Cover Page

Title:A Phase 2 Multi-Center Pharmacodynamic Study of TVB-2640 in KRAS Mutant Non-Small Cell Lung Carcinomas

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UTSouthwestern
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Comprehensive Cancer Center

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A Phase 2 Multi-Center Pharmacodynamic Study of TVB-2640 in *KRAS* Mutant Non-Small Cell Lung Carcinomas

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Study Drug: TVB-2640

IND Number(s):
136566 (David Gerber, MD)
137383 (^{11}C Acetate IND under Orhan Oz, MD, PhD)
118181 (Cross-referenced IND authorized by Sagimet Biosciences)

Study Sponsor/IND Holder: David Gerber, MD., UT Southwestern Medical Center

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UT Southwestern Medical Center (UTSW)
Harold C. Simmons Comprehensive Cancer Center
Attn: Clinical Research Office

Modification / Update, MOD033-STU 022017-058, David Gerber, 1/20/2026

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Signature Page

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Protocol Version 13: November 26, 2025

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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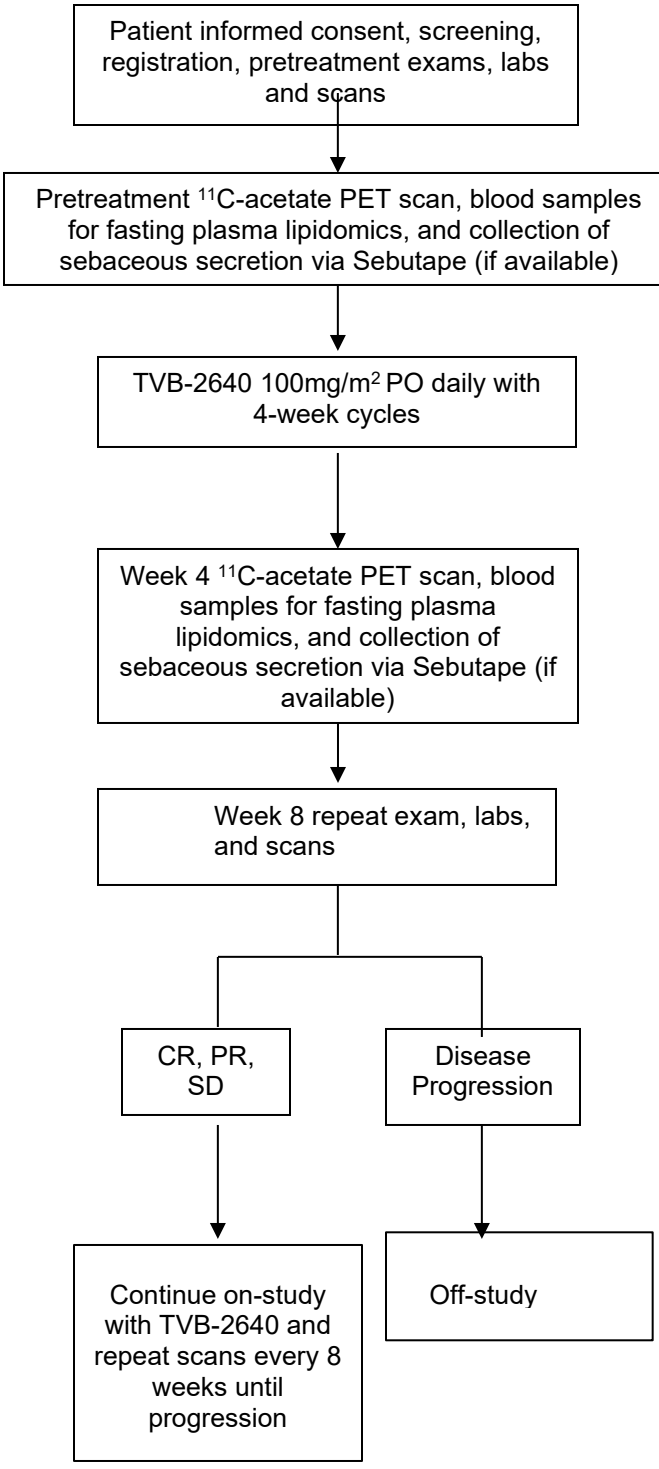
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CTC	Circulating Tumor Cells
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PO	peros/by mouth/orally
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	A phase 2 multi-center pharmacodynamics study of TVB-2640 in *KRAS* mutant non-small cell lung carcinomas
Short Title	TVB-2640 in *KRAS* mutant cancers
Protocol Number	UTSW Protocol SCCC 05517
Phase	Phase 2
Methodology	Open label, non-randomized single arm, multi-site phase 2 study
Study Duration	Two years
Study Center(s)	UTSW, University of Cincinnati
Objectives	Establish preliminary response rate and response duration and correlate with ^{11}C-acetate tumor retention (performed at selected sites), plasma lipids, and collection of sebaceous secretion via Sebutape (if available) pre-treatment and at week 4; confirm safety profile.
Number of Subjects	13-34
Diagnosis and Main Inclusion Criteria	Advanced *KRAS* mutant non-small cell lung cancer with measurable disease and failed at least one chemotherapy regimen and one immunotherapy regimen and age $\geq$18 years and acceptable hematologic, coagulation, kidney, and liver status and no uncontrolled heart or liver disease or diabetes.
Study Product(s), Dose, Route, Regimen	TVB-2640 given at 100mg/m^2 orally daily
Duration of administration	4-week cycles that may continue if response or stable disease
Reference therapy	Third line therapy with docetaxel yielded 0-8% partial remissions and progression-free survival of 2-3 months (Janne, 2013; Kim, 2008; Hanna, 2004; Shepherd, 2000).
Statistical Methodology	Exact binomial method will be used to estimate the RR, DCR and toxicity rate in patients receiving TVB-2640 along with corresponding 95% confidence interval. Kaplan-Meier method will be used to estimate the response duration. Correlation analysis will be performed with tumor ^{11}C-acetate PET retention, fasting plasma lipidomics, and sebum fatty acid composition.

1.0 BACKGROUND AND RATIONALE

1.1 *KRAS* mutant non-small cell lung carcinoma background

KRAS mutant non-small cell lung cancer (NSCLC) occurs in 40,000 people per year in the U.S. and has a particularly poor prognosis with fewer than 10% of patients showing 5-year survival (Janne, 2013). These tumors tended to be adenocarcinomas or large cell carcinomas and were more frequent in younger patients. Brain metastases were more common in *KRAS* mutant NSCLC (Zhao, 2014). Among metastatic NSCLC patients, *KRAS* mutation was associated with shorter survival (Johnson, 2013). Therapy for metastatic *KRAS* mutant patients consists of first line platinum doublets and second line anti-PD1 immune checkpoint inhibition (Roberts, 2013). Nevertheless, almost all patients relapse and die from progressive disease (Wood, 2013). More recently, direct $KRAS^{G12C}$ inhibitors have demonstrated promising efficacy in this subset of *KRAS* mutations.

1.2 Fatty Acid Metabolism and *KRAS* mutant NSCLC

Fatty acids are fundamental cellular components that are building blocks for cellular membranes, parts of post-translational protein modifications, key elements of signal-transducing lipid rafts, and substrates for energy generation through β-oxidation. While tumor cells import fatty acids from the environment, the need for large numbers of phospholipids for proliferating cell membranes and the increased metabolic rate of cancer cells leads to overexpression of fatty acid synthase (Menendez, 2007). The de novo synthesis of fatty acids requires four key enzymes. The first is mitochondrial ATP citrate lyase that generates acetyl-coenzyme A from citrate. The second is acetyl coenzyme A carboxylase that catalyzes carboxylation of acetyl-coenzyme A to malonyl-coenzyme A. The third enzyme is fatty acid synthase that sequentially adds 2-carbon units until a long-chain fatty acid is produced. Synthesis entails a series of decarboxylative Claisen condensation reactions from acetyl-CoA and malonyl-CoA. Following each round of elongation, the beta keto group is reduced to the fully saturated carbon chain by the sequential action of NADPH-dependent ketoreductase, dehydratase, and enoyl reductase (Maier, 2008). The growing fatty acid chain is carried between these active sites while attached covalently to an acyl carrier protein, and is released by the action of a thioesterase upon reaching a carbon chain length of 16--palmitidic acid. Finally, acyl-coenzymeA synthetases (ACLSs) convert long-chain fatty acids into fatty acyl-coenzymeA esters. The esters are substrates for lipid synthesis and β-oxidation (Coleman,2002). Their hydrophilic nature traps them in the cytosol (Kamp, 2006). ACSL3 is localized to the endoplasmic reticulum and lipid bodies and is specific for palmitate. Watkins and coworkers demonstrated ASCL3 overexpression and growth dependence of NCSLC cell lines (Pei, 2013). Scaglioni and colleagues showed mutant *KRAS* regulates ASLC3 expression and activity. They also observed *KRAS* mutant NSCLCs overexpress ASLC3 and loss of ASLC3 leads to tumor cell death (Padanad, 2016). Based on these findings, we hypothesize that *KRAS* mutant NSCLCs should be sensitive to fatty acid synthase inhibitors.

1.4 ^{11}C-acetate PET Imaging

Positron emission tomography—PET employing ^{11}C-acetate has been used to detect patient tumor metastases in a variety of malignancies including lung adenocarcinoma (Shibata, 2009; Challapalli, 2016). Preclinical work with *KRAS* mutant bearing lung cancers in genetically engineered mice showed enhanced tumor: normal tissue contrast with delayed image acquisition to 90 minutes from 15 minutes (Lewis, 2014). The late ^{11}C incorporation is within the fatty acid palmitate and hence a measure of tumor fatty acid synthase activity. Consequently, pretreatment scans offer a target biomarker and post-treatment scans provide pharmacodynamic evidence for inhibitor-driven reduced fatty acid synthesis.

1.5 Plasma lipidomics

Blood plasma contain thousands of distinct lipid molecular species including fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterols and prenols (Quehenberger,

2011). Most of the lipids are associated with proteins including albumin and plasma lipoproteins. Mutant *KRAS* transfected fibroblasts showed increased neutral lipids including triglycerides as well as acetyl-CoA synthetase long-chain family member 3—ACSL3 protein and mRNA and enzymatic activity (Padanad, 2016). ACSL3 is downstream of fatty acid synthase. Rodent tumor xenograft plasma lipids post-TVB-2640 show reduction in fatty acids, triglyceride, and percent saturation of fatty acids, tripalmitin and lysophosphatidylcholine. There are concomitant increases in malonyl carnitine, and diacylglycerol (Scaglioni, unpublished data). Lipids are measured by "shotgun lipidomics" with a Blight-Dyer extract applied to a triple-TOF mass spectrometer as previously described (Fahy, 2009). Thus, plasma lipidomics can serve as an indirect pharmacodynamics marker of TVB-2640 activity.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective is to determine the preliminary disease control rate—DCR and response rate--RR and duration of disease control and response of TVB-2640 in *KRAS* mutant NSCLC patients.

2.2 Secondary Objectives

2.2.1 To further characterize the safety profile of TVB-2640 in *KRAS* mutant NSCLC patients.

2.2.2 To establish the predictive value of ^{11}C-acetate PET pretreatment and post-treatment tumor uptake for DCR and RR and correlate with fasting plasma lipidomics.

2.2.3 Examine fasting plasma lipidomics pretreatment and post-treatment and assess relationship to DCR, RR, and ^{11}C-acetate PET uptake.

2.2.4 Examine sebaceous secretion of fatty acids via Sebutape (if available) and assess relationship to DCR, RR, ^{11}C-acetate PET uptake, and fasting plasma lipidomics

2.3 Endpoints

Primary endpoints are RECIST v1.1 best response and response duration and NCI CTCAE v5.0 toxicity profile over eight weeks. Secondary endpoints are ^{11}C-acetate tumor uptake pretreatment and at four weeks of treatment, fasting plasma lipidomics pretreatment and at four weeks of treatment,sebum fatty acid composition pretreatment and at four weeks of treatment, overall survival (OS).

3.0 Subject ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Metastatic or advanced stage, histologically or cytologically confirmed NSCLC and molecular identification of oncogenic *KRAS* mutation.

- *KRAS* mutant NSCLC must be refractory, relapsed, and previously treated with doublet chemotherapy and immune checkpoint inhibitor (unless there is a specific contraindication to checkpoint inhibitor).
- Molecular characterization (tissue- or blood-based [ie, cell-free/circulating tumor DNA]) must have been performed and must have demonstrated an oncogenic *KRAS* mutation (e.g., exon 12, 13, 61, or 117 mutation detected by sequencing) by a CLIA-certified assay (source documentation required). *KRAS* mutations at other codons require review and approval by Study Chair.

3.1.2 Subjects' *EGFR* mutation and *ALK* gene rearrangement status must be known prior to study entry. Subjects with *EGFR* mutation or *ALK* gene rearrangement must have progressed after appropriate FDA-approved targeted therapy options prior to eligibility.

3.1.3 Patient has evidence of disease progression on most recent line of therapy.

3.1.4 Patient has measurable disease by RECIST v1.1 (Eisenhauer, 2009).

3.1.5 Age ≥ 18 years.

3.1.6 ECOG performance status of 0 or 1.

3.1.7 Predicted life expectancy of ≥3 months.

3.1.8 Adequate organ and marrow function as defined below:

- absolute neutrophil count	≥ 1,500/mcL
- platelets	≥ 75,000/mcL
- total bilirubin	<2X institutional upper limit of normal
- AST and ALT	≤5X institutional upper limit of normal
- serum creatinine	≤1.5X institutional upper limit of normal
- LVEF	≥50%
- QTcF	<470msec

3.1.9 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for *90* days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.9.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.10 No significant ischemic heart disease or myocardial infarction within 6 months of first dose of TVB-2640 and with current adequate cardiac function as in 3.1.8.

3.1.11 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Patient is unable to swallow oral medications or has impairment of GI function or GI disease that may significantly alter drug absorption such as active inflammatory bowel disease, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome.

3.2.2 Patient has a history of risk factors for torsade de pointes such as uncontrolled heart failure, severe hypokalemia with potassium less than 3mM/L, history of long QT syndrome or require use during study participation of concomitant medications

known to prolong QT/QTc interval—see http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=US.

3.2.3 Patients who require use of strong CYP3A4/5 agonists or inhibitors during study participation.

3.2.4 Patient has uncontrolled or severe intercurrent medical condition including uncontrolled brain metastases. Patients with stable brain metastases either treated or untreated, on a stable dose of steroids/anticonvulsants, with no dose increase within 4 weeks before the first dose of TVB-2640, and no anticipated dose change, are allowed.

3.2.5 Patient underwent major surgery within 4 weeks before the first dose of TVB-2640 or received cancer-directed therapy either chemotherapy, radiotherapy, hormonal therapy, biologic or immunotherapy, etc. or an investigational drug or device within 2 weeks (6 weeks for mitomycin C and nitrosoureas) or 5 half-lives of that agent, whichever is shorter before the first dose of TVB-2640. In addition, any drug-related toxicity, with the exception of alopecia, an endocrinopathy controlled with replacement therapy, or a clinically stable toxicity not expected to increase from study therapy (eg, cisplatin-associated ototoxicity) should have recovered to ≤Grade 1.

3.2.6 If female, patient is pregnant or breast-feeding.

3.2.7 Patient has evidence of a serious active infection—infection requiring treatment with intravenous antibiotics.

3.2.8 Patient has known immunodeficiency virus—HIV or hepatitis B or C infection, as such patients may be at increased risk for toxicity due to concomitant treatment and disease-related symptoms may preclude accurate assessment of the safety of TVB-2640.

3.2.9 Patient has an important medical illness or abnormal laboratory finding that, in the Investigator's opinion, would increase the risk of participating in this study.

3.2.10 Patients with prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational agent.

3.2.11 History of clinically significant dry eye (xerophthalmia) or other corneal abnormality or, if a contact lens wearer, does not agree to abstain from contact lens use from baseline through the last study drug dose.

3.2.12 Patient has a known allergy or hypersensitivity to components of TVB-2640.

3.2.13 Patient has a prior history of hypersensitivity, drug/radiation-induced, or other immune-mediated pneumonitis.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

^{11}C-acetate PET (UTSW site only) will be done, blood samples for fasting plasma lipidomics will be collected, and Sebutape collection (if available) will be performed as described in Section 4.2.4 and Section 9 prior to TVB-2640 administration.

4.1.2 The MTD of TVB-2640 as monotherapy and in combination has been identified as 100 mg/m2 (based on BSA dosing). The flat dose of TVB 2640 to be administered orally once a day for 4 week cycles, based on the patient's BSA, is as follows:

BSA	DOSE
BSA <1.5 m^2	TVB-2640 100 mg flat dose
BSA ≥1.5 and <2.0 m^2	TVB-2640 150 mg flat dose
BSA ≥2.0 and <2.5 m^2	TVB-2640 200 mg flat dose
BSA ≥2.5 m^2	TVB-2640 250 mg flat dose

4.1.3 Patients should be instructed to take their daily dose at approximately the same time of day at least 2 hours after last food consumption and at least 1 hour before next food consumption. Patients are to self-administer TVB-2640. Patients should be instructed to swallow the tablets whole and to not chew or cut them. Patients will be given a diary to track dosing. The study coordinator will review at each visit for drug compliance.

4.1.4 Repeat ^{11}C-acetate PET (UTSW site only), blood sampling, and Sebutape collection (if available) in week 4 of TVB-2640 administration as described in Section 9.

4.2 Toxicities and Dosing Delays/Dose Modifications

During a cycle of treatment, TVB-2640 should continue to be administered as planned unless clinically significant, treatment-related CTCAE grade 3-4 toxicities occur. Patients who experience a≥ Grade 3 hematologic or non-hematologic treatment-related toxicity will have their dose held until resolution to ≤ Grade 2 or baseline. Toxicities will be graded according to the NCI CTCAE version 5.0. If the toxicity returns to ≤ Grade 2 or baseline, and the decision is made that the patient can resume study drug, then TVB 2640 dosing should be restarted at the next lower dose level according to the table above in section 4.1.2. Dose reductions for intolerable grade 2 adverse events may be permitted but PI approval must be obtained. If a dose reduction is indicated but the patient is already taking TVB-2640 at a dose of 100mg, the patient must discontinue treatment permanently. If, after TVB-2640 has been withheld for 28 days and the toxicity does not return to at least Grade 2 or lower, then the patient will have drug discontinued permanently. Refer to the Investigator Brochure--IB for details regarding the management of TVB-2640-related hand-foot syndrome—palmar-plantar erythrodysaesthesia as well as ocular toxicities. Patients whose treatment is interrupted or permanently discontinued because of toxicities will be followed until the toxicity resolves or stabilizes.

4.3 Concomitant Medications/Treatments

All prescriptions and non-prescription medications and therapies including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicine, taken from 28 days prior to first dose of TVB-2640 through final study visit will be recorded in the case report form. Medications prohibited during study participation include investigational agents for the treatment of lung cancer, other anti-neoplastic treatments, strong inhibitors or inducers of cytochrome P450 3A4/5 as shown in http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm, and medications with known association with Torsades de pointes (TdP) as listed in http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=US. Radiation therapy to target lesions or surgical removal of target lesions is considered indicative of progressive disease—PD and will result in the patient being unevaluable for disease response. Medications and treatments other than those

specified above, including palliative and supportive care for disease-related symptoms, are permitted during the study. Patients should be closely monitored, and treatment is to be instituted for disease-related symptoms, as appropriate. Antiemetic treatment may be used at the Investigator's discretion and in accordance with the American Society of Clinical Oncology guidelines after documented nausea and vomiting has occurred. The choice of anti-emetic treatment, if required, will be made at the Investigator's discretion. However, high-dose steroids are to be avoided if possible as an anti-emetic therapy. Antidiarrheals also may be used at the Investigator's discretion. Hematopoietic growth factors may be used at the discretion of the Investigator and in accordance with the American Society of Clinical Oncology guidelines. Patients who experience febrile neutropenia may receive treatment with colony-stimulating factors at the Investigator's discretion.

4.4 Other Modalities or Procedures

During protocol treatment, other modalities—such as surgery or radiation therapy—are permitted for palliative purposes. Examples include management of pain inadequately controlled medically, management of pathologic fracture, etc. In such cases, TVB-2640 study therapy should be withheld starting the day before such treatment and resumed two days after such treatment is completed.

4.5 Duration of Therapy

Treatment will continue for 4-week cycles until disease progression or inter-current illness that prevents further administration of treatment or unacceptable adverse events/drug-related toxicities, subject decides to withdraw from the study, or general or specific changes in the patient's condition that render the subject unacceptable for further treatment in the judgment of the investigator. Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from TVB-2640 may continue to receive the study medication upon approval by the principal investigator. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments.

4.6 Duration of Follow Up

Patients will be followed post treatment until time of disease progression, death, or initiation of another cancer treatment, whichever occurs first. Additionally, subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For these subjects, visits will be every 4 weeks on study and every 4 weeks in follow-up off study until toxicities resolved or stabilized.

4.7 Removal of Subjects from Protocol Therapy

TVB-2640 treatment is to be permanently discontinued for patients having progressive disease, unacceptable treatment-related adverse event, or female patients who become pregnant.

NOTE: Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from TVB-2640 may continue to receive the study medication upon approval by the principal investigator. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments.

To consider treatment with TVB-2640 beyond RECIST-defined PD, the following conditions must be met: (1) absence of clinical symptoms or signs indicating clinically significant disease progression; (2) no decline in performance status; (3) absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., symptomatic CNS metastasis, respiratory failure due to tumor compression, symptomatic spinal cord

compression) requiring urgent alternative medical intervention; and (4) no significant, unacceptable or irreversible toxicities related to study treatment.

In addition, written informed consent must be obtained for treatment beyond radiologic disease progression. As part of this process, the following must occur: (1) acknowledgement that this practice is not considered standard in the treatment of cancer; (2) discussion of alternative treatment options, including any available approved therapies and participation on alternative clinical trials.

All patients must have end-of-treatment assessments for safety within 30 days after the last dose of study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for an end of treatment visit, will be contacted for safety evaluations during the 30 days following the last dose of study drug. All patients will be followed for ongoing treatment related adverse events and serious adverse events every 4 weeks for 8 weeks following the last dose of TVB-2640 until resolved

Patients will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. Additionally, the sponsor may terminate the study. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Patient withdraws consent
- Refusal of treatment at patient's request
- Protocol violation
- Failure to return for follow-up
- Alternative therapy or medication
- Administrative reasons
- Intercurrent illness
- Adverse event
- Death

All patients should be encouraged to continue, if possible, with the scheduled study and follow-up visits. If a patient is withdrawn, he or she should complete the end of study visit. The reason(s) for a patient's withdrawal from the study are to be recorded in the patient's source record and on the case report form. Following withdrawal of consent to participate in this trial by a patient, no new information will be collected from the patient or added to the existing data or any database, if requested by the patient. However, every effort will be made to follow all patients for safety.

4.8 Subject Replacement

Patients who fail to complete 8 weeks of therapy and be evaluated for safety and efficacy may be replaced.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

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

All screening/baseline procedures must be performed within 28 days prior to treatment initiation. All screening procedures to confirm eligibility must be performed within 28 days prior to registration.. The screening procedures include:

5.1.1 ***Informed Consent***

Written informed consent in accordance with federal, local, and institutional guidelines. The patient must provide informed consent prior to the first screening procedure. However, the Investigator should not repeat procedures that are performed as part of standard of care (SOC) if they are within the screening window and are done prior to signing the ICF.

5.1.2 ***Medical history***

Complete medical and surgical history, history of infections

5.1.3 ***Demographics***

Age, gender, race, ethnicity

5.1.4 ***Review subject eligibility criteria***

5.1.5 ***Review previous and concomitant medications***

5.1.6 ***Physical exam including vital signs, height and weight***

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 ***Performance status***

Performance status evaluated prior to study entry and every 4 weeks while on treatment.

5.1.8 ***Adverse event assessment***

Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

5.1.9 ***Hematology***

CBC, Differential

5.1.10 ***Urinalysis***

5.1.11 Serum chemistries

Comprehensive metabolic panel--CMP to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes--sodium, potassium, calcium, chloride, bicarbonate, glucose, and total bilirubin.

5.1.12 Pregnancy test for females of child bearing potential

See section 3.1.8 for definition. Serum pregnancy test is required.

5.1.13 Tumor assessment

CT scans of the neck, chest, abdomen and/or pelvis will be performed at baseline and every two cycles for all known sites of disease according to standard of care. Other imaging of these areas such as PET/MRI will be allowed if CT cannot be performed.
MRI of the brain will be performed only as clinically indicated. Wherever it can be safely given, radiographic contrast agents should be given for the imaging studies.

5.1.14 Electrocardiogram

A twelve lead ECG will be obtained as part of the screening evaluation and every cycle day 1 during study therapy. Fridericia correction formula should be used to evaluate QT.

5.1.15 *ECHO*

5.1.16 *Ophthalmology testing for visual acuity and slit lamp exam*

5.1.17 *Coagulation Tests*

PT, PTT

5.1.18 *Hepatitis B test*

Per local regulations/standard of care.

5.1.19 *Disease response assessment*

5.1.20 *Sample collection of plasma for lipidomics*

See Section 9.0. NOTE: samples for plasma lipidomics must be collected after overnight fast; in cases where plasma lipidomics are collected on the same day as ^{11}C-acetate PET scan, the samples must be collected before ^{11}C-acetate administration.

5.1.21 *Pre-dose sample collection for PH profiling*

See section 9.5

5.1.22 *^{11}C-acetate PET scan (UTSW site only)*

See Section 9.0. Informed consent is required for 11C-acetate PET scan. NOTE: in cases where ^{11}C-acetate PET scan is performed on the same day as fasting plasma lipidomics samples are collected, the ^{11}C-acetate must be administered after collection of fasting plasma lipidomics samples. Patients who are unable to have 11C-acetate PET scan performed for any reason may still be able to participate in the trial with the principal investigator's review and approval.

5.1.23 *Sebutape collection of sebaceous secretions (if available)*

See Section 9.0

5.1.24 *Quality of Life Assessment*

The FACT-L/LSS and EORTC-QLQ-C30 will be completed at baseline, at each disease assessment time-point (every 2 treatment cycles or 8 weeks), and at end-of treatment.

5.1.25 *Subject Registration*

See Section 11.3 for details.

5.2 Procedures During Treatment

5.2.1 Every Cycle Day 1 on Treatment (+/- 3 days)

- History, Physical exam, vital signs, ECOG performance status, Adverse events, Concomitant medications
- Hematology
- Serum chemistries
- TVB-2640 100mg/m^2 PO daily

5.2.2 Cycle 1 Day 8

- PK Sample collection as outlined in section 9.5

5.2.3 Cycle 2 Day 1 (+/- 3 days)

- History, Physical exam, vital signs, ECOG performance status, Adverse events, Concomitant medications
- Hematology
- Serum chemistries
- TVB-2640 100mg/m^2 PO daily
- Sample collection for plasma lipidomics. See Section 9.0. NOTE: samples for plasma lipidomics must be collected after overnight fast; in cases where plasma lipidomics are collected on the same day as ^{11}C-acetate PET scan, the samples must be collected before ^{11}C-acetate administration.
- ^{11}C-acetate PET scan. Informed consent is required for 11C-acetate PET scan. See Section 9.0. NOTE: in cases where ^{11}C-acetate PET scan is performed on the same day as fasting plasma lipidomics samples are collected, the ^{11}C-acetate must be administered after collection of fasting plasma lipidomics samples.
- Sebaceous secretion via Sebutape (if available). See Section 9.0.

5.2.4 Every 8 weeks on Treatment

- Repeat CT or MRI scans
- Disease response assessment
- Quality of Life Questionnaires

5.3 Follow-up Procedures

At time of study discontinuation, patient will have history and physical exam and vital signs and ECOG performance status and adverse events and concomitant medications, CBC, and CMP and CT or MRI and disease response assessment. If patient has unresolved grade 3 toxicities, patients will be followed every 4 weeks until resolved with appropriate laboratory studies and history and exam until resolved.

5.3.1 Survival Follow Up

Patients' overall survival will be documented, retrospectively. Study will record anti-cancer treatments after EOT and date of death. Information will be retrieved from medical records and/or publicly available information.

5.4 Time and Events Table

Assessment	Screening/ Baseline	Cycle 1 Day 1 (+/-3 days)	Cycle 1 Day 8	Cycle 2 Day 1 (+/-3 days)	Subsequent Cycles Day 1 (+/-3 days)	Every 8 weeks on treatment (+/-5 days)	End of Treatment/ Follow-Up[i] (+/-3 days)
Informed consent	X						
Demographics	X						
Pregnancy[a]/ Hepatitis B	X			X	X		
ECHO	X						

ECG[g]	X	X			X		X
Ophthalmology tests[b]	X						
Urinalysis	X						
PT/PTT	X						
History/PE/VS/PS	X	X		X	X		X
Review eligibility	X						
Adverse events	X	X		X	X		X
Review Concomitant meds	X	X		X	X		X
CT or MRI [c]	X					X	X
TVB-2640[d]		X		X	X		
Disease response assessment[e]	X					X	X
CBC	X	X		X	X		X
Chemistry[f]	X	X		X	X		X
^{11}C-acetate PET[j]	X			X			
Plasma lipidomics[k]	X			X			
PK Samples[l]	X		X				
Sebaceous secretion via Sebutape (if available) [h]		X		X			
QoL Questionnaires	X					X	X
Subject Registration	X						
Archival Tissue Collection[m]	X						
Overall Survival							

Notes:
[a]Serum test in women of child bearing potential at screening and every cycle day 1 per standard of care; Hepatitis B core Ab and surface Ag at performed at screening per standard of care
[b]visual acuity and slit lamp exam;
[c] CT scans of the neck, chest, abdomen and pelvis will be performed at baseline and every two cycles according to standard of care. MRI of the brain will be performed only as clinically indicated.
[d]100mg/m^2 po daily for 4 week cycles;
[e]RECIST measurements.
[f]Chemistry includes albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes—sodium, potassium, calcium, chloride, bicarbonate, glucose and total bilirubin.;
[g] ECG (single) performed at screening, every Cycle Day 1 while on treatment, and at end of treatment
[h]At each scheduled timepoint, the Sebutape patches (if available) must remain on the patient's forehead for 30±5 minutes and be removed prior to administration of the TVB 2640 dose.
[i] Patients will be followed post treatment until time of disease progression, death, or initiation of another cancer treatment, whichever occurs first. Additionally, subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For these subjects, visits will be every 4 weeks on study and every 4 weeks in follow-up off study until toxicities resolved or stabilized.[j] This will be performed only at the UTSW site and is not required at other study sites. Informed consent is required for ^{11}C-acetate PET scan. In cases where ^{11}C-acetate PET scan is performed on the same day as fasting plasma lipidomics samples are collected, the ^{11}C-acetate must be administered after collection of fasting plasma lipidomics samples.
[k]Samples for plasma lipidomics must be collected after overnight fast; in cases where plasma lipidomics are collected on the same day as ^{11}C-acetate PET scan, the samples must be collected before ^{11}C-acetate administration. Screening/baseline sample may be collected on C1D1 before treatment initiation.
[l] Collection will be dependent on group assignment. See Section 9.5 for more details.

	[m] Archival tissue may be collected at any time during study participation. See section 9.6 for more details.

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reasons for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment--follow-up permitted

5.5.2 Subject withdraws consent--termination of treatment and follow-up

5.5.3 Subject is unable to comply with protocol requirements

5.5.4 Subject demonstrates disease progression

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe

5.5.6 Treating physician judges continuation on the study would not be in the subject's best interest

5.5.7 Subject becomes pregnant--pregnancy to be reported along same timelines as a serious adverse event

5.5.8 Development of second malignancy--except for basal cell carcinoma or squamous cell carcinoma of the skin that requires treatment, which would interfere with this study

5.5.9 Lost to follow-up

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

For the purposes of this study, patients should be reevaluated for response after every 8 weeks.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee [Eur J Cancer. 2009;45(2):228-247]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. Note: Subjects who exhibit objective disease progression prior to the end of 8 weeks will also be considered evaluable.

6.1.2 Disease Parameters

Measurable Disease: Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

1. 10 mm by CT scan. (CT scan slice thickness no greater than 5 mm)

2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target lesions. All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

CT or MRI scans will be done pretreatment and at every 8 weeks while on study

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started, (nadir) and minimum 5 mm increase over the nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. There can be no unequivocal new lesions.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time point response: patients with target (+/– non-target) disease.			
Target Lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not all evlautated	No	PR
SD	Non-PD or not all evlautated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease.			

Time point response: patients with non-target disease only.		
Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease

A 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

6.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.1.7 Overall Survival

Overall Survival (OS) is defined as the duration from start of treatment to time of death.

6.2 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study therapy. The study will use the CTCAE version 5.0 for reporting of adverse events https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.0 ADVERSE EVENTS

7.1 TVB-2640

For the most recent safety update, please refer to the current Investigator's Brochure.

7.1.1 Contraindications

Inability to swallow or significant gastrointestinal function causing malabsorption or increased risk of prolonged QTc due to personal or family history, potassium <3mEq/L, or congestive heart failure.

7.1.2 Special Warnings and Precautions for Use

The most consistent and predictable toxicity observed in TVB-2640 treated patients has been dose-dependent, reversible and non-cumulative ocular edema and palmar-plantar erythrodyaesthesia. Other TVB-2640-related side effects include alopecia, dry eyes and increased lacrimation.

7.1.3 Interaction with other medications

There may be interactions with medications that can significantly prolong QTc including amiodarone, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, clarithromycin, disopyramide, dofetilide, domperiodone, droperidol, erythromycin, flecainide, halofantrine, haloperidol, ibutilide, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quinidine, sotalol, sparfloxacin, terfanadine, thioridazine, and vandetanib. Medications that are strong agonists or inhibitors of CYP3A4/5 are also prohibited. They are referenced in Section 4.5 and website noted:**http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm**

7.1.4 Adverse Reactions

Adverse events associated with TVB-2640 included corneal edema, palmar-plantar dysesthesias, alopecia, dry eyes, skin exfoliation, dry skin, anorexia, fatigue, nausea, vomiting, dyspepsia, dry mouth, diarrhea, iritis, keratitis, uveitis, xerophthalmia, and increased lacrimation.

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those

who will enroll in future studies using similar agents. Adverse events are assessed in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

7.2.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through end of treatment/follow-up assessment will be considered acute adverse events.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

OHRP and UTSW HRPP define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization[1,2] or prolongation of existing hospitalization;

- results in persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.3 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Step 2: Grade the adverse event using the NCI CTCAE v5.0.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

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

Note: This includes all events that occur to the end of treatment/follow-up visit (section 7.2.1). Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.3.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

SAEs and UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs occurring during the protocol-specified monitoring period and all UPIRSOs should be submitted to the SCCC DSMC within 5 business days of the study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB of record guidance should be followed for local reporting of serious adverse events or unanticipated problems.

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site or other designee. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE or UPIRSO documentation that is available are also submitted to the

DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the IIT Project Manager or designee ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs and UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Send Initial SAE and follow-up Reports to:

<table>
<tr><td colspan="3">Should you need to discuss any SAE initial or follow-up reports contact:
Sponsor-Investigator/Principal Investigator: Dr. David Gerber
Phone Number: 214-648-1579
Email Address: david.gerber@UTSouthwestern.edu</td></tr>
<tr><td>LEAD SITE (UT SOUTHWESTERN) AND SUB-SITE(S): SEND SAE INITIAL AND FOLLOW-UP REPORTS TO EACH OF THE FOLLOWING CONTACTS:

● UTSW Principal Investigator – David Gerber, MD
Email: david.gerber@UTSouthwestern.edu

● UTSW Investigator Initiated Trial Team
Email: SCCC-IIT@utsouthwestern.edu

● Ebele Mbanugo-Clinical Research Manager
Email:
ebele.mbanugo@UTSouthwestern.edu

● UTSW SCCC Data Safety Monitoring Committee
Website for entering SAEs for UT Southwestern site
https://utsouthwestern.inforeadv4.com/</td><td>Reporting Time Frame

Within 24 hours of knowledge of event for initial report</td><td>Report Form

UT Southwestern Data Safety & Monitoring Committee (DSMC) SAE Report form to be used</td></tr>
<tr><td>LEAD SITE (UT SOUTHWESTERN): FDA REPORTABLE EVENTS

For SAE reports required to be submitted to the FDA as determined by the Sponsor-Investigator, Lead Site (UT Southwestern) will submit the FDA MedWatch 3500A form to the FDA and a copy sent to:

● Katharine Grimmer
Sagiment Biosciences Inc.
Email: katharine.grimmer@sagimet.com</td><td>Reporting Time Frame

Per FDA Guidelines</td><td>Report Form

FDA MedWatch 3500A Form</td></tr>
<tr><td>Lead Site:
UT Southwestern (UTSW) Institutional Review Board (IRB)
Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation</td><td>Per policy</td><td>Per policy</td></tr>
<tr><td>Sub-Site(s):
IRB of Record</td><td>Per policy</td><td>Per policy</td></tr>
</table>

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW HRPP within 5 working days of study team awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of study team awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/hrpp/quality-assurance/

7.4 Stopping Rules

The entire study will be stopped if:

- The protocol-specified treatment is considered too toxic to continue the study
- Evidence has emerged that, in the opinion of the DSMC or investigator, makes the continuation of the study unnecessary or unethical
- The stated objectives of the study are achieved
- Sagimet Biosciences, Inc. discontinues the development of TVB-2640

In terminating the study, the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

8.0 DRUG/TREATMENT INFORMATION

8.1 TVB-2640

- Other names for the drug(s): 4(1-{[4-Cyclobutyl-2-methyl-5-(5-methyl(1,2,4-triazol-3-yl))phenyl]carbonyl}-4-piperidyl)benzenecarbonitrile
- Classification - type of agent: small molecule
- Mode of action: It is a potent and reversible inhibitor of the fatty acid synthase enzyme. It inhibits the β-ketoacyl reductase enzyme activity of the enzyme. It is uncompetitive with both NADPH and acetoacetyl-CoA in inhibiting ketoacyl reductase activity. The result is reduced palmitate synthesis.
- Storage and stability: Stored at room temperature, the compound is stable for over one year. Store in a secure, limited access storage area. Do not freeze or refrigerate.
- Protocol dose: 100 mg/m^2 equivalent to two to four 50-mg tablets
- Preparation: 50-mg tablets
- Route of administration for this study: Orally
- Incompatibilities: None
- Availability: Packaged in bulk, screw-top plastic bottles provided free of charge to UTSW IDS Pharmacy by Sagimet Biosciences, Inc.
- Side effects: Alopecia, dry eyes, increased lacrimation, palmar-plantar dysaesthesias, corneal edema, skin exfoliation, dry skin, anorexia, fatigue, nausea, vomiting, dyspepsia, dry mouth, diarrhea, iritis, keratitis, uveitis, xerophthalmia, and increased lacrimation.

8.2 Toxicity Management and Monitoring

8.2.1 Eye Toxicity

Treatment: to be symptomatic. At the first sign (deemed a grade 1 per Common Terminology Criteria for Adverse Events CTCAE 5.0; asymptomatic, clinical or diagnostic observations only, mild symptoms relieved by lubricants) of dryness, itchiness, redness or otherwise “gritty” eye.

- Ophthalmologist consult: Patient should be referred for further evaluation and treatment recommendations within 48 hours of report of symptoms

- Eye drops: soothe XP-Xtra Protection Emollient (Lubricant) Eye Drops (or similar product) can be used 4-6 times daily. If the patient finds this to be too cumbersome and/or altering to his/her vision, then a less oily eye drop such as Soothe Hydration Lubricant Eye drop or Visine (or similar product) can be used during the day with the mineral oil based [Soothe XP-Xtra Protection Emollient (Lubricant) Eye Drops or similar products] drops to be used nightly before bed.

- Warm compresses: patient can apply warm compresses to eyes 4-6 times a day or as needed to unblock tear ducts and reduce inflammation. Patient should be instructed to place a warm, wet washcloth over the eyelids (a fresh/sterile cloth to be used with each compress application) for up to 10 minutes.

- Azasite: patient can apply to eyelid with a cotton swab such as Q-Tip once daily to reduce inflammation (as needed).

8.2.2 Hand and Foot Syndrome

Prophylaxis: patient can use a daily moisturizing cream on hands and feet with a high

emollient factor such as Eucerin, Vanicream, O'Keefe's Working Hands (or similar product), 4-6 times a day. Patient can also use a non-drying daily wash on hands and feet such as Cetaphil or Vanicream Soap (or similar product).

If hand-foot symptoms/signs are detected despite the above prophylaxis recommendations:

Treatment: to be symptomatic. At the first sign (deemed a grade 1; per CTCAE 5.0; minimal skin changes or dermatitis (e.g. erythema, edema, or hyperkeratosis without pain):

- Moisturizing: daily cream on hands and feet to continue;
- Urea cream: can be considered if scaling, peeling present;
- Antihistamines: oral antihistamine medication to be considered for reduction of itchiness.

If hand-foot symptoms/signs present at or escalate to a grade 2 or above:

- Steroid Ointment (N.B. not cream): patient can apply ointment based barrier layer of topical steroid cream Diprolene (or similar product) once daily.
- Dermatologist consult: should be considered for further evaluation and treatment recommendations.

8.2.3 Pulmonary Toxicity

Suspected Pneumonitis will be managed as follows:

- Patients who experience pneumonitis or any unexpected or otherwise unexplained significant respiratory symptoms are to have all study treatment interrupted and treatment with systemic corticosteroids should be considered immediately. It is the Investigator's choice whether empirical antibiotic therapy should be instituted, even in the absence of a causative organism being isolated. When symptoms improve to ≤Grade 1, a steroid taper should be started.
- Treatment is to be interrupted until symptoms and signs of possible pneumonitis resolve to ≤Grade 1. If symptoms do not resolve to ≤Grade 1 within 8 weeks or prednisone or equivalent corticosteroid is not reduced to ≤10 mg/day within 12 weeks, then study treatment is to be permanently discontinued.
- Study treatment is to be permanently discontinued for patients who experience Grade 3 or 4 pneumonitis. For such patients, intravenous steroid treatment as well as additional anti-inflammatory measures should be considered and administered, as needed. Prophylactic antibiotics for opportunistic infections should be considered in the case of prolonged steroid administration.
- Patients who experience a return of symptoms upon re-challenge with study treatment are to have study treatment permanently discontinued.
- Any sign of pneumonitis of any grade should be reported in the same manner as an SAE and the study Principal Investigator should be alerted immediately.

8.3 Return and Retention of Study Drug

Accountability for the study drug at the trial site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Sagiment Biosciences or disposal of the drug, if approved by Sagimet Biosciences, will be maintained by the clinical site.

These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Sagimet Biosciences. Accountability records will include dates, quantities, batch/serial numbers, expiration dates, and patient numbers. The sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits. All non-dispensed, and dispensed but unused, study drug will be retained at the site until it is inventoried by the monitor. All non-dispensed, dispensed but unused, or expired study drug will be returned to Sagimet Biosciences, 3715 Haven Avenue, Suite 220 Menlo Park, CA 94025, phone 650-561-8600 ext. 7 or if authorized, disposed of at the study site and documented. All material containing study drug will be treated and disposed of as hazardous waste in accordance with governing regulations.

9.0 CORRELATIVES/SPECIAL STUDIES

9.1 Fasting Plasma Lipidomics Sample Collection Guidelines

Samples will be collected at the following time points: pretreatment and prior to dosing during week 4, 10mL blood in EDTA containing purple top tubes. Plasma will be isolated and frozen at -80^{o}C until assayed.

NOTE: Samples for plasma lipidomics must be collected after overnight fast; in cases where plasma lipidomics are collected on the same day as ^{11}C-acetate PET scan, the samples must be collected before ^{11}C-acetate administration.

9.2 Fasting Plasma Lipidomics Assay Methodology

After thawing plasma samples, 10uL is added to 1mL of dichloromethane/methanol 2:1 mixture along with 20ul of a custom surrogate standard mix containing representative lipids that have either odd-chain fatty acids or deuterated fatty acids or both. The sample is vortexed, and centrifuged to pellet precipitated protein. 600uL of supernatant is transferred to a fresh vial, 200uL phosphate buffered saline is added, and the sample is vortexed and centrifuged to separate phases. 300uL of organic phase--lower layer is added to 300uL of isopropanol/methanol 1:1 containing 16mM ammonium fluoride to generate the appropriate sample matrix for mass spectral analysis. The sample is infused into the mass spectrometer via an autosampler--LEAP DLW that loads a 100µl syringe and infuses the sample through a two-way valve into a Sciex 5600+ TripleTOF at 12µl/min for 6 minutes. Two datasets are acquired: A TOF scan from 200-1200 Da. The TOF scan yields a high-resolution, accurate-mass analysis of all lipid molecular species--protonated/ deprotonated, adducts, etc.. In addition to acquisition of the TOF spectrum, this one-minute acquisition allows for the electrospray signal to stabilize following the injection cycle where valves, syringes, and other components were activating to initiate sample delivery and the second acquisition requires a stable signal during acquisition. Immediately following the TOF acquisition, the instrument begins the MS/MS^{ALL} acquisition. The mass spectrometer acquires a product-ion spectrum at *m/z* 200 Da using a fixed collision energy. It then collects a product-ion spectrum at *m/z* 201 Da, 202 Da, 203 Da, etc. Product-ion spectra are collected at each unit mass adjusted for the mass defect of hydrogen to *m/z* 1200 Da. This infusion-based acquisition is performed once in positive and once in negative ionization modes to insure coverage of the lipidome--acidic, basic, and neutral compounds. The acquired datasets are unique in that they contain a complete mass spectral picture of the sample. The TOF data can be used to definitively identify molecular ions as it can be internally recalibrated to yield <2ppm mass accuracy. Elemental composition can be assigned to any mass feature to verify a signal if necessary. The MS/MS^{ALL} data can be interrogated in many ways to identify lipid species by precursor-ion or neutral loss interrogation. This is facilitated by a customized suite of software--basic data visualization, principal component analysis, and quantitation software that incorporate the unique MS/MS^{ALL} data format. Previous analysis of human plasma has identified hundreds of unique lipid species from over 18 classes of lipids.

Relative changes between lipid classes, and changes within lipid classes--acyl chain length, degree of saturation can then be evaluated.

9.3 ^{11}C-acetate PET Scans

^{11}C-Acetate PET/CT scans will be performed only at the UTSW site and are not required at other study sites. Informed consent is required for ^{11}C-acetate PET scan. In certain circumstances (eg, ^{11}C-Acetate PET/CT not available), upon discussion with and approval by the Principal Investigator, patients may be enrolled at UTSW without undergoing ^{11}C-Acetate PET/CT.

The [^{11}C]-Acetate is an investigational PET radiopharmaceutical and the PET/CT scans will be performed under IND No 137383 held by Dr. Rofsky, a co-investigator. [^{11}C]-Acetate PET/CT scans will be performed at baseline and during week four of treatment. The patient will be positioned supine in the PET/CT scanner for a dynamic scan over the lung tumor. [^{11}C]-Acetate PET/CT will be performed using the standard dose of 0.3 mCi/kg up to a maximum of 30mCi for [^{11}C]-Acetate. The injection line will be flushed with normal saline post-injection. A maximum of two [^{11}C]-Acetate PET/CT scans will be performed – at baseline and during week four of therapy. For detailed information regarding [^{11}C]-Acetate PET/CT acquisition, please reference the corresponding [^{11}C]-Acetate protocol.

NOTE: In cases where ^{11}C-acetate PET scan is performed on the same day as fasting plasma lipidomics samples are collected, the ^{11}C-acetate must be administered after collection of fasting plasma lipidomics samples.

Potential adverse events for ^{11}C Acetate:

The following are extremely rare potential risks that are associated with the use of IV injected radiopharmaceuticals that could apply to the IV administration of [^{11}C]-Acetate. There is the potential with intravenous injection of [^{11}C]-Acetate for allergic reactions and potentially anaphylaxis. This has not been observed in limited human exposure to date. Throughout the PET procedure, patients will be monitored by trained personnel for any symptoms or signs of an allergic reaction. Emergency equipment and medical personnel are available in the event of an allergic reaction. The injection site may become infected. The dose might be extravasated, leading to localized pain / discomfort. [^{11}C]-Acetate is a positron emitting radiopharmaceutical. As such, it poses an intrinsic radiation exposure risk. However, when administered in accordance with the Investigator's Brochure as a PET imaging agent, this risk is felt to be extremely small. The organ and total body doses associated with this PET imaging agent is comparable to those associated with other widely used clinical nuclear medicine procedures and referenced in the FDA approved IND at UTSW (IND No 137383), under which ^{11}C Acetate PET/CT.

[^{11}C]-Acetate PET/CT Image Analysis

Volumes of interest--VOIs will be drawn around the target lesions on the [^{11}C]-Acetate PET images based on tumor localization from the baseline CT. [^{11}C]-Acetate PET studies will be registered based on their CT transmission scan images, and time activity curves--TACs will be calculated. [^{11}C]-Acetate kinetic analysis will be used to distinguish how much uptake of tracer acetate in tumor tissue is true retention in the biosynthetic pathway as opposed to CO_2 metabolite. Failure to account for CO_2 could result in significant errors in the estimation of the incorporation of acetate in biosynthetic pathways. The most significant metabolite for acetate is $^{11}CO_2$, liberated when acetylcoenzyme A enters the tricarboxylic acid cycle. This is conveniently modeled because CO_2 transport into tissues is largely reversible and is easily separated from acetate retained in membranes and proteins, which is largely irreversible. Several methods of analysis will be used for the evaluation of acetate images and results: 1) Visual inspection of the images to see if one can distinguish uptake in tumors and normal tissues. This requires coregistration of CT images to aid localizing tumor and normal body structures. 2) Quantification by the standardized uptake value--SUV in a region of interest. SUV is defined as the activity per

gram in the tissue divided by the activity per gram in the whole body. If the tracer distributes throughout the body in a completely uniform manner, then the SUV for any tissue would by 1.0. Implicit in this definition is the requirement that the tomogram be properly calibrated so that the activity in tissue can be determined in µCi/mL. This value is then divided by µCi injected and divided by body weight in kilograms. We will also calculate the metabolic volume of the tumor at baseline as well as during week 4 of therapy. 3) We have also formulated a compartmental approach to analyze acetate retention. Tracer kinetic modeling of dynamic studies can separate the contributions of delivery of the tracer from the incorporated or trapped species, free compound and labeled metabolites. Both compartmental and graphical analysis of similar compounds, such as ^{11}C-thymidine have been reported (Mankoff, 1996; Mankoff, 1998) to provide more rigorous measure of biochemical flux from dynamic PET data. This approach is important for [^{11}C]-Acetate, where the compound undergoes both incorporation into lipids (and therefore tissue trapping) and energy metabolism to $^{11}CO_2$. We will apply similar methods to the [^{11}C]-Acetate portion of this study to test if more rigorous image analysis to measure flux of acetate through the *fatty acid synthase* pathway into lipids leads to a better marker of response. Compartmental models are used for data analysis in conjunction with a method for parameter optimization. This approach requires an input function, a blood or plasma time activity-curve. In our acetate model this includes the quantitation of labeled CO_2 and acetate in the blood. The tissue time-activity-curve is determined from dynamic PET images. These curves are then fit using the compartmental models and a parameter optimization program.

9.4 Biomarkers in Sebaceous Secretions

This is a non-invasive procedure. Sebaceous secretions (sebum) for biomarker assessments are to be collected via Sebutape patches (if available) placed on the forehead, for all patients over 30±5 minutes pre-dose at screening and C2D1. At each scheduled timepoint, the Sebutape patches (if available) must remain on the patient's forehead for 30±5 minutes and be removed prior to administration of the TVB-2640 dose. Refer to the Study Manual for details regarding sebaceous secretion sample collection, processing, storage, and shipment.

9.5 Pharmacokinetic Assessments

PK samples will be taken according to the scheduled shown in the table below. PK timepoints have been selected and grouped to provide sufficient PK data and fit within hours of operation. The PK group will be assigned at enrollment by the study team in repeating numerical order. For instance, subjects 1-4 will be assigned to groups 1-4, then subject 5 will be assigned to group 1 and subject 6 will be assigned to group 2.

One vacutainer tube (6ml lavender top, K2 EDTA) will be collected at each time point.

Time points for PK Samples

		Group 1	Group 2	Group 3	Group 4
Sampling Time point	**Window**				
Screening/Baseline: Prior to 1st dose	-4 hours	X	X	X	X
Cycle 1, Day 8: 24 hours after Cycle 1 Day 7 dose	±1 hour	X	X	X	X
Cycle 1, Day 8: 30 minutes post dose	±15 min	X			
Cycle 1, Day 8: 4 hours post dose	±30 min	X			

Cycle 1, Day 8: 1 Hour post dose	±15 min		X		
Cycle 1, Day 8: 5 Hours post dose	±30 min		X		
Cycle 1, Day 8: 2 Hours post dose	±15 min			X	
Cycle 1, Day 8: 6 Hours post dose	±30 min			X	
Cycle 1, Day 8: 3 Hours post dose	±15 min				X
Cycle 1, Day 8: 8 Hours post dose	±30 min				X

9.6 Archival Tissue Collection

If available, archival tissue from diagnostic biopsies will be collected for biomarker analysis. Ten unstained slides (5-10 micron, preferably 10 microns) will be requested for each subject. If 10 slides are not available, a smaller number of slides may be requested if adequate for the analysis. Tissue may be requested at any time during participation.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a prospective one-arm, two-stage phase 2 trial of TVB-2640 in *KRAS* mutant NSCLC patients. 13 patients will be treated with a minimum of 1 cycle of TVB-2640 therapy over 8 weeks. Patients with stable disease or partial/complete remissions will continue therapy. The endpoints are response rate—RR, disease control rate—DCR, PFS—progression-free survival, CTCAEv5.0 toxicities, plasma lipid levels, collection of sebaceous secretion via Sebutape (if available), and ^{11}C-acetate PET tumor imaging.

10.2 Sample Size Justification

This is a two-stage phase 2 trial of TVB-2640 in patients with previously treated advanced NSCLC. The primary endpoint is radiographic response rate, which is selected because (a) single-agent responses were observed in *KRAS* mutant cancers in the earlier phase 1 trial, and (b) it is more reliable than a disease control rate or progression-free survival endpoint in a single-arm trial. We project a response rate of 25% (H1, alternate hypothesis), compared to a historical control of 10% (H0, null hypothesis).

In the first stage, we will enroll **13 patients.** If fewer than 2 patients achieve response, the study will be stopped. If 2 or more patients have a radiographic response, we will enroll an **additional 21 patients,** for a **total accrual of 34 patients.** The null hypothesis will be rejected if 6 or more responses are observed in 34 patients. This design yields a type I error rate of 0.1 and power of 81% when the true response rate is 25%.

10.3 Data Analyses Plans

Exact binomial test will be used to estimate the RR and DCR and the toxicity rate in patients receiving TVB-2640 along with corresponding 95% confidence interval. Paired t-tests or Wilcoxon signed rank tests will be conducted to compare the changes in plasma lipids pretreatment and after 4 weeks of therapy. We anticipate TVB-2640 will decrease fatty acids, triglycerides, percent fatty acid saturation, tripalmitin and lysophosphatidylcholine and will increase malonyl carnitine and diacylglycerols after four weeks of therapy based on results in rodents. We also predict high tumor ^{11}C-acetate 90minute uptake with TVB-

2640-induced decreases in uptake. Exact binomial will be used to compare RR and DCR with the historical RR and DCR. Exact binomial test will be performed to evaluate the RR/DCR for patients with high pretreatment ^{11}C-acetate tumor uptake. Kaplan-Meier method will be used to estimate the response duration and disease control rate along with the 95% confidence interval using Greenwood's formula. Spearman rank correlation will be computed to estimate the correlation between tumor TVB-2640 exposure and tumor ^{11}C-acetate retention. Student's t-tests or Wilcoxon rank-sum tests will be used to examine the change in plasma lipid levels between responders and non-responders.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any sub-site, the following documentation must be provided to the Multi-Center Investigator Initial Trials email: SCCC-IIT@UTSouthwestern.edu.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal-wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form

- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.4 Registration/Randomization Procedures

All subjects must be registered with the Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Research Office Study Coordinator. To register a subject, email IIT Team at SCCC-IIT@UTSouthwestern.edu Monday through Friday 9:00am-5:00pm CST.

New subjects will receive a number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 001 will become 001-01 upon enrollment. If subject 002 screen fails, and subject 003 is the next subject enrolled, subject 003 will become 003-02 and so-on.

For multi-center studies, which includes two sites, the first patient consented and enrolled at the first site will be subject 01-001-01. The second subject enrolled at the second site might be 02-003-02.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study ID in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

11.5 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project.

In order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed.

Trial monitoring will be conducted according to the study specific monitoring plan. For guidance on creating a monitoring plan, refer to the UTSW SCCC IIT Management Manual.

Toxicity reviews will be performed at every cycle day 1. These reviews will be documented in the case report forms. Serious Adverse Events will be reported to Sagimet Biosciences and SCC-DSMC.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local

serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The Quality Assurance Coordinator (QAC) works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

  ➢ **Reporting requirement***: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

11.6.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

  ➢ **Reporting requirement***: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

11.6.3 Serious Noncompliance (formerly called **major deviations** or **violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or
- adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
- adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research)

  ➢ **Reporting requirement***: Serious Noncompliance must be promptly

reported tothe IRB within 5 working days of discovery.

11.6.4 Continuing Noncompliance: includes a pattern of repeated noncompliance (in or more protocols simultaneously, or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

- **Reporting requirement***: Continuing Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

11.6.5 Noncompliance (that is neither serious nor continuing; formerly called minor deviations) any departure from IRB-approved research that:

- Does not meet the definition of serious noncompliance or continuing noncompliance
  - **Reporting requirement***: Noncompliance that is neither serious nor continuing should be tracked and summarized the next IRB continuing review, or the notice of study closure- whichever comes first..

*Reporting Requirements reflect UTSW HRPP/IRB guidelines; participating sites should follow the reporting guidelines for their IRB of record

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

1. FACT-L Questionnaire
2. QLQ-C30 Questionnaire
3. Pill Diary for TVB-2640

FACT-L (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-L (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-L (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

General Instructions- TVB-2640 Dosing Diary

TVB-2640 tablets must be stored at room temperature. Keep out of reach of children. The study medication may not be taken by anyone but you.

- Take TVB-2640 tablets by mouth once each day. Take the tablets on an empty stomach (either one hour before or two hours after a meal). Swallow the tablets whole.
- Each dose should be separated by 24 hours (± 4 hours).
- Each day, record the date and time the tablet(s) were taken on the diary card. If a dose is missed, include the reason the dose was not taken.
- Return the diary card to your study doctor at each visit and discuss any side-effects experienced with your study nurse or doctor.
- Return any unused TVB-2640 tablets that were dispensed at the next visit.

Patient Number: _____
Patient Initials: _____
Cycle #: _____

Please contact _____ at _____ if you have any questions or concerns about your treatment.

TVB-2640 Dosing Diary – Week 1

	Date (MM/DD/YY)	Time of dose	*Check if dose missed ☐	Number of Tablets Taken	Dose taken on empty stomach?	Comments
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	

Patient Number: _____ Patient Initials: _____ Cycle #: _____

TVB-2640 Dosing Diary – Week 2

	Date (MM/DD/YY)	Time of dose	*Check if dose missed ☐	Number of Tablets Taken	Dose taken on empty stomach?	Comments
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	

Patient Number: _____ Patient Initials: _____ Cycle #: _____

TVB-2640 Dosing Diary – Week 3

	Date (MM/DD/YY)	Time of dose	*Check if dose missed ☐	Number of Tablets Taken	Dose taken on empty stomach?	Comments
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	

Patient Number: _____ Patient Initials: _____ Cycle #: _____

TVB-2640 Dosing Diary – Week 4

	Date (MM/DD/YY)	Time of dose	*Check if dose missed ☐	Number of Tablets Taken	Dose taken on empty stomach?	Comments
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	
	___/___/___	___:___ AM PM	☐		YES NO	

Patient Number: _____ Patient Initials: _____ Cycle #: _____