tract infection (13%).

1.3.3 Pharmacokinetics

Preliminary pharmacokinetics (PK) results from study P3B115717 indicate that GSK2636771 is absorbed orally with a median time to achieve the peak blood concentration (tmax) of 4 to 5 hrs after single doses of 25 to 500 mg. The median half-life of GSK2636771 ranged from 17.1 to 38.6 hrs across the dose range of 25 mg to 500 mg once daily. Mean maximum observed concentration (Cmax) and area under the concentration-time curve from zero (pre-dose) to 24 hrs (AUC(0-24)) values on Day 22 were greater than the mean values observed after a single dose, demonstrating that GSK2636771 accumulated in plasma after repeated doses.

1.3.4 Efficacy

There are limited data available to assess the clinical activity of GSK2636771. In the FTIH study P3B115717 in patients with PTEN loss as determined by IHC, one subject with mCRPC who received 200 mg GSK2636771 once daily had a partial response (PR) per RECIST. There were 16 subjects (with various solid tumors) with stable disease and 8 subjects (with various solid tumors) who continued treatment for at least 6 months.

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:

Patients must meet all of the following 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).

_____ 2.1.2 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: _____

_____ 2.1.3 Patients must not have known hypersensitivity to GSK2636771 or compounds of similar chemical or biologic composition.

_____ 2.1.4 Patients must have complete loss of cytoplasmic and nuclear PTEN staining on immunohistochemistry as determined by the MATCH PTEN IHC assay performed at MD Anderson. Patients can have any PTEN mutation or deletion status, but MUST have PTEN loss by IHC.

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_____ 2.1.5 Patients must not have tumors harboring co-existing aberrations activating the PI3K/MTOR and MAPK pathways, such as PIK3CA,

PIK3R1, BRAF, KRAS and AKT1, TSC1/2, mTOR, NF2, NRAS, HRAS, NF1 (See Appendix II for exclusion mutations and corresponding Levels of Evidence).

_____ 2.1.6 Patients must not have received prior treatment with agents targeting the PI3K beta, AKT, or mTOR:

2.1.6.1 This includes (but is not limited to):

i. mTOR inhibitors: temsirolimus, everolimus, ridaforolimus, sirolimus, salirasib, CC-223, INK128, DS-3078, CC-115, AZD-2014

ii. dual PI3K/mTOR inhibitors: BEZ235, XL-765, GDC 0980, PF-04691502, GSK 2126458, Quinacrine, PKI-587, P-P7170, LY3023414, GDC 0084, DS 7423, CBLC-137

iii. pan-PI3K inhibitors: BKM-120 (buparlisib), PX-866, XL-147, GDC-0941 (pictilisib), BAY-806946, ZSTK-474, WX 037, SRX5000, SRX2523, AMG511, PQR308, BAY 94-9343

iv. PI3K inhibitors with β isoform activity: prior GSK2636771 is not allowed, nor is GS-9820, PQR3XX, KAR4139

2.1.6.2 The following previous treatments are allowed:

i. BYL719 (PI3Kα inhibitor)

ii. GDC-0032 (PI3Kαinhibitor)

iii. INK1117 (PI3Kα inhibitor)

iv. Idelalisib (PI3Kδ inhibitor)

v. IPI-125 (PI3K γδ inhibitor)

vi. TGR1202 (PI3Kδ inhibitor)

vii. SRX2558 (PI3Kδ inhibitor)

viii. RP6530 (PI3K γδ inhibitor)

ix. PWT143 (PI3Kδ inhibitor)

x. IPI443 (PI3K γδ inhibitor)

xi. GNE293 (PI3Kδ inhibitor)

_____ 2.1.7 Patients with a history of interstitial lung disease or pneumonitis are excluded.

_____ 2.1.8 Patients must have hemoglobin ≥ 9 g/dL.

_____ 2.1.9 Patients must have a serum creatinine that is < 1.5 x ULN or have a 24-hour creatinine clearance of > 50 mL/min.

_____ 2.1.10 Patients must not have any congenital platelet function defects and cannot be on any of the following anti-platelet drugs: clopidogrel, ticlopidine, prasugrel, that act at platelet purinergic receptors.

2.1.10.1 Any need for starting anti-platelet therapy in a patient enrolled to this arm will have to be evaluated by the subprotocol chair.

Physician Signature Date

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

3. GSK2636771 Treatment Plan

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3.1 Administration Schedule

GSK2636771 will be administered on an oral, daily, continuous administration schedule. The starting dose of the drug will be 400mg (four 100 mg capsules), once daily, which was deemed the maximum tolerated phase II dose from the company sponsored phase I study.

Each cycle of therapy will be 28 days and there will not be any breaks between dosing cycles. Patients must meet the following criteria in order to proceed with the next cycle of treatment:

- ANC ≥ 1,000/μL
- Platelets ≥ 75,000/μL
- Hemoglobin ≥ 9 g/dL
- Phosphorous, magnesium, potassium, and calcium (corrected for albumin) must either be within normal range for labs or no worse than grade 2. Supplementations may be used to keep within these ranges.
- Serum creatinine must be ≤ 1.5 x ULN or 24-hour creatinine clearance of ≥ 50 mL/min.

Please refer to Section 3.4 for dose modifications. Within cycle toxicity that meets grade 3 or 4 criteria, will necessitate holding of the drug until the toxicity are improved to grade 1 or baseline, unless otherwise specified in the protocol.

Repeat cycles until progression.

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 EAY131 – Subprotocol P

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 P 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 GSK2636771 or within 28 days of the subject's last dose of GSK2636771, 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 P specific expedited reporting exceptions:

For Subprotocol P, 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.

3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for GSK2636771 (NSC 781258)

The Comprehensive Adverse Event 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 via CTEP-AERS (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. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for GSK2636771.

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 1.1, November 10, 2015[1]

Adverse Events with Possible Relationship to GSK2636771 (CTCAE 4.0 Term)	**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
GASTROINTESTINAL DISORDERS	
Abdominal pain	
Diarrhea	***Diarrhea (Gr 2)***
Nausea	***Nausea (Gr 2)***
Vomiting	***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue	***Fatigue (Gr 2)***
INVESTIGATIONS	
Aspartate aminotransferase increased	
Creatinine increased	
METABOLISM AND NUTRITION DISORDERS	
Anorexia	***Anorexia (Gr 2)***
Hypocalcemia	
Hypophosphatemia	
NERVOUS SYSTEM DISORDERS	
Dysgeusia	
Headache	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Pruritus	
Rash maculo-papular	***Rash maculo-papular (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.

Adverse events reported on GSK2636771 trials but for which there is insufficient evidence to suggest that there was a reasonable possibility that GSK2636771 caused the adverse event:

GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Mucositis oral; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever; General disorders and administration site conditions - Other (mucosal inflammation); Pain

INFECTIONS AND INFESTATIONS - Upper respiratory infection

INVESTIGATIONS - Alanine aminotransferase increased; GGT increased; Investigations - Other (N-terminal prohormone brain natriuretic peptide increased); Neutrophil count decreased

METABOLISM AND NUTRITION DISORDERS - Hypoalbuminemia; Hypokalemia; Hypomagnesemia

PSYCHIATRIC DISORDERS - Depression; Insomnia

RENAL AND URINARY DISORDERS - Proteinuria; Urinary retention

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Productive cough

VASCULAR DISORDERS - Hypertension

Animal Data: The following toxicities have been observed in animal studies with GSK2636771:

Dogs

HEPATOBILIARY DISORDERS - Single cell hepatocellular necrosis with perivascular mixed inflammatory cell infiltrate; pigmented macrophages and kupffer cells

IMMUNE SYSTEM DISORDERS - Lymphoid necrosis (spleen, lymph node, GALT)

INVESTIGATIONS - Increased glutamate dehydrogenase (GLDH)

RENAL AND URINARY DISORDERS - Tubular degeneration/regeneration

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Seminiferous tubular depletion

Rats

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

GASTROINTESTINAL DISORDERS - Focal erosions and/or erosion/ulcer and mucous cell hypertrophy in glandular region

IMMUNE SYSTEM DISORDERS - Decreased thymus weight

INVESTIGATIONS - Increased serum urea; weight loss

RENAL AND URINARY DISORDERS - Hyaline droplets in cortical proximal tubule; increased kidney weight; increased urinary biomarkers; inflammatory cell infiltrate in cortex; necrosis of cortical tubules; tubular basophilia

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Decreased testis weight; reddened ovarian cysts; spermatid retention; spermatocyte depletion

NOTE: GSK2636771 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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3.4 Dose Modifications

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).

GSK2636771 will be administered on an oral, daily, continuous administration schedule. The starting dose of the drug will be 400mg (four 100 mg capsules), once daily which was deemed the maximum tolerated phase II dose from the company sponsored phase I study.

Each cycle of therapy will be 28 days and there will not be any scheduled breaks between dosing cycles. Patients must meet the following criteria in order to proceed with the next cycle of treatment:

- ANC ≥ 1,000/μL
- Platelets ≥ 75,000/μL
- Hemoglobin ≥ 9 g/dL
- Phosphorous, magnesium, potassium, and calcium (corrected for albumin) must either be within normal range for labs or no worse than grade 2. Supplementations may be used to keep within these ranges.
- Serum creatinine must be ≤ 1.5 x ULN or 24-hour creatinine clearance of ≥ 50 mL/min.

At the beginning of a cycle, patients experiencing any toxicity that meets definition of grade 3 or 4 toxicity will have the study drug held until resolution of symptoms to grade 1 or baseline, unless otherwise specified in the protocol. Within cycle toxicity that meets grade 3 or 4 criteria, will necessitate holding of the drug until the toxicity are improved to grade 1 or baseline, unless otherwise specified in the protocol. In general, except as directed for specific examples in the following tables, if there is need to interrupt dosing for grade 3/4 toxicity, then there will be a dose reduction as per the table below, once toxicity improved to grade 1 or baseline. Dose may be suspended for up to 2 weeks due to toxicity. If treatment held for laboratory abnormality; recheck labs in one week. GSK2636771 will not be re-escalated once dose reduced.

For diarrhea, nausea and vomiting, optimal supportive care should be initiated prior to dose reduction. If symptoms persist despite maximal supportive care, or at investigator discretion, doses may be reduced per criteria below. Suspend GSK2636771 for grade 3 or 4 symptoms and hold until resolved to grade 1 or baseline, unless otherwise specified in the protocol.

Dose Reduction Table:

Dose levels and dose reductions:	GSK2636771 dose
Starting dose level	400 mg po daily
Dose level -1	300 mg po daily
Dose level -2	200 mg po daily

Renal Insufficiency/ Creatinine Increased:

Toxicity grade	Action	Dose modification	Subsequent occurrences
Grade 1	Continue with current dose	none	none
Grade 2	Hold until grade 1	Reduce one dose level	2nd occurrence: reduce additional dose level 3rd occurrence: discontinue GSK2636771
Grade 3	Hold until grade 1	Reduce one dose level	2nd occurrence: reduce additional dose level 3rd occurrence: discontinue GSK2636771
Grade 4	Hold until grade 1	Reduce two dose levels	2nd occurrence: discontinue GSK2636771

Neutropenia:

Toxicity grade	Action	Dose modification	Subsequent occurrences
Grade 1 or 2	None	Maintain current dose level	
Grade 3	Hold GSK2636771 until grade 2	None	Reduce one dose level
Grade 4	Hold GSK2636771 until grade 2	Reduce one dose level	Reduce one dose level

Thrombocytopenia:

Toxicity grade	Action	Dose Modification	Subsequent Occurrences
Grade 1	None	Maintain current dose level	None
Grade 2	Hold until grade 1	Maintain current dose level	Reduce one dose level
Grade 3	Hold until grade 1	Reduce one dose level	Reduce one dose level
Grade 4	Hold until grade 1	Reduce one dose level	Reduce one dose level

Liver Function Tests (bilirubin, AST and ALT):

Toxicity grade	Action	Dose modification	Subsequent occurrences
Grade 1	None	Maintain current dose level	
Grade 2	None	Maintain current dose level	
Grade 3	Hold until grade 1	Reduce one dose level	Reduce one dose level
Grade 4	Hold until grade 1	Reduce one dose level	Reduce one dose level

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Toxicity grade	Action	Dose modification	Subsequent occurrences
Grade 1: < LLN-2.5 mg/dL	Continue with current dose	None	None
Grade 2: < 2.5-2.0 mg/dL	Replace phosphorous per institutional guidelines	Maintain current dose level	2nd occurrence: reduce additional dose level 3rd occurrence: discontinue GSK2636771
Grade 3: < 2.0-1.0 mg/dL	Replace phosphorous per institutional guidelines, hold until grade 1	Reduce one dose level	2nd occurrence: reduce additional dose level 3rd occurrence: discontinue GSK2636771
Grade 4: < 1.0 mg/dL	Replace phosphorous per institutional guidelines, hold until grade 1	Reduce one dose level	2nd occurrence: reduce additional dose level 3rd occurrence: discontinue GSK2636771

3.5 Supportive Care

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

Diarrhea, nausea and vomiting have all been reported with GSK2636771. Supportive measures with anti-diarrheals and anti-emetics are recommended per investigator discretion or local institutional guidelines for emergence of treatment related symptoms.

GSK2636771 may enhance anti-platelet activity of agents that are irreversible or that act through platelet purinergic receptors. Any need for starting anti-platelet therapy in a patient enrolled to this arm will have to be evaluated by the subprotocol chair. Although aspirin does not act at the purinergic receptor, caution is recommended when GSK2636771 and aspirin are used concomitantly.

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.

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4. Study Parameters

4.1 Therapeutic Parameters for GSK2636771 Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving GSK2636771 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	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
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]			
Urinalysis	X[I]	X[I]			
Tumor biopsy and blood sample submission for MATCH Master Protocol[E]			X	X	

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

B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of 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 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. See Section 9.3.2.3 of MATCH Master Protocol. 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.

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 the Principal Investigator (or their authorized designees) 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 responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password..

NCI Supplied Agent(s) – General Information

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

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

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

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

5.1 GSK2636771 (NSC 781258)

5.1.1 Other Names:

GSK2636771B where B denotes the tris (hydroxymethyl) aminomethane salt

5.1.2 Classification:

Phosphoinositide 3-kinase beta (PI3Kβ) inhibitor

5.1.3 Mode of Action:

GSK2636771 is a potent, orally bioavailable, adenosine triphosphate (ATP) competitive, selective inhibitor of phosphoinositide 3-kinase beta (PI3Kβ).

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5.1.4 Storage and Stability:

Storage: Store at room temperature up to 30° C (86° F).

Stability: Shelf life studies are ongoing. If needed, sites may repackage capsules in pharmacy bottles and assign a 30-day expiration date.

If a storage temperature excursion is identified, promptly return GSK2636771 to room 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:

GSK2636771 will be supplied in 100mg capsules. Starting dose will be 400 mg (4 x 100mg capsules) once daily for 28 days per cycle. Dose reductions will be to 300mg and 200mg.

5.1.6 Preparation:

GlaxoSmithKline supplies and the PMB/CTEP/DCTD distributes GSK2636771 as size 0, opaque pink 100 mg capsules (free acid equivalent). Excipients include microcrystalline cellulose, croscarmellose sodium and sodium stearyl fumarate. The capsule shell contains gelatin, titanium dioxide (E171) and red iron oxide (E172)).

Capsules are packaged in high density polyethylene bottles with induction seal liners and child-resistant caps. Each bottle contains 35 capsules.

5.1.7 Route of Administration:

Oral. Take at least 1 hour before or 2 hours after a meal with 200 mL water (about 7 ounces).

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5.1.8 Incompatibilities:

GSK2636711 is highly protein bound (99%) in humans. Use caution in patients who are receiving concomitant medications that are also highly protein-bound.

In vitro studies demonstrate that GSK2636711 is not a substrate for CYP450 enzymes or efflux transporter, P-glycoprotein (P-gp). It is primarily eliminated by acyl glucuronidation via unspecified UGT isozymes. Potent inhibitors and inducers of UGT may alter GSK2636711 exposure.

Studies conducted *in vitro* show that GSK2636711 is not an inhibitor of CYP 450 enzymes or an inhibitor of transporters P-gp, breast cancer resistant protein (BCRP) and OATP1B1 and OATP1B3.

GSK2636771 is a weak *in vitro* inhibitor of OAT1, OAT3 and OCT2; however, the interaction risk appears to be low at clinical concentrations.

In vitro studies show that GSK2636711 does not activate the pregnane X receptor (PXR) and theoretically has a low potential to induce CYP450 isozymes.

5.1.9 Side Effects:

See CAEPR in Section 3.3

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5.1.10 Nursing/Patient Implications:

GSK2636771 may enhance antiplatelet activity of agents that are irreversible (aspirin) or that act through platelet purinergic receptors (e.g. clopidogrel, ticlopidine, prasugrel). Avoid concomitant use of GSK2636771 in patients taking these anti-platelet agents or in patients who have a history of congenital platelet function defects.

6. Translational Studies

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

7. References

1. Druker BJ, Talpaz M, Resta DJ, et al: Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 344:1031-7, 2001
2. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-39, 2004
3. Flaherty KT, Puzanov I, Kim KB, et al: Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809-19, 2010
4. Falchook GS, Long GV, Kurzrock R, et al: Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet 379:1893-901, 2012
5. Janku F, Hong DS, Fu S, et al: Assessing PIK3CA and PTEN in Early-Phase Trials with PI3K/AKT/mTOR Inhibitors. Cell Rep 6:377-87, 2014
6. Liu P, Cheng H, Roberts TM, et al: Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov 8:627-44, 2009
7. Hollander MC, Blumenthal GM, Dennis PA: PTEN loss in the continuum of common cancers, rare syndromes and mouse models. Nat Rev Cancer 11:289-301, 2011
8. Engelman JA, Chen L, Tan X, et al: Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. Nat Med 14:1351-6, 2008
9. Weigelt B, Warne PH, Downward J: PIK3CA mutation, but not PTEN loss of function, determines the sensitivity of breast cancer cells to mTOR inhibitory drugs. Oncogene 30:3222-33, 2011
10. Ni J, Liu Q, Xie S, et al: Functional Characterization of an Isoform-Selective Inhibitor of PI3K-p110beta as a Potential Anticancer Agent. Cancer Discov 2:425-33, 2012
11. Ihle NT, Lemos R, Jr., Wipf P, et al: Mutations in the phosphatidylinositol-3-kinase pathway predict for antitumor activity of the inhibitor PX-866 whereas oncogenic Ras is a dominant predictor for resistance. Cancer Res 69:143-50, 2009
12. Di Nicolantonio F, Arena S, Tabernero J, et al: Deregulation of the PI3K and KRAS signaling pathways in human cancer cells determines their response to everolimus. J Clin Invest 120:2858-66, 2010
13. Tsimberidou AM, Iskander NG, Hong DS, et al: Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. Clin Cancer Res 18:6373-83, 2012
14. Li J, Yen C, Liaw D, et al: PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 275:1943-7, 1997

15. Steck PA, Pershouse MA, Jasser SA, et al: Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 15:356-62, 1997

16. Maehama T, Dixon JE: The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem 273:13375-8, 1998

17. Shi Y, Paluch BE, Wang X, et al: PTEN at a glance. J Cell Sci 125:4687-92, 2012

18. Lee JO, Yang H, Georgescu MM, et al: Crystal structure of the PTEN tumor suppressor: implications for its phosphoinositide phosphatase activity and membrane association. Cell 99:323-34, 1999

19. Chalhoub N, Baker SJ: PTEN and the PI3-kinase pathway in cancer. Annu Rev Pathol 4:127-50, 2009

20. Song MS, Salmena L, Pandolfi PP: The functions and regulation of the PTEN tumour suppressor. Nat Rev Mol Cell Biol 13:283-96, 2012

21. Garcia JM, Silva J, Pena C, et al: Promoter methylation of the PTEN gene is a common molecular change in breast cancer. Genes Chromosomes Cancer 41:117-24, 2004

22. Goel A, Arnold CN, Niedzwiecki D, et al: Frequent inactivation of PTEN by promoter hypermethylation in microsatellite instability-high sporadic colorectal cancers. Cancer Res 64:3014-21, 2004

23. Janku F, Broaddus R, Bakkar R, et al: PTEN assessment and PI3K/mTOR inhibitors: Importance of simultaneous assessment of MAPK pathway aberrations. J Clin Oncol 30, 2012

24. Jia S, Liu Z, Zhang S, et al: Essential roles of PI(3)K-p110beta in cell growth, metabolism and tumorigenesis. Nature 454:776-9, 2008

25. Arkenau HT, Mateo J, Lemech CH, et al: A phase I/II, first-in-human dose-escalation study of GSK2636771 in patients (pts) with PTEN-deficient advanced tumors. J Clin Oncol 32:abstr 2514, 2014

26. GSK2636771 Investigator's Brochure (March 2014). GlaxoSmithKline (GSK) Group Company.

27. Cheung LW, Yu S, Zhang D, Li J, Ng PK, Panupinthu N, Mitra S, Ju Z, Yu Q, Liang H, Hawke DH, Lu Y, Broaddus RR, Mills GB. Naturally occurring neomorphic PIK3R1 mutations activate the MAPK pathway, dictating therapeutic response to MAPK pathway inhibitors. Cancer Cell. 2014 Oct 13;26(4):479-94. doi: 10.1016/j.ccell.2014.08.017. Epub 2014 Oct 2. PubMed PMID: 25284480; PubMed Central PMCID: PMC4198486.

28. Ni J, Liu Q, Xie S, Carlson C, Von T, Vogel K, Riddle S, Benes C, Eck M, Roberts T, Gray N, Zhao J. Functional characterization of an isoform-selective inhibitor of PI3K-p110β as a potential anticancer agent. Cancer Discov. 2012 May; 2 (5): 425-33. doi: 10.1158/2159-8290.CD-12-0003. Epub 2012 Apr 12. PubMed PMID: 22588880; PubMed Central PMCID: PMC3384541.

29. Polivka J Jr, Janku F. Molecular targets for cancer therapy in the PI3K/AKT/mTOR pathway. Pharmacol Ther. 2014 May;142(2):164-75. doi: 10.1016/j.pharmthera.2013.12.004. Epub 2013 Dec 9. Review. PubMed PMID: 24333502.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol P: GSK2636771 (PTEN Loss)

Appendix I

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Patient Pill Calendar

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Storage: Store at Room Temperature

Pill Calendar Directions

1. Take your scheduled dose of each capsule.
2. If you forget, the missed capsules will not be taken later.
3. Please bring the empty bottle or any leftover capsules and your pill calendar to your next clinic visit.
4. Take GSK2636771 once daily by mouth either 1 hour before or 2 hours after a meal with about 7 ounces of water only.
5. Swallow capsules whole, do not crush, chew or open capsules.

Patient Pill Calendar

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

GSK2636771

DAY	Date			Time capsule taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year		
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol P: GSK2636771 (PTEN Loss)

Appendix II

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Excluded Mutations for Sub-Protocol EAY131-P

Exclusion mutations and corresponding Level of Evidence are listed below:

NOTE: A function has been implemented in MATCHBOX to identify any deleterious mutations in NF1, NF2, TSC1, TSC2, PIK3R1 genes at Level of Evidence code 3.

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
NRAS	COSM585	SNV	2	p.Q61H
NRAS	COSM586	SNV	2	p.Q61H
NRAS	COSM583	SNV	2	p.Q61L
NRAS	COSM584	SNV	2	p.Q61R
NRAS	COSM582	SNV	2	p.Q61P
NRAS	COSM581	SNV	2	p.Q61E
NRAS	COSM580	SNV	2	p.Q61K
NRAS	COSM574	SNV	2	p.G13V
NRAS	COSM575	SNV	2	p.G13A
NRAS	COSM573	SNV	2	p.G13D
NRAS	COSM570	SNV	2	p.G13C
NRAS	COSM569	SNV	2	p.G13R
NRAS	COSM571	SNV	2	p.G13S
NRAS	COSM566	SNV	2	p.G12V
NRAS	COSM565	SNV	2	p.G12A
NRAS	COSM564	SNV	2	p.G12D
NRAS	COSM562	SNV	2	p.G12C
NRAS	COSM561	SNV	2	p.G12R
NRAS	COSM563	SNV	2	p.G12S
HRAS	COSM502	SNV	2	p.Q61H
HRAS	COSM503	SNV	2	p.Q61H
HRAS	COSM498	SNV	2	p.Q61L
HRAS	COSM499	SNV	2	p.Q61R
HRAS	COSM500	SNV	2	p.Q61P
HRAS	COSM497	SNV	2	p.Q61E
HRAS	COSM496	SNV	2	p.Q61K

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
HRAS	COSM489	SNV	2	p.G13V
HRAS	COSM490	SNV	2	p.G13D
HRAS	COSM488	SNV	2	p.G13C
HRAS	COSM486	SNV	2	p.G13R
HRAS	COSM487	SNV	2	p.G13S
HRAS	COSM483	SNV	2	p.G12V
HRAS	COSM485	SNV	2	p.G12A
HRAS	COSM484	SNV	2	p.G12D
HRAS	COSM481	SNV	2	p.G12C
HRAS	COSM482	SNV	2	p.G12R
HRAS	COSM480	SNV	2	p.G12S
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

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
KRAS	COSM516	SNV	2	p.G12C
KRAS	COSM518	SNV	2	p.G12R
KRAS	COSM517	SNV	2	p.G12S
KRAS	COSM19404	SNV	3	p. A146T
BRAF	COSM1127	SNV	**2**	p.V600R
BRAF	COSM1583011	SNV	2	p.V600R
BRAF	COSM308550	SNV	2	p.V600D
BRAF	COSM473	SNV	1	p.V600K
BRAF	COSM474	SNV	2	p.V600R
BRAF	COSM476	SNV	1	p.V600E
BRAF	COSM477	SNV	2	p.V600D
BRAF	AGTRAP-BRAF.A5B8.COSF828	Fusion	3	AGTRAP-BRAF.A5B8.COSF828
BRAF	AKAP9-BRAF.A8B9.COSF1013	Fusion	3	AKAP9-BRAF.A8B9.COSF1013
BRAF	CDC27-BRAF.C16B9	Fusion	3	CDC27-BRAF.C16B9
BRAF	FAM131B-BRAF.F2B9.COSF1189	Fusion	3	FAM131B-BRAF.F2B9.COSF1189
BRAF	FCHSD1-BRAF.F13B9.COSF404	Fusion	3	FCHSD1-BRAF.F13B9.COSF404
BRAF	KIAA1549-BRAF.K16B11	Fusion	3	KIAA1549-BRAF.K16B11
BRAF	KIAA1549-BRAF.K16B9	Fusion	3	KIAA1549-BRAF.K16B9
BRAF	KIAA1549-BRAF.K17B10.COSF509	Fusion	3	KIAA1549-BRAF.K17B10.COSF509
BRAF	KIAA1549-BRAF.K18B10	Fusion	3	KIAA1549-BRAF.K18B10
BRAF	KIAA1549-BRAF.K19B9	Fusion	3	KIAA1549-BRAF.K19B9
BRAF	PAPSS1-BRAF.P5B9	Fusion	3	PAPSS1-BRAF.P5B9
BRAF	SLC45A3-BRAF.S1B8.COSF871	Fusion	3	SLC45A3-BRAF.S1B8.COSF871
BRAF	SND1-BRAF.S16B9	Fusion	3	SND1-BRAF.S16B9

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
BRAF	TAX1BP1-BRAF.T8B11	Fusion	3	TAX1BP1-BRAF.T8B11
BRAF	TRIM24-BRAF.T9B9	Fusion	3	TRIM24-BRAF.T9B9
BRAF	COSM1125	SNV	3	L597Q
BRAF	COSM1126	SNV	3	L597S
BRAF	COSM21612	SNV	3	F595L
BRAF	COSM449	SNV	3	G464E
BRAF	COSM451	SNV	3	G466V
BRAF	COSM450	SNV	3	G464V
BRAF	COSM459	SNV	3	G469V
BRAF	COSM460	SNV	3	G469A
BRAF	COSM461	SNV	3	G469E
BRAF	COSM462	SNV	3	N581S
BRAF	COSM466	SNV	3	D594V
BRAF	COSM467	SNV	3	D594G
BRAF	COSM470	SNV	3	L597V
BRAF	COSM471	SNV	3	L597R
BRAF	COSM472	SNV	3	T599I
BRAF	COSM478	SNV	3	K601E
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

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
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
PIK3R1	COSM85926	SNV	3	p. R348*
AKT1	COSM33765	SNV	3	p.E17K
MTOR	COSM1686998	SNV	3	p.S2215F
MTOR	COSM20417	SNV	3	p.S2215Y
MTOR	COSM462604	SNV	3	p.F1888L
MTOR	COSM893813	SNV	3	p.F1888L
MTOR	OM5	SNV	3	p.F1888L
MTOR	OM7	SNV	3	p.F1888I
MTOR	COSM180789	SNV	3	p.E1799K
MTOR	OM9	SNV	3	p.C1483W
MTOR	COSM462616	SNV	3	p.C1483F
MTOR	COSM462615	SNV	3	p.C1483Y
MTOR	OM12	SNV	3	p.C1483R
MTOR	COSM414183	SNV	3	p.L2209V
MTOR	COSM462592	SNV	3	p.A2210P

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
MTOR	COSM462618	SNV	3	p.L1460P
MTOR	COSM462619	SNV	3	p.A1459P
MTOR	COSM527403	SNV	3	p.N2206S
MTOR	COSM1560108	SNV	3	p.S2215P
MTOR	COSM3965698	SNV	3	p.L2216P
MTOR	MCH4	SNV	3	p.R2217W

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol P: GSK2636771 (PTEN Loss)

Rev. 12/16
Rev. 3/17

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, **GSK2636771**. 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:

GSK2636771 has the following qualities:

- Is highly protein-bound and may prevent other drugs from binding to blood protein. Patients receiving other medications that are also highly protein bound may need to be monitored more frequently.
- Is primarily broken down by UGT enzymes and may be affected by other drugs that strongly inhibit or induce these enzymes.
- May enhance the antiplatelet activity of agents that are irreversible (aspirin) or that act through platelet purinergic receptors like clopidogrel, ticlopidine and prasugrel

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

GSK2636771 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:

GSK2636771 must be used very carefully with other medicines that are highly protein-bound or avoided with other medicines that affect platelets to thin your blood, including aspirin. 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 highly protein-bound or affect platelet activity.

- 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.
- Patients receiving other medications that are also highly protein bound may need to be monitored more frequently.
- 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 **GSK2636771.** This clinical trial is sponsored by the NCI. **GSK2636771** may interact with drugs that are strong inhibitors or inducers of UGT, highly protein-bound or affect platelet activity, like aspirin. 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.
- **GSK2636771** may interact with drugs that affect UGT liver enzymes, is highly-protein bound and may interact with other drugs that are bound to blood protein or drugs that affect platelets to thin blood. It must be used very carefully with other medicines that are also highly-protein bound or avoided with other medicines that affect platelet activity.
- 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 inhibitors or inducers of UGT, highly protein-bound or affect platelet activity, like aspirin, clopidogrel, ticlopidine, and prasugrel.
- 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 _____.