A phase II study of maintenance vorolanib and atezolizumab in patients with extensive-stage SCLC

Washington University School of Medicine
Division of Oncology
660 South Euclid Avenue, Campus Box 8056
St. Louis, MO 63110

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Principal Investigator: **Daniel Morgensztern, M.D.**
Phone: (314) 362-5817
E-mail: danielmorgensztern@wustl.edu

Sub-Investigators	**Modality**
Maria Baggstrom, M.D.	Medical Oncology
Siddhartha Devarakonda, M.D.	Medical Oncology
Ramaswamy Govindan, M.D.	Medical Oncology
Peter Oppelt, M.D.	Medical Oncology
Kevin Palka, M.D.	Medical Oncology
Timothy Rearden, M.D.	Medical Oncology
Caron Rigden, M.D.	Medical Oncology
Saiama Waqar, M.D.	Medical Oncology
Jeff Ward, M.D., Ph.D.	Medical Oncology
Brett Herzog, M.D., Ph.D.	Medical Oncology
Feng Gao, M.D., Ph.D.	Biostatistics
Danielle Turlington, PharmD	Pharmacy

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Protocol Revision History

Initial Approval Version	**19 June 2020**
Amendment #1 Version	**16 February 2021**
Amendment #2 Version	**05 November 2021**
Amendment #3 Version	**10 May 2022**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
BMT	Bone marrow transplant
CBC	Complete blood count
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRc	Cytogenetic complete remission
CRi	Complete remission incomplete
CRm	Morphologic complete remission
CRF	Case report form
CST	Central standard time
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose limiting toxicity
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
DSMC	Data Safety Monitoring Committee
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FWA	Federal wide assurance
GCP	Good Clinical Practice
HHS	Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IND	Investigational New Drug
IRB	Institutional Review Board
MDS	Myelodysplastic syndrome
MM	Multiple myeloma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Cancer Center Network

NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
OHRP	Office of Human Research Protections
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PR	Partial response
PSA	Prostate-specific antigen
QASMC	Quality Assurance and Safety Monitoring Committee
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RFS	Relapse free survival
RR	Response rate
SAE	Serious adverse event
SCLC	Small cell lung cancer
SCC	Siteman Cancer Center
SCT	Stem cell transplant
SD	Stable disease
TSH	Thyroid stimulating hormone
TTP	Time to progression
UPN	Unique patient number
US	Ultrasound
VEGF	Vascular endothelial growth factor
WBC	White blood cell (count)

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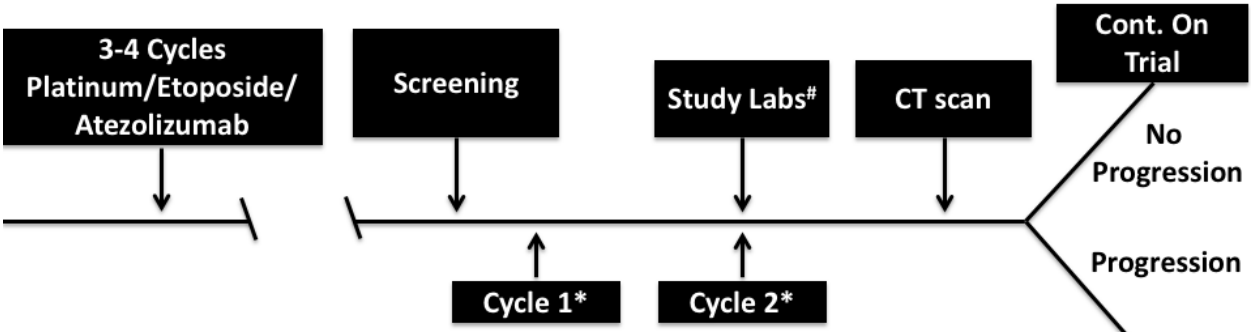
PROTOCOL SUMMARY

Synopsis

Title:	A phase II study of maintenance vorolanib and atezolizumab in patients with extensive-stage SCLC
Study Description:	Our hypothesis is that the addition of vorolanib to atezolizumab during the maintenance phase of first-line therapy for extensive-stage small cell lung cancer after at least 3 but not more than 4 cycles of induction therapy with platinum, etoposide, and atezolizumab will improve progression-free survival (PFS) compared to single agent atezolizumab or sunitinib used in historical controls. Consenting and eligible patients who have no evidence of tumor progression after 3 to 4 cycles of induction therapy will receive atezolizumab IV every 3 weeks and vorolanib by mouth daily. Note that the induction chemotherapy is standard of care; only the maintenance treatment with vorolanib and atezolizumab are considered investigational for purposes of this protocol.
Objectives:	Primary Objective: To determine PFS at 6 months for maintenance vorolanib with atezolizumab after treatment with platinum, etoposide, and atezolizumab in patients with extensive-stage SCLC. Secondary Objectives: 1. To determine the PFS for maintenance vorolanib with atezolizumab after treatment with platinum, etoposide, and atezolizumab in patients with extensive-stage SCLC. 2. To determine the overall survival (OS) for the combination of maintenance vorolanib and atezolizumab in patients with extensive-stage SCLC. 3. To evaluate toxicity and tolerability for the combination of maintenance vorolanib and atezolizumab in patients with extensive-stage SCLC.
Endpoints:	1. Kaplan-Meier product limit estimator will be used to estimate the PFS at 6 months, with the inclusion of 90% confidence interval. 2. Kaplan-Meier product limit estimator will be used to estimate the PFS. 3. Kaplan-Meier product limit estimator will be used to estimate the OS. 4. Toxicity will be assessed using NCI-CTCAE v 5.0.

Study Population:	Thirty-three (33) adults with extensive stage small cell lung cancer will be enrolled to this study.
Phase:	II
Description of Sites / Facilities Enrolling:	This is a single center study enrolling at Siteman Cancer Center at Washington University School of Medicine in St. Louis, MO.
Description of Study Intervention:	Atezolizumab is administered intravenously at a dose of 1200 mg on Day 1 of each 21-day cycle. Vorolanib is administered orally at a dose of 200 mg on Days 1 through 21 of each 21-day cycle.
Study Duration:	30 to 36 months
Participant Duration:	Participants may receive treatment until evidence of disease progression, severe toxicity, or other protocol-defined termination point.

SCHEMA



*Cycle = 21 days
Vorolanib 200 mg PO QD
Atezolizumab 1,200 mg IV Q21 days

⊣ ⊢: 3-6 weeks

Screening: CT Scan/Brain MRI/Study Labs#
#Peripheral Research Blood (see Section 10.1.1)

1.0 SCHEDULE OF ACTIVITIES

Screening can only start after confirmation of no tumor progression after at least 3 and not more than 4 cycles of induction chemotherapy (as prescribed per standard of care treatment). Baseline imaging should be conducted within 21 days and laboratory tests within 7 days prior to start of study treatment. There is a 5-day window for each cycle of treatment. Cycles are 21 days. The first cycle should begin no more than six weeks and no sooner than three weeks after last dose of induction treatment. This period may be extended to 8 weeks in patients requiring brain radiotherapy after completion of induction chemo/immunotherapy for brain metastases.

	Screening[6]	**C1D1[12]**	**C2D1**	**D1 of every subsequent cycle**	**Every 6 Weeks through Week 24[9, 10]**	**Every 12 weeks[10]**	**EOT**	**F/U[3]**
Informed Consent	X							
H&P, ECOG PS	X	X	X	X			X	
CBC diff, plts	X	X	X	X				
CMP, lipase, amylase[5]	X	X	X	X				
LDH	X	X						
PTT/aPTT, INR	X	X	X	X				
TSH with reflex free T4	X	X		X[13]				
Urinalysis	X			X				
Hepatitis B and C test	X							
Pregnancy test	X[1]							
ECG	X							
CT scan	X				X	X[9]	X	
Brain MRI	X					X		
Vorolanib		X----------(Daily)----------X						
Atezolizumab		X	X	X				
Research blood[11]	X[7]		X				X	
Tissue collection	X[4]						X[4]	
AE assessment	X[8]	X----------X[2]						
Progression and survival								X

1. For women of childbearing potential only, pregnancy test must be obtained within 7 days prior to C1D1.
2. For 90 days after end of treatment.
3. Every 6 months for 3 years. Patient status will be reviewed through the medical record or phone contact.
4. When available, archival tissue will be used. Baseline fresh biopsy will be optional. If a repeat biopsy is done at the time of disease progression, a research tissue sample will be taken at that time.
5. CMP includes glucose, calcium, sodium, potassium, CO2, chloride, BUN, creatinine, alkaline phosphatase, alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, albumin, and total protein.

6. Once consent is obtained, screening lab tests should be performed within 7 days prior to C1D1, with the exception of research blood sample.
7. Research blood sample at screening should be obtained within 21 days prior to start of C1D1. Patient must be determined eligible for the study prior to research blood draw.
8. AE assessment at baseline is intended to establish patient's current medical condition. No regulatory reporting of AEs at baseline is required.
9. CT should be performed every 6 weeks for the first 6 months. After the Week 24 scans, CT should be performed every 12 weeks thereafter (ie, Week 36, Week 48, etc). Imaging will follow calendar days without adjustments for delays in cycle starts.
10. +/- 7 days
11. Patients with hemoglobin below 9 mg/dL will not have blood collection.
12. Baseline labs should be checked to verify eligibility.
13. TSH should be checked at the end of every 2 cycles.

2.0 INTRODUCTION

2.1 Background

2.1.1 Small cell lung cancer

Small cell lung cancer (SCLC), which accounts for approximately 13% of all cases of lung cancer in the United States, is an aggressive tumor characterized by rapid doubling time and early development of metastases.[1] Despite the good response to initial therapy, essentially all patients with metastatic disease and the majority of those with earlier stages develop tumor progression.[2] The standard therapy for SCLC has been a combination of platinum plus etoposide, with response rates, median progression-free survival (PFS) and median overall survival (OS) of approximately 60%, 5 months and 9 months respectively.[3-5] In the phase II Cancer and Leukemia Group B trial 30504, patients with extensive stage SCLC who did not have tumor progression after four to six cycles of carboplatin plus etoposide were randomized to maintenance sunitinib or placebo.[6] The median PFS from randomization was increased in the sunitinib arm (3.7 months vs 2.1 months). More recently, the addition of programmed death ligand 1 (PD-L1) atezolizumab to carboplatin plus etoposide was associated with increased PFS and OS when compared to chemotherapy alone, with the former increasing from 4.3 months to 5.2 months and the latter from 10.3 months to 12.3 months respectively in the IMPower 133 trial.[7] More recently, data from the CASPIAN trial demonstrated that the addition of durvalumab to platinum-etoposide doublet therapy improved OS from 10.3 months to 13 months.[8]Although CASPIAN and the IMPower 133 trials represent landmark trials in the treatment of SCLC, the added benefit from immune checkpoint blockers is still modest, with an absolute increase in the median OS of only 2.0 months and 2.7 months for atezolizumab and durvalumab, respectively. At the time of relapse, SCLC is usually resistant to additional therapy, with modest efficacy from topotecan,[9,10] other chemotherapy drugs,[11] or immune checkpoint blockers. [12,13]

2.1.2 Atezolizumab

Under normal physiologic conditions, the immune checkpoint molecules maintain self-tolerance preventing autoimmunity and limiting collateral damage to the normal tissues during response to infections.[14,15] Cancer cells however, may co-opt these molecules to evade immune destruction. Programmed death 1 (PD-1), one of the key checkpoint molecules, may bind to two ligands, PD-L1/PD-L2. PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer.[16,17] Binding of PD-L1 to PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells.[18] Atezolizumab is a humanized IgG1 monoclonal antibody against PD-L1, which was approved in combination with carboplatin plus etoposide in patients with extensive stage SCLC.[7]

2.1.3 Vorolanib (X-82)

Vorolanib is an oral multi-kinase inhibitor of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), colony-stimulating factor 1 receptor (CSF1R), stem cell factor (c-Kit), and FMS-like tyrosine kinase 3 (FLT3). Vorolanib inhibits angiogenesis by binding its target receptors (VEGFR and PDGFR). Vorolanib is structurally related to sunitinib and was been designed to improve upon the safety profile without compromising the efficacy of sunitinib. The combined effect on VEGFR and PDGFR allows these drugs to target endothelial cells and pericytes, respectively. In addition to the primary targets of VEGFR and PDGFR, CSF1R blockage reprograms tumor-infiltrating macrophages and might improve responses to T-cell checkpoint inhibitor therapy.[19]

2.1.4 Study Rationale

Although the combination of platinum doublet with atezolizumab showed improved outcomes compared to chemotherapy alone and became the new standard of care in eligible patients, the benefit is modest and the survival for patients with extensive stage SCLC remains poor.

Preclinical models and biospecimens collected from patients who have participated in checkpoint inhibitor clinical trials have shown that the paucity and dysfunction of T-cells in tumors along with malformation of T memory cells were found to be associated with resistance to checkpoint inhibitors.[20] However, emerging evidence suggests that angiogenesis may play a key role in tumor-mediated immune regulation. VEGF may inhibit dendritic cell maturation[21,22] and T lymphocyte infiltration into the tumor microenvironment,[23] while anti-VEGF therapy can improve T-cell infiltration into tumors.[24] The combination of the monoclonal antibody against VEGFR2, ramucirumab, with the anti-PD1 antibody

pembrolizumab showed promising efficacy in patients with non-small cell lung cancer, urothelial and upper gastrointestinal malignancies.[25] Furthermore the combination of atezolizumab with the VEGF inhibitor bevacizumab was safe and improved PFS compared to sunitinib in patients with metastatic renal cell carcinoma expressing PD-L1.[26] The combination of immune checkpoint blockers with anti-angiogenic tyrosine kinase inhibitors, including axitinib[27] has also been shown to be feasible. In the phase I study with single agent vorolanib, the study ended prior to the determination of the maximum tolerated dose due to the apparent saturation of absorption at doses of 400 to 800 mg per day, with 400 mg per day becoming the recommended dose.[28] Nevertheless, in a phase I/II study evaluating the combination of nivolumab 240 mg every two weeks plus escalating doses of vorolanib from 200, 300 or 400 mg per day, the treatment was considered safe, although there was one dose-limiting toxicity of elevated liver enzymes in a patient enrolled into dose cohort 2 (300 mg).[29] Therefore, we chose voloranib 200 mg per day as the dose for the combination with atezolizumab.

Based on the data from maintenance sunitinib, which improved the median PFS from 2.1 to 3.7 months compared to placebo after induction chemotherapy,[6] estimated PFS from atezolizumab in the maintenance therapy of approximately 2.2 months,[7] and likely synergism between immune checkpoint blockers and anti-angiogenesis drugs, we propose the addition of voloranib to atezolizumab during the maintenance phase of first-line therapy for extensive-stage SCLC after three to four cycles of induction therapy with platinum, etoposide, and atezolizumab. We hypothesize that the addition of vorolanib to atezolizumab during maintenance therapy will improve the PFS compared to single agent atezolizumab or sunitinib from historical controls.

2.1.5 Correlative studies rationale

Vorolanib is a multikinase inhibitor mainly targeting VEGFR and PDGFR. Emerging evidence suggests that angiogenesis may play a key role in tumor-mediated immune regulation. In addition, high baseline angiopoietin-2 was found to be associated with poor survival in patients receiving CTLA-4 or PD-L1 inhibitors, and levels of angiopoietin-2 increase in patients after receiving CTLA-4 or PD-L1 inhibitors.[30] Exploring the change of a panel of markers including angiopoietin-2 and VEGF in the study may shed light on treatment response and mechanisms of resistance. Additionally, we plan to assess the predictive and prognostic value of PD-L1 expression level and other immune-related biomarkers such as tumor immune infiltrates in patients enrolled in the study.

3.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	

To determine the PFS at 6 months for maintenance vorolanib with atezolizumab after treatment with platinum, etoposide, and atezolizumab in patients with extensive stage SCLC.	Kaplan-Meier product limit estimator will be used to estimate the PFS at 6 months, with the inclusion of 90% confidence interval (CI).
Secondary	
To determine the PFS for maintenance vorolanib with atezolizumab after treatment with platinum, etoposide, and atezolizumab in patients with extensive stage SCLC.	Kaplan-Meier product limit estimator will be used to estimate the PFS.
To determine the overall survival (OS) for the combination of maintenance vorolanib and atezolizumab in patients with extensive stage SCLC.	Kaplan-Meier product limit estimator will be used to estimate the OS.
To evaluate toxicity and tolerability for the combination of maintenance vorolanib and atezolizumab in patients with extensive stage SCLC.	Toxicity by CTCAE v 5.0.
Tertiary/Exploratory	
To evaluate the duration of benefit for the combination of vorolanib and atezolizumab in patients with extensive stage SCLC.	
To evaluate for blood and tissue (when available) biomarkers before and after (if available) the maintenance therapy.	

4.0 STUDY POPULATION

4.1 Inclusion Criteria

1. Histologically or cytologically confirmed extensive stage small cell lung cancer without prior specific systemic therapy aside from induction with platinum, etoposide, and atezolizumab. Measurable disease is not required for eligibility.

2. Receipt of at least 3 cycles (and no more than 4 cycles) of platinum plus etoposide and atezolizumab during the induction phase, without tumor progression as determined by CT scan and brain MRI. Patients should be able to start the study treatment no more than 6 weeks from the last dose of induction chemo/immunotherapy. This period may be extended to 8 weeks in patients requiring brain radiotherapy after completion of induction chemo/immunotherapy for brain metastases.

3. At least 18 years of age.

4. ECOG performance status ≤ 1 (see Appendix A)

5. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1.5 K/cumm
   b. Platelets ≥ 100 K/cumm

c. Hemoglobin ≥ 9.0 g/dL
d. Total bilirubin ≤ 1.5 x IULN
e. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN (≤ 5 x IULN for patients with liver metastases)
f. Creatinine ≤ 1.5 x IULN OR measured or calculated creatinine clearance > 50 mL/min for patients with creatinine levels > 1.5 x IULN
g. Urine protein ≤ 1+ or urine protein to creatinine ratio ≤ 1; if UPC ratio is > 1 on urinalysis, then 24-hour urine collection for protein must be obtained and level must be < 1,000 mg for patient enrollment
h. aPTT and either INR or PT ≤ 1.5 x IULN unless participant is receiving anticoagulant therapy as long as PT or a PTT is within therapeutic range of intended use of anticoagulants.

6. Patients receiving therapeutic non-Coumadin anticoagulation are eligible, provided they are on a stable dose (per investigator judgment) of anticoagulant.

7. The effects of atezolizumab and vorolanib on the developing human fetus are unknown. For this reason, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of the study, and 31 weeks after last dose of study treatment. Women must use birth control for at least 31 weeks after last dose of study treatment. Women must not be breastfeeding.

8. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

4.2 Exclusion Criteria

1. A history of other malignancy with the exception of malignancies for which all treatment was completed at least 2 years before registration and the patient has no evidence of disease.

2. Currently receiving any other investigational agents.

3. Patients with untreated brain metastases are excluded. Patients with clinically evident CNS hemorrhage are excluded. Prophylactic cranial irradiation is not allowed. Patients with brain metastases treated with whole brain radiation therapy, radiosurgery, or surgery are eligible.

4. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to vorolanib, atezolizumab, or other agents used in the study.

5. Use of chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.

6. Systemic glucocorticoids with prednisone dose higher than 10 mg/day or equivalent.

7. Arterial or venous thromboembolic event, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to enrollment.

8. Uncontrolled or poorly controlled hypertension with systolic blood pressure (BP)> 160 mmHg systolic or diastolic > 100 mmHg for > 3 weeks prior to C1D1), despite standard medical management.

9. Gastrointestinal perforation, and/or fistula, or risk factors for perforation within 6 months prior to enrollment.

10. Grade 3 or 4 gastrointestinal bleeding within 3 months prior to enrollment.

11. History of active autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.

12. History of idiopathic pulmonary fibrosis, pneumonitis (including drug-induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan.

13. Hemoptysis (defined as bright red blood or ≥ ½ teaspoon) within 28 days prior to Cycle 1 Day 1 or with radiographic evidence of intratumor cavitation or radiologically documented evidence of major blood vessel invasion or encasement by cancer.

14. Serious or non-healing wound, ulcer, or bone fracture within 28 days prior to Cycle 1 Day 1.

15. Undergone major surgery within 28 days prior to Cycle 1 Day 1, or minor surgery/subcutaneous venous access device placement within 7 days prior to Cycle 1 Day 1, or has elective or planned major surgery to be performed during the course of the clinical trial.

16. Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis at a level of Child-Pugh B or worse, cirrhosis (any degree) with a history of hepatic encephalopathy or clinically meaningful ascites resulting from

cirrhosis (defined as ascites from cirrhosis requiring diuretics or paracentesis), fatty liver, and inherited liver disease.

17. Active tuberculosis.

18. Administration of a live, attenuated influenza vaccine within 4 weeks before Cycle 1 Day 1 or at any time during the study.

19. Severe infections within 2 weeks prior to Cycle 1 Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

20. Received oral or intravenous (IV) antibiotics within 2 weeks prior to Cycle 1 Day 1. Note: Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

21. History of deep venous thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to Cycle 1 Day 1.

22. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to C1D1.

23. Active hepatitis B (chronic or acute) defined as having a positive hepatitis B surface antigen (HBsAg) test at screening. Note: Patients with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test are eligible.

24. Patients known to be HIV positive are ineligible.

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

5.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

5.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below

1. The registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

5.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

5.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but do not meet all eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

6.0 TREATMENT PLAN

6.1 Study Intervention Description

Atezolizumab is a PD-L1 blocking antibody indicated for the treatment of urothelial carcinoma, non-small cell lung cancer, triple-negative breast cancer, and extensive stage small cell lung cancer (in combination with carboplatin and etoposide).

Vorolanib is an investigational agent not approved by the FDA.

6.2 Study Intervention Administration

Atezolizumab will be given intravenously at a dose of 1200 mg over 60 minutes on Day 1 of each 21-day cycle. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Vorolanib is administered orally at a dose of 200 mg on Days 1 through 21 of each 21-day cycle.

Vorolanib is an oral tablet intended to be taken whole with food at the same time (+/- 6 hours) every day. If a patient misses a dose, the patient should take the missed dose as soon as possible, but within 12 hours from the time they usually take their dose If more than 12 hours have passed the patient should restart at the next dose. If vomiting occurs after taking the study medication, the patient should be instructed not to retake the dose, and should just take his/her next scheduled dose of vorolanib. Patients will be instructed to bring all unused drug and their medication diary (Appendix D) to each study visit for assessment of compliance.

6.3 Definitions of Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 90-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment prior to completion of Cycle 2 and have not had any disease assessment.

6.4 Concomitant Therapy and Supportive Care Guidelines

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

6.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

6.4.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies while on the trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than atezolizumab and vorolanib
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza

vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the PI.
- Chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
- Vorolanib is primarily metabolized by CYP3A4 based on in vitro studies using human liver microsome. Therefore, concurrent use of any medication, herbal supplement or food known to be a strong inhibitor or strong inducer of CYP3A4 is prohibited unless there are no therapeutic alternatives.

Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator and the participant.

6.4.3 Rescue Medications and Supportive Care for Patients Receiving Atezolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to atezolizumab.

Note: If after the evaluation of the event, it is determined not to be related to atezolizumab, the Investigator does not need to follow the treatment guidance.

6.5 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to

have a negative serum pregnancy test within 7 days prior to the first dose of study treatment. Women must not be breastfeeding.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 31 weeks following the last dose of study treatment.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. A positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 31 weeks after the last dose of study treatment, the investigator must be notified in order to facilitate outcome follow-up.

6.6 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

Treatment may continue for up to two-years or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- Siteman Cancer Center or Xcovery Holdings decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

6.7 Duration of Follow-up

Patients will be followed by review of the medical record or through direct contact for survival every 6 months for up to 3 years after discontinuation of study treatment. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.8 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 6 weeks and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.0 DOSE DELAYS/ DOSE MODIFICATIONS

Dosing for atezolizumab and vorolanib should be modified as described in the sections below. If dosing is suspended due to an adverse event that does not resolve within 6 weeks and is deemed related to one but not the other agent, the unrelated drug(s) may be restarted at the PI's discretion depending on the toxicity profile. Other holds and modifications may be made at the discretion of the PI.

7.1 Atezolizumab Dose Modifications

Atezolizumab dose modification is not allowed. However, study treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment for up to 60 days after the last dose if they experience toxicity that require a dose to be withheld. If atezolizumab is withheld because of toxicity for > 60 days after the last dose, then the patient will be discontinued from atezolizumab treatment and will be followed for safety and efficacy.

Adverse Reaction	Severity/Grade of Reaction	Management
Pneumonitis	Grade 2	Withhold dose until improved to $\leq$ Grade 1 and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent
	Grade 3 or 4	Permanently discontinue

Hepatitis	AST or ALT >3-8 x ULN OR total bilirubin > 1.5-3 x ULN	Withhold dose until improved to ≤ Grade 1 and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	AST or ALT > 8 x ULN OR total bilirubin > 3 x ULN	Permanently discontinue
Colitis or Diarrhea	Grade 2 or 3	Withhold dose until improved to ≤ Grade 1and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 4	Permanently discontinue
Endocrinopathies (including hypophysitis, adrenal insufficiency, hyperthyroidism, and type 1 diabetes)	Grade 2, 3 or 4	Withhold dose until improved to ≤ Grade 1and clinically stable on hormone replacement therapy.
Pancreatitis	Amylase OR Lipase greater than 2 x ULN	Withhold dose until improved to ≤ Grade 1and clinically stable
Other immune-mediated adverse reactions	Grade 3	Withhold dose until improved to ≤ Grade 1and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 4	Permanently discontinue
Infections	Grade 3 or 4	Withhold dose until improved to ≤ Grade 1
Infusion-Related Reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

7.2 Vorolanib Dose Modifications

Patients will be initiated on 200 mg once daily of vorolanib. If toxicity occurs reduce dose according to the table below. Doses will not be re-escalated once reduced.

Starting Dose	200 mg
Level -1	100 mg

7.2.1 Dose Modifications Due to Hematologic Toxicity

If hematologic toxicity occurs, treatment with vorolanib should be held, and re-evaluated in at least 1 week. ANC and platelets should be monitored at least weekly until recovery. If ANC and/or platelets do not recover within 4 weeks, the patient will be discontinued from the trial unless the treating physician and PI agree that continued treatment at a reduced dose is in the best interest of the patient.

Event	Vorolanib Dose
Neutropenia (ANC)	
Grade 3-4	Hold dose until recovery to ≤ grade 2, then resume vorolanib at100 mg QD
Recurrent grade 4	Hold dose until recovery to ≤ grade 2, then resume vorolanib at 100 mg QD.
Thrombocytopenia	
Grade 3	Hold dose until improvement of platelets ≥ 75 x 10^9/L • If resolved in ≤ 5 days, then resume without a dose reduction. • If resolved in > 5 days, but < 4 weeks, then resume vorolanib at 100 mg QD.

7.2.2 Dose Modifications Due to Non-Hematologic Toxicity

Vorolanib can be held for one cycle due to toxicity. If vorolanib is held for longer than one cycle, discussion with the PI is required before restarting vorolanib. If a grade 3 non-hematologic toxicity that is possibly, probably, or definitely related to vorolanib occurs, that is expected to be manageable and reversible with dose reduction, treatment with vorolanib should be held until the toxicity resolves to ≤ grade 1 and resumed at 100 mg QD. Patients with grade 3 related non-hematologic toxicity that does not resolve to ≤ grade 1 within 2 weeks or any grade 4 related non-hematological toxicity on vorolanib at 100 mg QD should be removed from the trial.

Specific Recommendations for Rash, Nausea, Vomiting and Diarrhea:
For patients with grade 3 rash, nausea, vomiting, and/or diarrhea that is thought to be possibly, probably, or definitely related to vorolanib, then vorolanib should be held and supportive care initiated. If the grade 3 toxicity lasts ≤ 7 days, patients may restart vorolanib at 100 mg QD when toxicity returns to ≤ grade 1. If the patient has recurrent grade 3 toxicity despite supportive care, the patient will restart vorolanib 100 mg QD once toxicity has resolved to ≤ grade 1.

Specific Recommendations for Liver Function Test Abnormalities:
For patients with grade 3 liver enzyme elevations (AST/ALT) regardless of the cause, vorolanib should be held until the values recover to ≤ grade 1. Patients with a CTCAE v5 Grade 2 elevation of ALT in conjunction with a bilirubin ≥ 2 x ULN may remain in the study if a correctable, non-drug related cause of the liver test evaluations can be documented; otherwise, the patient must be discontinued from the trial.

Specific Recommendations for the Treatment of Hypertension:
Medication recommendations for the treatment of hypertension should be applied based on the patient and clinical status. General recommendations on initial management of hypertension are:

Patients should have optimally managed BP (≤160/90 mmHg) prior to starting study treatment. After starting treatment with vorolanib, BP should be monitored regularly. Patients with persistent HTN with readings above 140/90 mmHg, should initiate treatment with an ACE inhibitor (e.g. benazepril, lisonopril), angiotensin II receptor blocker (ARB) (e.g. losartan), thiazide diuretic (e.g. HCTZ), or dihydropyrimidine calcium channel blocker (e.g. amlodipine). Titrate to BP control with dose escalation of the chosen drug, or if additional agents are needed, choose a second agent from the recommended list.

For patients whose HTN is ≥160/90, vorolanib should be held and initiation of combination therapy with an ACE inhibitor and dihydropyrimidine calcium channel blocker is recommended. Patients should check BP daily and return to clinic within 3 weeks.

8.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through 90 days after end of treatment. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the electronic data capture system (EDC).

8.1 Washington University Sponsor-Investigator Reporting Requirements

8.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

8.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Washington University Sponsor/Investigator is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

8.1.3 Reporting to Xcovery

If a vorolanib event requires expedited safety reporting to the FDA, then Xcovery will need a copy of the final 7 or 15-day MedWatch report via email to safety@xcovery.com. Submit to Xcovery no later than calendar day 4 for a 7-day report and no later than calendar day 10 for a 15-day report, when possible, for submission to Competent Authorities, and any central/local ECs, and investigators as applicable per U.S. specific regulatory reporting requirements.

The Xcovery Safety Reporting specialist will generate an Expedited Safety Report/Cross Report Investigator Letter Template and will distribute the Safety Cross-Report packet (Expedited Safety Cross Report Investigator Alert Letter and MedWatch) to participating Xcovery investigators no later than calendar day 7 for a 7-day report and no later than calendar day 15 for a 15-day report, as per country U.S. specific reporting requirements.

8.1.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University Sponsor-Investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix B for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix B) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix B) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
- An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

8.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 8.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

9.0 PHARMACEUTICAL INFORMATION

9.1 Atezolizumab

Commercial supply of atezolizumab will be used.

Other Names: Tecentriq™, MPDL3280A
Classification: monoclonal antibody
M.W.: 150 KD
Mode of Action: anti-PD-L1

9.1.1 Description

Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte et al. 2007).

9.1.2 How Supplied

Atezolizumab is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Atezolizumab is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, at a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

9.1.3 Preparation

The prescribed dose of atezolizumab should be diluted in 250 mL 0.9% NaCl and infused through a 0.2 micrometer in-line filter. The IV bag may be constructed of PVC or PO; the IV infusion line may be constructed of PVC or PE; and the 0.2 micrometer in-line filter may be constructed of PES. The prepared solution may be stored at 2°C-8°C or room temperature for up to 8 hours.

9.1.4 Storage

2°C-8°C (36°F-46°F) Vial contents should not be frozen or shaken and should be protected from direct sunlight.

If a storage temperature excursion is identified, promptly return atezolizumab to 2°C-8°C (36°F-46°F) and quarantine the supplies.

9.1.5 Stability

Stability studies are ongoing.

CAUTION: No preservative is used in atezolizumab; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial.

9.1.6 Route of Administration

IV infusion.

9.1.7 Method of Administration

Atezolizumab is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. No premedication is indicated for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions.

9.1.8 Potential Drug Interactions

Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

9.2 Vorolanib

9.2.1 Vorolanib Description

Oral vorolanib drug product has been formulated as orange tablets with dosage strengths of 50 mg (oblong tablets) or 100 mg (oblong tablets) of vorolanib drug substance. The tablets are coated with a colored, nonfunctional, globally accepted film coating.

Additional information may be found in the vorolanib investigator's brochure.

9.2.2 Clinical Pharmacology

Clinical pharmacology studies have not been performed to date.

9.2.3 Pharmacokinetics and Drug Metabolism

Vorolanib is primarily metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 and CYP2C9 based on *in vitro* studies using human liver microsomes. Thus,

coadministration of vorolanib with potent CYP3A4 inhibitors and inducers should be avoided.

9.2.4 Supplier(s)

Vorolanib will be provided free of charge by Xcovery Holdings, Inc.

9.2.5 Dosage Form and Preparation

Vorolanib will be supplied in 100 mg tablets.

9.2.6 Storage and Stability

Vorolanib tablets (100 mg) are stored in 60cc wide mouth round HDPE bottles with a pharmaceutical desiccant canister, closed with a white polypropylene child resistant cap and foil induction inner seal. Thirty tablets are included in each bottle.

Vorolanib should be stored at room temperature (15ºC-30ºC/59ºF- 86ºF).

9.2.7 Administration

Vorolanib is an oral drug which will be administered daily on an outpatient basis at the assigned dose level. Patients should take vorolanib at approximately the same time every day with food. If a patient misses a dose, the patient should be instructed not to make up that dose and resume dosing with the next scheduled dose. Patients will be instructed to bring all unused medication and their medication diary to each study visit for assessment of compliance.

10.0 CORRELATIVE STUDIES

10.1 Peripheral Research Blood

10.1.1 Collection of Specimen(s)

Patients will have 40 mL of blood collected in 3 green heparinized tubes and 1 red top tube at baseline (within 21 days prior to start of the therapeutic intervention), Day 1 of Cycle 2, and end of treatment. Patients with hemoglobin below 9 mg/dL will not have blood collection.

The samples will be processed by standard operating procedures by centrifugation. All samples will be frozen in liquid nitrogen and stored under liquid nitrogen vapor in an inventoried storage unit at the Siteman Cancer Center Tissue Procurement Core Facility until analysis.

We will evaluate whether the combination of vorolanib and atezolizumab (a) alters populations of circulating monocytes and myeloid derived suppressor cells, (b) increases the number and affects the phenotype of circulating NK cells, effector CD8+ and effector CD4+ T-cell subsets, (c) results in the generation of durable populations of memory CD8+ and CD4+ T-cells and (d) alters the ratio of circulating regulatory T-cells to effector CD8+ cells. We will utilize mass cytometry for these analyses, a high dimensional technique that allows the assessment of approximately 40 individual markers using metal labeled antibodies to enable deep profiling of selected phenotypic and functional makers on individual cells as well as unique statistical analyses to simplify the interpretation of complex relationships of large numbers of cells.

10.2 Biopsy Sample Collection

10.2.1 Collection of Specimens

When available, archival biopsy tissue will be used for a baseline biopsy. A baseline fresh biopsy will be optional.

At progression, a repeat biopsy will be attempted when feasible aiming for up to 5 cores if possible.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Within 4 weeks prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Treatment Form	Every cycle
Patient Medication Diary	Every cycle
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Research Specimen form	At time of specimen collection
Follow Up Form	Every 6 months for 3 years
Tumor Measurement Form	Baseline, every 6 weeks for the 6 months, every 12 weeks thereafter, and end of treatment
MedWatch Form	See Section 8.0 for reporting requirements
Progression Form	Time of progression
Death Form	Time of death

11.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 8.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks for the first 6 months and every 12 weeks thereafter using the same methods as the baseline imaging. Brain MRIs will also be performed every 12 weeks for all patients. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 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, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Baseline tumor imaging

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be within 21 days from starting 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

12.4 Tumor imaging during the trial

Study imaging will be performed, with the same imaging method used for baseline, every 6 weeks (42 days +/- 7 days) for the first 6 months and every 12 weeks (84 days +/- 7 days) thereafter. Brain imaging will be performed every 12 weeks (84 days +/- 7 days). Imaging will follow calendar days without adjustments for delays in cycle starts. Patient should continue to undergo imaging studies until tumor progression, withdrawal of consent, or death, whichever occurs first.

12.5 Response Criteria

12.5.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.5.2 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).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.5.3 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	

SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

12.5.4 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 progressive 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, including the baseline measurements.

12.5.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

14.1 Sample Size Estimates

This single institution study will be designed using Simon's two-stage MiniMax design. We plan to enroll thirty-three (33) SCLC patients with extensive stage disease.

Given historic rates of PFS at 6 months of approximately 20% for maintenance sunitinib [6] or atezolizumab,[7] we determined that a 6 month PFS of 40% with the combination vorolanib and atezolizumab would warrant further evaluation of this strategy. Based on Simon's Minimax two-stage design, a total number of 33 patients allows 80% power at 1-sided alpha of 0.05 to detect the expected difference. Eighteen (18) evaluable patients will be enrolled in stage I. Patient enrollment will continue while waiting for the data from stage I to mature for an interim futility analysis. If 5 or more patients from stage I exhibit progression-free survival of >6 months, then 15 additional patients will be enrolled in stage II. If 11 or more patients exhibit progression-free survival at 6 month out of all 33 evaluable patients, we would conclude that preliminary evidence for efficacy exists and that further investigation is warranted. With this design, we will have 5% chance to erroneously stop the trial in stage 1 if the true 6-month PFS is ≥ 40%. However, there is a 72% chance of ending the trial during stage I, given a true 6-month PFS of 20% or less.

Since the probability of disease-free survival at 3 months with standard therapy is approximately 40%, an additional analysis will also be performed based on the outcomes for the 18 patients at 3 months. If 10 or more patients develop tumor progression or death by the third month of maintenance treatment, the study accrual will be held until the 6 month PFS becomes available for the decision to proceed to stage II of the trial.

14.2 Accrual Rate

The rate of accrual for this study is expected to be 1-2 patients per month. The study is expected to complete within two to two and a half years.

14.3 Populations of Analysis

Evaluable patients for safety will include those patients who receive at least 1 dose maintenance treatment of vorolanib with atezolizumab.

Evaluable patients for efficacy will include those patients who receive at least 1 dose maintenance treatment of vorolanib with atezolizumab, and have a post-baseline disease assessment.

14.4 Statistical Analysis Plan

Demographic and clinical characteristics of the sample, as well as response to treatment, toxicity by grade and loss to follow up will be summarized using descriptive statistics.

An interim futility analysis will be performed at the time when 18 efficacy-evaluable patients are available. The patient enrollment will continue while the interim data is analyzed. However, if 10 or more patients develop tumor progression or death by the third month of maintenance treatment, the study accrual will be held until the 6 month PFS becomes available for the decision to proceed to stage II of the trial. If 4 or less patients exhibit progression-free survival of >6 months, the trial will be recommended for an early

termination due to futility. If 5 or more patients exhibit progression-free survival of >6 months, then an additional 15 patients will be enrolled in the stage II.

At the end of study, if 11 or more patients achieve progression-free survival at 6 month out of all 33 evaluable patients, we would conclude that preliminary evidence for efficacy exists and that further investigation is warranted. Kaplan-Meier product limit estimator will be used to describe the distribution of progression free survival (PFS) and overall survival (OS). The PFS at 6 month and its 90% confidence interval (CI) will also be calculated.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death

- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Xcovery**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	If a vorolanib-related event requires expedited safety reporting to the FDA, then Xcovery will need a copy of the final 7 or 15-day MedWatch report via email to safety@xcovery.com. Submitno later than calendar day 4 for a 7-day report and no later than calendar day 10 for a 15-day report.
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse reaction of			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	If a vorolanib-related event requires expedited safety reporting to the FDA, then Xcovery will need a copy of the final 7 or 15-day MedWatch report via

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Xcovery**
that list in the protocol or IB				email to safety@xcovery.com. Submitno later than calendar day 4 for a 7-day report and no later than calendar day 10 for a 15-day report.
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Xcovery**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant			

	enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

APPENDIX D: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: vorolanib Cycle: _____

Patient Name: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _____mg (___tablets) of vorolanib daily at approximately the same time each day with food. Take it with a glass of water and drink the glass of water in as little time as possible. Do not chew.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forget to take your vorolanib, the dose should be taken as soon as possible, but not more than 12 hours from the time you usually take your dose. If more than 12 hours has passed since the usual time you take your dose, then do not take a dose that day. Restart taking it the next day.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit and do not retake the medicine until the next scheduled treatment.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each study visit.

Day	Date	What time was dose taken?	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
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