Phase 1/2 Study to Evaluate the Safety and Preliminary Activity of Nivolumab in Combination with Vorolanib in Patients with Refractory Thoracic Tumors

VICC THO 1802

CA209-982 NCT03583086

Protocol Chair/Sponsor-Investigator: Katy Beckermann, PhD, MD

Statistician: Yu Shyr

Coordinating Center: Vanderbilt University Medical Center

28 March 2024

1. SYNOPSIS 6

2. BACKGROUND AND RATIONALE 11
2.1. Introduction 11
2.2 Targeting Angiogenesis 12
2.3 Vorolanib, Multi-Kinase Inhibitor of Angiogenesis 13
2.4 Nivolumab 16
2.5 Rationale for Combinatorial Therapy Against PD-1 and VEGF 16
2.6 Correlative Science Background 17

3. OBJECTIVES and ENDPOINTS 18
3.1. Objectives 18
3.2. Endpoints 19

4. Patient Selection 19
4.1. Inclusion Criteria 19
4.2. Exclusion Criteria 21
4.3. Inclusion of Underrepresented Populations 24
4.4. Number of Patients and Replacement of Patients Who Discontinue Early 24

5. ENROLLMENT Procedures 24
5.1. Registration Procedures 24
5.2. Screen-Failures 26

6. SCHEDULE OF ASSESSMENTS 27
6.1. Study Calendar 27
6.2. Screening Visit Assessments 31
6.3. Cycle 1, Day 1 Assessments 32
6.4. Cycle 1, Day 8 Assessments (Phase I - Dose Escalation ONLY) 32
6.5. Cycle 1, Day 15 Assessments 33
6.6. Cycle 1, Day 22 Assessments (Phase I - Dose Escalation ONLY) 33
6.7. Cycle 1, Day 29 Assessments 34
6.8. Cycle 1, Day 43 Assessments 34
6.9. Cycle 1, Day 56 Assessments 35
6.10. Cycles 2+, Day 1 and Day 29 Assessments 35
6.11. Cycles 2+, Day 15 and Day 43 Assessments 36
6.12. Cycles 2+, Day 56 Assessments 37
6.13. End-of-Treatment / Withdrawal Assessments 37
6.14. Follow-Up Visit Assessments (28-Day and 100-Day) 38

7. Study Procedures 39
7.1. Informed Consent 39
7.2. Physical Examination 39
7.3. Performance Status 39
7.4. Vital Signs, Body Weight, and Oxygen Saturation 39
7.5. Review of Concomitant Medications and Adverse Events 39
7.6. Surveillance and Expedited Reporting of Dose Limiting Toxicity 40
7.7. Complete Blood Count with Differential 40
7.8. Blood Chemistry 40
7.9. Thyroid Function Testing 40
7.10. Hepatitis Testing 40
7.11. ECG 40
7.12. Urinalysis 40

7.13. Pregnancy Test....40
7.14. Disease Assessment by CT/MRI....41
7.15. Tumor Tissue and Correlative Blood Samples....41
7.16. Handling of Biological Samples....42
7.17. Specimen Banking....42

8. PROTOCOL Treatment....42
8.1. Dose Level Summary....42
8.2. Oral Vorolanib....43
8.3. Nivolumab Infusion....43
8.4. Discontinuation of Protocol-Indicated Treatment....45
8.5. Treatment Beyond Progression....46
8.6. Duration of Follow-Up....47
8.7. Withdrawal from Study....47

9. Concomitant Treatment....47
9.1. Prohibited or Restricted Treatments....47
9.2. Permitted Therapy....48
9.3. Hematopoietic Growth Factors and Transfusion Support....48
9.4. Clarifications about Steroid Use including Hormones....49
9.5. Palliative Local Radiotherapy....49

10. Adverse Event Management....50
10.1. Definition of Dose-Limiting Toxicity....50
10.2. Dose Modifications and Delays of vorolanib....52
10.3. Dose Modifications of Nivolumab....55
10.4. Criteria for Dose Delays of Nivolumab....55
10.5. Criteria to Resume Nivolumab Treatment....56
10.6. Criteria to Permanently Discontinue Nivolumab Treatment....57
10.7. Management Algorithms for Immuno-Oncology Agents....58
10.8. Guidelines for the Management of Infusion Reactions....59

11. Drug Formulation, Supply and Storage....60
11.1. Description of Vorolanib....60
11.2. Packaging of Vorolanib....61
11.3. Handling and Storage of Vorolanib....61
11.4. Description of Nivolumab....61
11.5. Packaging of Nivolumab....61
11.6. Handling and Storage of Nivolumab....61
11.7. Drug Accountability and Compliance Check....62

12. Safety Reporting of Adverse Events....62
12.1. General....62
12.2. Risks Associated with Vorolanib....63
12.3. Risks Associated with Nivolumab....64
12.4. Adverse Event (AE)....64
12.5. Serious Adverse Event (SAE)....64
12.6. Assessment of Adverse Events....65
12.7. Expectedness....65
12.8. Attribution....65
12.9. Specific Instructions for Recording Adverse Events....66
12.10. Diagnosis versus Signs and Symptoms....66
12.11. Deaths....66

12.12. Pre-existing Medical Conditions 66
12.13. Hospitalizations for Medical or Surgical Procedures 66
12.14. Pregnancies in Female Patients 67
12.15. Pregnancies in Female Partners of Male Patients 67
12.16. Overdose 67
12.17. Post-Study Adverse Events 67
12.18. Serious Adverse Events 68
12.19. Institutional Review Board 68
12.20. Food and Drug Administration (FDA) 68
12.21. Expedited 7 and 15 Day Reporting Requirements for IND 68
12.22. Xcovery (Equinox Sciences) 69
12.23. Bristol-Myers Squibb 70

13. DATA SAFETY AND MONITORING 70
13.1. Data Management and Reporting 70
13.2. Meetings 71
13.3. Monitoring 71
13.4. Data Handling and Record Keeping 72

14. REGULATORY CONSIDERATIONS 72
14.1. Protocol Review and Amendments 72
14.2. Informed Consent 73
14.3. Ethics and GCP 73
14.4. Confidentiality 74
14.5. Study Termination 74

15. MULTI-CENTER GUIDELINES 74
15.1. Pre-Study Documentation 74
15.2. Protocol Review and Amendments 75
15.3. Study Documentation 75
15.4. Records Retention 75
15.5. Publication 75

16. StatISTICAL CONSIDERATIONS 76
16.1. Phase I (Dose-Escalation) Design 76
16.2. Phase II (Dose-Expansion) Design 76
16.3. Data Analysis Plan 78
16.4. Anti-Tumor Activity Analyses 78

17. REFERENCES 78

TABLES

TABLE 1: Comparison of Objective Response Rates (ORR) after PD-1 / VEGF Inhibition in patients with Previously Treated Renal Cell Carcinoma (RCC) 17
TABLE 2: Dose Escalation Summary 42
TABLE 3: Vorolanib Dose Modifications for Hematologic Toxicities 53
TABLE 4: Methods of Contraception 86
TABLE 5: Response Criteria for Evaluation of *TARGET* Lesions 90
TABLE 6: Response Criteria for Evaluation of *NON-TARGET* Lesions 90
TABLE 7: Overall Response Status for Patients with Baseline Measurable Disease 91
TABLE 8: Best Overall Response when Confirmation of CR and PR Required 92

APPENDICES

APPENDIX 1 ***Cockcroft-Gault Formula*** **82**

APPENDIX 2 ***ECOG Performance Status*** **83**

APPENDIX 3 ***New York Heart Association (NYHA) Functional Classification*** **84**

APPENDIX 4 ..... **85**

APPENDIX 5 ***Acceptable Contraception*** **86**

APPENDIX 6 ***Response Evaluation Criteria in Solid Tumors (RECIST v1.1)*** .. **88**

APPENDIX 7 ***Guidelines for the Management of Immune-Related Adverse Events (irAEs)*** **93**

1. SYNOPSIS

Trial Title	Phase 1/2 Study to Evaluate the Safety, and Preliminary Activity of Nivolumab in Combination with Vorolanib in Patients with Refractory Thoracic Tumors.
Phase and Overall Trial Design	This is a two-agent, open-label, non-randomized, Phase 1/2 dose escalation and dose expansion study of combinatorial oral vorolanib plus infusional nivolumab in patients with Non-Small Cell Lung Cancer (NSCLC) naïve to checkpoint inhibitor therapy, NSCLC who have progressed on checkpoint inhibitor therapy, Small Cell Lung Cancer (SCLC) who have progressed on platinum-based chemotherapy, and thymic carcinoma.
Trial Sites	Vanderbilt University Medical Center, Stanford University, University of Chicago, Fox Chase Cancer Center, Emory University, Baptist Clinical Research Institute, and Providence Cancer Institute.
Concept and Rationale	The successful development of therapeutic agents targeting the PD-1/PD-L1 axis has been a major therapeutic advancement in oncology. In particular, nivolumab, a potent, highly selective, fully humanized monoclonal antibody against PD-1, has been approved for the treatment of NSCLC patients. The ORR in many tumor types are generally in the range of 19-25%. Thus, combination with other therapies is necessary to further increase the response rate and efficacy. The potential for increased efficacy of combining anti-angiogenic therapy with immunotherapy is supported by preclinical evidence in NSCLC, where the combination significantly inhibited tumor growth compared to each single agent alone, as well as increased the tumor infiltration of immune cells. Preliminary data from one phase Ib study observed a longer median progression-free survival when bevacizumab was added to nivolumab (9 months) compared to single agent nivolumab (4 months in squamous and 5 months in nonsquamous histology) maintenance therapy. Thymic epithelial tumors are rare cancers, which are classified as either thymomas or thymic carcinomas. The latter is usually more aggressive and less responsive to chemotherapy and has a higher probability of producing distant metastases. The 5-year overall survival rate for thymic carcinomas is only 30%-50%. Complete and radical surgical resection remains the standard therapeutic approach for localized disease and is currently the only potentially curative option. Patients with unresectable or recurrent disease usually receive palliative chemotherapy. Although the data are limited, angiogenesis appears to have a role in the development and progression of thymic epithelial tumors. For thymic carcinomas in particular, one study observed that VEGF was expressed in a majority of tumors, and VEGF expression and microvessel density was associated with invasiveness. Sunitinib, a multi-targeted TKI that inhibits VEGFR, KIT, and PDGFR, achieved a >90% disease control rate in patients with thymic cancers who were refractory to platinum-based chemotherapy. Based on this study, sunitinib is recommended as second-line therapy. Several studies have found high PD-1/PD-L1 expression in thymic epithelial tumors suggesting that targeting the PD-1/PD-L1 pathway is a potential immunotherapeutic approach. It is known that tumor cells secrete VEGF-A which, in addition to promoting angiogenesis, decreases dendritic cell expression of co-stimulatory molecules and T cell priming, and also encourages the formation of myeloid-derived suppressor cells (MDSCs). It has been shown that sunitinib, a VEGFR, PDGFR,

	CSF1R, Kit and Flt-3 inhibitor, reduces infiltration by MDSC and regulatory T lymphocytes, thereby potentially enhancing the efficacy of immunotherapy. Initial combinations with TKI of VEGFR and PD-1 inhibitors were not well tolerated at the full doses of both single agents in renal cell carcinoma. Thus, it is desirable to have a VEGFR inhibitor with lower toxicity for combination with immunotherapy. Vorolanib is a small molecule indolinone inhibitor of a family of type III and type V receptor tyrosine kinases characterized by an extracellular domain containing several immunoglobulin-like domains, a membrane spanning region, and a cytoplasmic split kinase domain (1). Included in this family are receptors for three isoforms of vascular endothelial cell growth factors (VEGFR 1,2,3), two isoforms of platelet derived growth factor (PDGFR α and β), stem cell factor (c-Kit), colony-stimulating factor 1 receptor (CSF1R), Fms-related tyrosine kinase 3 like receptor (Flt-3), and ligand for the receptor tyrosine kinase (RET). Vorolanib is a novel analog of sunitinib with similar kinase profiles. It was designed to lower the toxicity by changing the PK/PD of sunitinib. Phase I clinical data suggested safety and tolerability with only three grade 3 adverse events including hypertension and pain with a 36% ORR in TKI resistant and naïve patient with RCC(2). In addition, combination trial of vorolanib and everolimus in the phase I was tolerated at full doses of both drugs in patients with RCC some of whom experience a partial response. We propose to test in a Phase I/Phase II study to evaluate the safety, and preliminary activity of nivolumab in combination with vorolanib in patients with refractory thoracic tumors.
Protocol Treatment and Mechanisms	Vorolanib is an oral angiogenesis inhibitor being developed to treat malignant solid tumors and age-related macular degeneration (AMD). Vorolanib is not approved or marketed in any country. The study will provide vorolanib to each site. This drug is taken orally once daily at the dosage determined in phase I dose escalation. Nivolumab (OPDIVO) is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor found on T cells. Nivolumab infusion is approved for a variety of indications, the study will provide nivolumab to each site for infusion every 2 weeks at a flat dose of 240 mg. **Of note**: If the patient has not exhibited evidence of disease progression (non-PD) and is undergoing treatment in cycles 3+, then nivolumab will be administered every 4 weeks at a flat dose of 480 mg.
Treatment Schedule	Treatment will consist of cycles lasting 8 weeks (56 days) each. All patients are scheduled to receive oral vorolanib once daily (QD) on a continuous dosing schedule as determined by the recommended phase I combination dose. All patients are scheduled to receive nivolumab as a 30 minute intravenous infusion every two weeks (i.e. on Days 1, 15, 29, and 43 of each 56-day cycle) for the first two treatment cycles. After which, the treatment schedule can change to every four weeks (i.e., on Days 1 and 29 of each 56-day cycle) if the patient is not exhibiting disease progression.

Objectives and Endpoints	mary Objectives: Phase I: To assess the safety and tolerability of nivolumab and vorolanib in combination in patients with refractory NSCLC naïve to checkpoint inhibitor therapy, NSCLC progressed on prior checkpoint inhibitor therapy considered primary refractory, NSCLC progressed on prior checkpoint inhibitor therapy considered acquired resistance, SCLC progressed on platinum-based chemotherapy, and thymic carcinoma. Phase II: To evaluate the efficacy as measured by response to the combination nivolumab and vorolanib in patients with refractory NSCLC naïve to checkpoint inhibitor therapy, NSCLC progressed on prior checkpoint inhibitor therapy considered primary refractory, NSCLC progressed on prior checkpoint inhibitor therapy considered acquired resistance, SCLC progressed on platinum-based chemotherapy, and thymic carcinoma as compared to historical controls. Secondary Objectives: Phase I: To assess antitumor activity of this novel combination. Phase II: To assess the effects of tumor PD-L1 status and tumor mutation burden (TMB) on the response to combinatorial treatment vorolanib and nivolumab. Exploratory Objectives: To assess the effects of combinatorial treatment on specific pharmacodynamic and pharmacogenetic biomarkers. mary Endpoints: Phase 2 recommended combination dose will be determined when >1/3 or >2/6 dose limiting toxicities measured using CTCAE criteria version 5.0 Phase 2 best response will be measured by RECIST v1.1 Secondary Endpoints: Phase II progression free survival at six months and one year intervals, duration of response, disease control rate, overall survival at one year, and ORR as related to PD-L1 status measured as <1%, 1-49%, and >50%. Exploratory Endpoints: To assess the effects of combinatorial treatment on specific pharmacodynamic and pharmacogenetic biomarkers, including but not limited to circulating levels of serum CSF1 and VEGF, protein expression using CyTOF, and multiplex immunofluorescence.
Main Inclusion/ Exclusion Criteria	**Main Inclusion Criteria:** Patients must be refractory or refuse first-line therapy NSCLC patients may have received up to three prior treatment regimens, except patients with EGFR, ALK, ROS1 and BRAF positive NSCLC must have progressed on at least one TKI and are not limited in the number of prior regimens they have received Patients with non-small cell lung cancer will be allowed to enter following progression on prior checkpoint inhibitor therapy or if they refuse standard platinum-based chemotherapy Treatment with prior bevacizumab or ramucirumab is allowed Thymic carcinoma patients may have received any number of prior lines of therapy

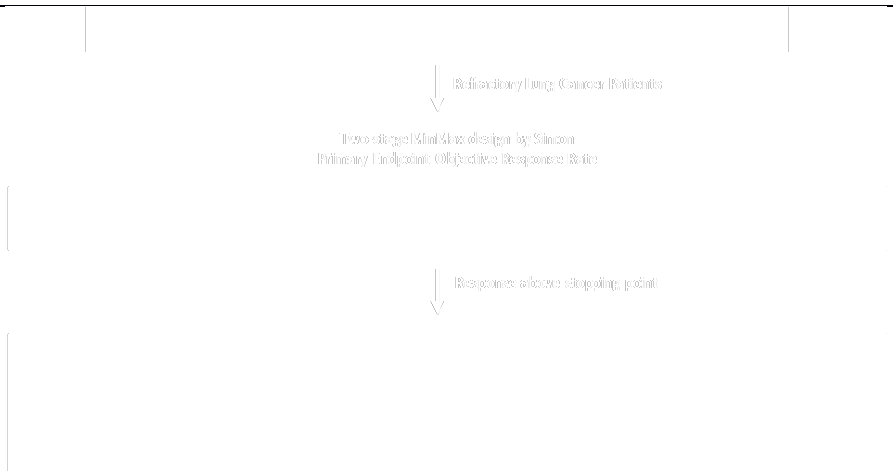
<table>
<tr><td></td><td>SCLC patients must have progressed on platinum-based chemotherapy and may have received up to three prior lines of therapy provided that no prior regimen contains an oral VEGF TKI; prior regimens can include an anti-PD-1 or PD-L1 agent.

Main Exclusion Criteria:

Prior treatment with VEGF TKI is not allowed but prior bevacizumab or ramucirumab is allowed in the NSCLC or thymic cohorts
Prior treatment with checkpoint inhibitor therapy in patients with thymic carcinoma is not allowed</td></tr>
<tr><td>Overall Trial Design</td><td>Dose-Escalation Phase:
Standard 3+3 design with the following intended dose levels:
<table><tr><th>Dose Level</th><th>Vorolanib
Oral
continuous QD</th><th>Nivolumab
I.V.
Days 1, 15, 29, and 43 (each cycle)</th></tr><tr><td>-1</td><td>100 mg</td><td>240 mg</td></tr><tr><td>1</td><td>200 mg</td><td>240 mg</td></tr><tr><td>2</td><td>300 mg</td><td>240 mg</td></tr><tr><td>3</td><td>400 mg</td><td>240 mg</td></tr></table>1 cycle = 56 days (8 weeks)

The first cohort of patients will be started at dose level 1. At least 3 patients will be studied at each dose level and evaluated for toxicity. If 0 of 3 patients experience a dose-limiting toxicity (DLT), the dose will be escalated. If 1 of 3 patients experiences a DLT, 3 additional patients will be treated. If none of the additional patients develop a DLT, the dose will be escalated, otherwise escalation ceases. If > 2 of 3, or > 2 of 6, patients experience a DLT, the Recommended Combination Dose (RCD) has been exceeded.

Dose-Expansion Phase:
In the phase 2 dose-expansion portion of the study, additional patients (about 159 total additional patients) will be split into five cohorts (about 21-41 evaluable patients/cohort), consisting of patients with refractory NSCLC either naïve to or progressed on checkpoint inhibitor therapy (primary refractory and acquired resistance), SCLC progressed on platinum-based chemotherapy, and thymic carcinoma, who will be treated at the RCD determined in the phase 1 portion of the study. Primary refractory is defined as radiographic progression of disease ≤ 12 weeks after initiation of treatment (+2 week window permitted for radiograph scheduling). Acquired resistance includes achieving RECIST defined partial, complete response, OR stable disease for at least 12 weeks (+2 week window permitted for radiograph scheduling) followed by radiographic progression of disease.</td></tr>
</table>

	
Number of Patients	Up to 177 patients: Approximately 9-18 evaluable patients in Dose Escalation; and about 159 evaluable patients in five Dose Expansion cohorts, consisting of Non-Small Cell Lung Cancer naïve to checkpoint inhibitor therapy (n=39), Non-Small Cell Lung Cancer primary refractory to prior checkpoint inhibitor therapy (n=21), Non-Small Cell Lung Cancer acquired resistance to prior checkpoint inhibitor therapy (n=21), Small Cell Lung Cancer (n=37) and Thymic carcinoma (n=41).
Study Assessments	See the Schedule of Assessments in Section 6.

2. BACKGROUND AND RATIONALE

2.1. Introduction

The successful development of therapeutic agents targeting the programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) axis has been a major therapeutic advancement in oncology. In particular, nivolumab, a potent, highly selective, fully humanized monoclonal antibody against PD-1, has been approved for the treatment of metastatic renal cell carcinoma, melanoma, urothelial, head and neck, Hodgkin Lymphoma and Non-small cell lung cancer (NSCLC) patients. It has also shown promising activities in a number of other tumor types such as gastric carcinoma and triple-negative breast cancer.

The objective response rates of immune checkpoint inhibitors in PD-L1 positive NSCLC are approximately 25-40% and in other tumor types without PD-L1 selection response rates are generally in the range of 10-25% (1). Thus, combination with other therapies is necessary to further increase the response rate and efficacy in PD-L1 negative, as well as PD-L1 positive, patients.

Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers diagnosed. The overall 5-year survival rate is only 17%; prognosis is worse for patients that are diagnosed with distant metastases, where 5-year survival rates are less than 5% (3). Cytotoxic chemotherapy for the treatment of metastatic disease has clearly hit a plateau in terms of improving clinical outcome. Additionally, the development of targeted therapies directed towards specific oncogenic drivers has been associated with meaningful improvements in survival, but only in a minority of patients whose tumors harbor those specific mutations (e.g., epidermal growth factor receptor and anaplastic lymphoma kinase alteration) (4-6).

To overcome these therapeutic limitations, investigators have explored the use of anti-angiogenic agents. The main driver for angiogenesis in NSCLC is the development of hypoxia within a growing tumor. Hypoxia activates the hypoxia-inducible factor-1A (HIF-1a) and HIF-2a that in turn activates multiple intracellular signaling pathways leading to the generation and release of pro-angiogenic factor from within the tumor and stroma (7,8). Thus, inhibition of this pathway could be a viable treatment option for NSCLC. Indeed, two monoclonal antibodies, bevacizumab and ramucirumab, are FDA approved therapies when administered in combination with chemotherapy.

As mentioned above, the anti-PD1 immunotherapy nivolumab is approved for patients with advanced NSCLC. Depending on subtype, the median overall survival was 9.2 or 12.2 months, which was an improvement over cytotoxic chemotherapy (6 and 9.4 months) (9-11). Despite this improvement in clinical outcome, the response rates were minimal at 20% suggesting there is room to develop new therapeutic strategies to increase tumor response.

The potential for increased efficacy of combining anti-angiogenic therapy with immunotherapy is supported by preclinical evidence in NSCLC, where the combination significantly inhibited tumor growth compared to each single agent alone, as well as increased the tumor infiltration of immune cells (12). Multiple trials investigating angiogenesis inhibitors (e.g., bevacizumab, ramucirumab, and nintedanib) administered in combination with immunotherapies (e.g., nivolumab, ipilimumab, pembrolizumab, and atezolizumab) in NSCLC are either ongoing or planned (13). Preliminary data from one phase Ib study observed a longer median progression-free survival when bevacizumab was added to nivolumab (9 months) compared to single agent nivolumab (4 months in squamous cell and 5 months in nonsquamous histology) maintenance therapy (14). Despite this improvement, the response rates were minimal (8% for the combination versus 10% single-agent nivolumab) and similar between the two treatment arms comparing maintenance therapy.

Thymic Carcinoma

Thymic epithelial tumors are rare cancers, which are classified as either thymomas or thymic carcinomas. The latter is usually more aggressive and less responsive to chemotherapy and has a higher probability of producing distant metastases. The 5-year overall survival rate for thymic carcinomas is only 30%-50% (15).

Due to the rarity of thymic carcinomas, sufficiently powered clinical trials that aid in the development of international guidelines concerning the treatment of these patients do not exist (16,17). Complete and radical surgical resection remains the standard therapeutic approach for localized disease and is currently the only potentially curative option. Patients with unresectable or recurrent disease usually receive palliative chemotherapy. National Comprehensive Cancer Network (NCCN) recommended first-line chemotherapeutic regimens include platinum-based combinations based on data from small phase II trials that showed excellent disease control rates of 71%-100% (18). Despite this success, tumor response rates were minimal (21%-25%) suggesting the need for new therapies.

Although the data are limited, angiogenesis appears to have a role in the development and progression of thymic epithelial tumors (19-21). For thymic carcinomas in particular, one study observed that vascular endothelial cell growth factor (VEGF) was expressed in a majority of tumors, and VEGF expression and microvessel density was associated with invasiveness (20). Also, the microvessel density of thymic cancers was higher than both noninvasive and invasive thymomas, suggesting that thymic carcinomas are extremely vascular and could benefit from anti-angiogenic therapies. Indeed, sunitinib, a multi-targeted tyrosine kinase inhibitor (TKI), that inhibits VEGFR, stem cell factor (KIT), and platelet derived growth factor receptor (PDGFR), achieved a >90% disease control rate in patients with thymic cancers who were refractory to platinum-based chemotherapy (19). Based on this study, sunitinib is recommended as second-line therapy. However, there is room for improvement as the response rate to sunitinib monotherapy was minimal at 26% and the median progression free survival (PFS) was 7.2 months.

Several studies have examined PD-1/PD-L1 expression in thymic epithelial tumors. A recent study observed that alterations in PD-L1 gene copy number was increased compared to normal in a subset of patients, and in those patients with high copy number gain, immunohistochemical (IHC) expression of PD-L1 was also higher (22). Furthermore, this study showed that high PD-L1 expression is associated with a favorable clinical outcome suggesting that targeting the PD-1/PD-L1 pathway is a potential immunotherapeutic approach.

Based on the above data, one would hypothesize that a treatment regimen combining an antiangiogenic agent with immunotherapy could be efficacious, and potentially synergistic, in patients with thymic carcinoma.

2.2 Targeting Angiogenesis

Angiogenesis, the process that describes the formation of new blood vessels, is increased in tumors, and thus has become a target of anti-tumor drug development. Tumor cells secrete growth factors, such as VEGF and PDGF, which induce angiogenesis in order to support tumor growth. These growth factors interact with cell surface receptors (e.g., VEGFR and PDGFR) inducing a cascade of signaling events that lead to formation of tumor blood vessels.

Although the VEGF pathway plays a significant role in the development of tumor blood vessels, tyrosine kinase inhibitors that target a single protein in the pathway is associated with a modest survival benefit most likely due to the development of tumor resistance induced by up-regulation of other pathways that stimulate angiogenesis (7). Thus, the use of TKIs that simultaneously inhibit multiple angiogenic pathways have been developed with the hypothesis that inhibiting multiple targets with one therapy leads to increased clinical benefit. Sorafenib and sunitinib are two multi-targeted TKIs that have received FDA approval for the treatment of multiple cancers, including renal cell carcinoma (RCC), gastrointestinal stromal tumors (GISTs), and hepatocellular carcinoma.

Both sorafenib and sunitinib along with several emerging TKIs have been evaluated in thoracic cancers, yet none are currently FDA approved (23). However, the NCCN guidelines recommend sunitinib as second-line therapy for thymic carcinomas. The monoclonal antibodies bevacizumab and ramucirumab that inhibit VEGF-A and VEGFR2, respectively, remain the only FDA approved antiangiogenic therapies in thoracic cancers.

2.3 Vorolanib, Multi-Kinase Inhibitor of Angiogenesis

Vorolanib is an oral multi-kinase inhibitor of VEGFR, PDGFR, colony-stimulating factor 1 receptor (CSF1R), stem cell factor (c-Kit), and FMS-like tyrosine kinase 3 (FLT3) that is intended for the treatment of solid tumors and pathologic angiogenesis in diseases such as neovascular “wet” age-related macular degeneration (AMD), and von Hippel-Lindau Disease.

The binding of vorolanib to its target receptors (VEGF and PDGF) results in angiogenesis inhibition. Vorolanib is structurally related to sunitinib and has been designed to improve upon the safety profile without compromising the efficacy of sunitinib. The expectation is that an improved safety profile will allow continuous daily dosing to deliver a stronger anti-angiogenic effect and permit combination modalities currently precluded by safety issues for sunitinib.

Vorolanib is a small molecule indolinone inhibitor of a family of type III and type V receptor tyrosine kinases characterized by an extracellular domain containing several immunoglobulin-like domains, a membrane spanning region, and a cytoplasmic split kinase domain (1). Included in this family are receptors for three isoforms of vascular endothelial cell growth factors (VEGFR 1,2,3), two isoforms of platelet derived growth factor (PDGFR α and β), stem cell factor (c-Kit), colony-stimulating factor 1 receptor, FMS-related tyrosine kinase 3 like receptor, and ligand for the receptor tyrosine kinase (RET).

The combined effect on VEGFR and PDGFR allows these drugs to target endothelial cells and pericytes, respectively. Endothelial cell proliferation necessary for new vessel formation is dependent on VEGF. The PDGF dependent pericytes are important for the stabilization of neovasculature (24). As such, the combined effect on these two targets (VEGFR and PDGFR) with nearly equal potency is thought to contribute to the increased efficacy of sunitinib over other tyrosine kinase inhibitors such as sorafenib that primarily target VEGF (25). 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.

Due to the unique binding mode and chemical scaffold of sunitinib it binds to receptor tyrosine kinases (RTKs) via the Type I binding mode where the kinase is in active conformation. In contrast, the two other VEGFR inhibitors approved by FDA (sorafenib and pazopanib) bind to RTKs via the Type II binding mode where the kinase is in an inactive conformation. The Type I inhibitors are less likely to have resistant mutations compared to Type II inhibitors.

Vorolanib is developed on the same chemical scaffold as sunitinib. Importantly, like sunitinib, Vorolanib is able to target the angiogenic regulators VEGFR and PDGFR with similar potency. The potent effect of both vorolanib and sunitinib on inhibition of phosphorylation of VEGFR2 and PDGFR was confirmed in cell based assays. In targeting the VEGF and PDGF receptors, vorolanib is expected to disrupt tumor angiogenesis and to be active in a broad spectrum of solid tumors.

Preclinical Experience

In a diverse panel of human tumor nude mouse xenograft models vorolanib displayed comparable activity to sunitinib with respect to tumor growth inhibition. Models of renal cell, colon, pancreatic, melanoma, and leukemia were studied. In these studies, the minimum effective dose that gave at least 50% inhibition of tumor growth in a sensitive model was 40 mg/kg twice a day (BID). The dose of vorolanib that induced a maximum effect (complete tumor stasis or regression) in most xenograft models was 160 mg/kg BID. Vorolanib has also been tested in a rat model of choroidal neovascularization (CNV), and it was observed to inhibit CNV at both 10 and 30 mg/kg ONCE A DAY.

Comparisons of exposures for vorolanib in toxicokinetic studies with exposures achieved at the maximum effective dose in mouse models also predict a large safety window for vorolanib. At a 150 mg/kg dose of vorolanib in nude mice (Study X82-NCL-010 and X82-NCL-018), an area under the plasma concentration time curve (AUC) of 33,844 ng.hr/ml was observed. Accounting for BID dosing, the exposure at an optimum efficacious dose in mice would then be about 67,688 ng.hr/ml. The toxicokinetic studies in female rats (most sensitive gender) established an STD10 of 160,418 ng.hr/ml. This relatively safe exposure in rats is 2.4 times the maximum efficacious exposure in mice and 9.6 times the exposure needed to inhibit tumor growth by 53% in the 786-O renal carcinoma xenograft model. Taken together, these data suggest a very high safety window for vorolanib, if translatable to man, would permit maximally effective dosing with reduced toxicity.

Likewise the 39 week dog study at 12.5, 25, or 50 mg/kg/day of vorolanib concluded that the only adverse effect was tubular degeneration/atrophy in the testes at >12.5 mg/kg/day observed at interim or terminal sacrifice. Other minor, nonadverse, vorolanib-related effects included reduced intraluminal sperm in epididymis in one male at 12.5 mg/kg/day (interim sacrifice only) and yellow discoloration of the hair coat, minor protein concentration changes, decreased testis and epididymis weights, cellular debris and/or reduced intraluminal sperm in the epididymis, increased extramedullary hematopoiesis in the spleen, and hypocellular bone marrow for animals given >25 mg/kg/day. Based on these results, the no observed adverse effect level (NOAEL) of vorolanib, when administered for at least 39 weeks, is 50 mg/kg/day for females and was not achieved for males.

Clinical Experience

As of January 2017, vorolanib has been administered to humans in ongoing Phase 1 and Phase 2 studies. The clinical development plan for 2016 includes continuing a Phase 1 study to assess the early clinical safety, tolerability, and preliminary pharmacokinetics of vorolanib in patients with advanced solid tumors (no new patients will be enrolled, but there are patients that remain on study). This study evaluated vorolanib at doses from 50 to 800mg QD. MTD was not reached at 800mg, but absorption seemed to reach plateau at 400 – 800mg. Thus, 400mg QD was the recommended dose. The Phase 1 study to evaluate the safety and preliminary biologic activity/efficacy of vorolanib in subjects with neovascular age-related macular degeneration (AMD) has been completed. Doses at up to 200mg QD were well tolerated. In addition, a pharmacokinetic study has been performed in elderly healthy volunteer subjects and a further bioequivalence study in healthy subjects aged 18 and above. A Phase 2b double masked, placebo controlled study was initiated in March 2015 to investigate the potential efficacy of vorolanib in previously treated patients with wet AMD. In oncology, there is an ongoing single agent Phase 1 study and a Phase 2/3 combination study with everolimus in RCC subjects in China, and there are ongoing Phase 1/2 combination studies with everolimus and docetaxel being conducted under Investigator INDs in US (2).

Preliminary Clinical Efficacy

Data regarding antitumor activity of vorolanib includes that available from the March 2016 version of the vorolanib Investigator's Brochure, including results from Clinical trial Protocol X82-CLI-101, a *Phase 1, First in Human, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of X-82 in Patients with Advanced Solid Tumors* [NCT01296581].

Of the 52 patients that had been treated, 46 were considered to be evaluable for efficacy [received at least 2 cycles of therapy (1 cycle for patients with PD) and had a post-baseline response assessment with a response of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD)] at the time of the data cut-off: 1 patient had a CR, 1 patient had a PR, 24 had SD, and 20 had PD as their best response.

The patient with a CR had adenocarcinoma of the pancreas. This patient was treated with vorolanib 400 mg capsule daily and was on study for 6 cycles before developing PD. This patient had a small

lesion at baseline and had previously been treated with adjuvant 5-fluorouracil and radiation, ending approximately 2.5 months prior to starting vorolanib.

The patient with a PR had a Hurthle cell carcinoma. This patient was treated with vorolanib 100 mg tablet daily and was on study for 16 cycles before developing PD. The patient had received prior radiation therapy and surgery. In addition, this patient had received one prior systemic agent (dovitinib/TKI258) and had been on that treatment for 11½ months.

Of the patients with SD as best response, 11 were on vorolanib for ≥ 6 cycles, 5 of whom were on VOROLANIB for ≥ 12 cycles, with 3 remaining on treatment as of the cut-off. These 3 patients have been on study for 25+ (carcinoid-low grade neuroendocrine) cycles. The latter patient was initially treated with the 200 mg capsule BID, then switched to 50 mg tablet daily, and then 100 mg tablet daily). The two latter patients had PD beginning approximately 13 and 15 months after starting treatment, but were allowed to remain on study because it was considered to be in their best interest. In the case of the latter patient, PD was based on an increase in tumor size from nadir, with little further change since then and comparable to baseline.

Anticipated Clinical Risk

The current risk profile for vorolanib is based on safety data collected from nonclinical studies and clinical experience with vorolanib, as well as from labeling from similar products, sunitinib (Sutent®), sorafenib (Nexavar®), pazopanib (Votrient®), and axitinib (Inlyta®).

The pathology findings from the toxicology studies for vorolanib include adrenal cortical changes, lymphoid depletion, pancreatic changes, and bone marrow hypocellularity. Laboratory findings include changes in red blood cell counts, hemoglobin, hematocrit, lower white blood cell and lymphocyte counts, lowering calcium, higher platelet counts, hyperglycemia, and increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, creatine kinase, and potassium. The toxicity studies also indicate increased toxicities in female rats compared with male rats, likely related to increased drug exposure. These findings were not observed in dogs. A phototoxicity study in guinea pigs demonstrated sensitivity to light when exposed to vorolanib.

As of Jan 2016, the most frequent (≥ 10%) drug-related adverse events reported with vorolanib from the first-in-human oncology Phase 1 single-agent study include: fatigue, nausea, diarrhea, hair color changes, vomiting, asthenia, rash, and peripheral edema, mostly grade 1 or 2. Ten patients have reported Grade 3 treatment-related AEs including acute pancreatitis, lymphocyte count decrease, neutropenia, diarrhea and fatigue, nausea, proteinuria, neutrophil count decreased and anemia. There have not been any Grade 4 treatment-related AEs. While not a consistent finding, some patients have had decreases in platelets and hemoglobin. Some patients receiving vorolanib in a study in subjects with age-related macular degeneration had increased transaminases. No subjects have met Hy's law criteria. Improvement in transaminases have been documented in all cases, either during a dose pause, permanent drug discontinuation, or with continued dosing.

Adverse events considered serious, unexpected and possibly related to vorolanib from these studies are acute pancreatitis and deep vein thrombosis. In addition, severe adverse events reported to the sponsor from studies from other sponsors or from investigator-sponsored IND studies and that were considered to be related to vorolanib by the investigator include cerebral infarction (resulting in facial weakness and slurred speech; temporary memory loss), fistula (between colon and tumor)/pleural effusion, infections, pulmonary embolism, low platelet count, and hemorrhage (intraperitoneal bleed with an outcome of death). The original assessment by the investigator for the hemorrhage was that the event was unrelated to vorolanib and was due to a mesenteric mass invading major vessels. However, because of the association of bleeding with this class of drugs, the causality assessment was changed to being possibly related to vorolanib. These events were from combination studies with everolimus or docetaxel, with the exception of the temporary memory loss, which was from a single agent study in China.

Approved vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) have a well characterized adverse event profile. The cardiotoxic effects include a high incidence of hypertension, less frequent occurrence of impaired cardiac function [decreased left ventricular ejection fraction (LVEF) or congestive heart failure], QT prolongation/Torsades de Pointes and cardiac ischemia/infarction. Other warnings or precautions include hepatotoxic effects, including liver failure; thyroid dysfunction, hemorrhage and thrombosis/thrombotic/thromboembolic events, thrombotic microangiopathy, hand-foot syndrome and other severe dermatologic toxicities (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, necrotizing fasciitis), gastrointestinal perforation/fistula, osteonecrosis of the jaw, proteinuria, reversible posterior leukoencephalopathy syndrome, tumor lysis syndrome, and serious infections. The recommendations to temporarily interrupt treatment with the TKI before major surgery because of the possibility of impaired wound healing and to monitor for adrenal insufficiency in case of stress such as surgery, trauma or severe infection because of adrenal toxicity in non-clinical studies. Warnings about fetal harm when administered to a pregnant woman and that safety and effectiveness have not been established in pediatric patients (due to the possibility of increased toxicity in developing organs). One label also warns about increased toxicity in combination with other anticancer agents.

The most common adverse events (>20%) noted in at least one of the labels for the approved TKIs are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, decreased appetite/anorexia, weight loss, dyspepsia, abdominal/ gastrointestinal pain, constipation, hypertension, peripheral edema, rash/desquamation, hand-foot syndrome, skin discoloration, dry skin, hair color changes, alopecia, altered taste, dysphonia, headache, back ache, musculoskeletal pain, arthralgia, myalgia, extremity pain, tumor pain, cough, dyspnea, and bleeding.

2.4 Nivolumab

Immune checkpoint inhibitors include agents that block negative regulators of T cell responses. Immune checkpoints are terms for molecules such as programmed death-1 programmed death-ligands 1) and 2 that downregulate the host anti-tumor immune response, and are expressed in many cancer types. Thus, these molecules play a key role in evading anti-tumor immunity. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody [HuMAb; immunoglobulin G4 (IgG4)-S228P] that targets the PD-1 cluster of differentiation 279 (CD279) cell surface membrane receptor. In the United States, nivolumab has been FDA approved for the treatment of patients with forms of melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, and squamous cell carcinoma of the head and neck. Additional information is presented in the full prescribing information (26).

2.5 Rationale for Combinatorial Therapy Against PD-1 and VEGF

The evidence to suggest that there is a complex relationship between angiogenesis and the immune system is growing (summarized in reference (13)). There is also literature that provides evidence to suggest that antiangiogenic agents can stimulate the immune system, and vice versa (27). Thus, combination regimens that include an antiangiogenic agent and immunotherapy could be synergistic when targeting tumors.

It is known that tumor cells secrete VEGF-A which, in addition to promoting angiogenesis, decreases dendritic cell co-stimulatory molecule expression and T cell priming, and also encourages the formation of myeloid-derived suppressor cells (MDSCs). It has been shown that sunitinib (a VEGFR, PDGFR, CSF1R, Kit, and Flt-3 inhibitor) reduces infiltration by MDSC and T

regulator lymphocytes and reverses immune suppression, thereby potentially enhancing the efficacy of immunotherapy (28,29). Indeed, in a few pilot clinical studies combining PD-1 and VEGFR inhibition in previously treated RCC patients, the combinations have consistently outperformed either single agent with ~100% higher response rates, as summarized below in **Table 1**.

TABLE 1: Comparison of Objective Response Rates (ORR) after PD-1 / VEGF Inhibition in patients with Previously Treated Renal Cell Carcinoma (RCC)

Therapy (anti-PD-1 + anti-VEGF)	**ORR** (%)
nivolumab	25% (n=410)
axitinib	19% (n=361)
nivolumab + sunitinib*	52% (n=33)
nivolumab + pazopanib	45% (n=20)
pembrolizumab + pazopanib	40% (n=20)
pembrolizumab + axitinib	50% (n=10)

** 58% of patients were treatment naïve.*

However, none of the above combinations were well tolerated at the full doses of both single agents. The combination of pazopanib with either nivolumab or pembrolizumab at full dose was too toxic due to overlapping liver toxicities. Although the full dose axitinib/pembrolizumab and sunitinib/nivolumab combinations were recommended, 3 of 11 patients (27%) in the axitinib/pembrolizumab study experienced a DLT, and 8 of 33 patients (24%) in the sunitinib/nivolumab study had Grade 3–4 related AEs which led to therapy discontinuation.

Thus, it is desirable to have a VEGFR inhibitor with lower toxicity for combination with immunotherapy. Given that vorolanib is structurally similar with parallel clinical activity as single-agent sunitinib, vorolanib has the potential to enhance the immunotherapeutic response of nivolumab in a similar manner to sunitinib, but with potentially lower toxicity.

2.6 Correlative Science Background

The immune system is composed of an innate and adaptive response that includes antigen specific T cell function. Most biomarker studies for immunotherapy in solid tumors have concentrated on evaluating the cell surface ligand and receptors PD-1 and PD-L1 as well as T cell infiltration. While PD-L1 has been used in NSCLC to optimize patient selection, in many tumor types these have not proven to be useful predictive biomarkers due to their variability (30). Therapies targeting negative regulators of T cells include FDA approved antibodies blocking cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein one, or its receptors including PD-L1. As discussed in detail above, the rationale to use vorolanib that blocks multiple tyrosine kinase pathways including VEGF, PDGF, CSF1, and c-KIT includes preclinical studies suggesting that vorolanib alters both the innate and adaptive immune system by targeting these various pathways. The suggested effects of

vorolanib include downregulation of T regulatory cells and increased antigen presentation by dendritic cells (31). In addition to preclinical data supporting changes in the adaptive immune response, inhibition of these pathways can also alter the innate immune system including immune repressive macrophages (28, 32). Thus studying the immune system as a whole monitoring changes in both the innate and adaptive immune response after treatment with combination vorolanib and nivolumab may yield important biologic answers on how the immune system responds to this novel combined treatment and provide putative clinical markers that could be monitored for response to treatment.

Mass cytometry is a technique similar to flow cytometry, which allows for analysis of individual cells as measured by time of flight for specific metal tagged antibodies that can capture clear detection of up to 30-40 markers per individual cell. Recently, mass cytometry was utilized to analyze the immune profile of peripheral blood in patients with stage IV melanoma who were undergoing treatment with checkpoint inhibitor therapy (33). The immune profiling from these patients suggested that differences in specific T cell subsets could be detected in the peripheral blood and that the numbers of T cells in relation to the tumor burden might be predictive of those patients who would respond to checkpoint inhibitor therapy (33).

Though mass cytometry will give significant insight to the changing immune milieu, only multiplexed immunofluorescence (IF) or immunohistochemistry will yield information in a spatial context important to understand the response to treatment with combined VEGF/PDGF inhibitor and nivolumab. In tumors such as melanoma, the presence of T cell infiltrate at the tumor margin has been suggestive as a marker of a response (34). In lung cancer, typical patient samples obtained for diagnosis are FNA or core biopsies which yield limited materials for correlative studies. Given that technology such as multiplex IF requires less material for analysis we hope to augment the amount of data yielded from each precious patient sample using this technique (35). We will characterize presence or expression of PD-1, PD-L1, PD-L2; T cell infiltrate by CD3, CD4, Foxp3, and CD8; T cell effector function by Granzyme B; markers of macrophages, and B cells.

Circulating angiogenic factors such as soluble VEGF and CSF1 can be produced by tumors and has been found in lung cancer cell lines (36, 37). CSF1 is known to be necessary for osteoclastogenesis and important in stimulating macrophages to promote an immunsuppressive environment that allows tumor growth (38). Vorolanib has activity blocking CSF1 and therefore it will be important to determine if pretreatment levels or levels during therapy with vorolanib and nivolumab correlate with tumor response. We will measure soluble VEGF and CSF1 prior to and after treatment with vorolanib and nivolumab to determine if levels correlate with response, PFS, or overall survival (OS).

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

Primary Objectives:

- Phase I: To assess the safety and tolerability of nivolumab and vorolanib in combination in patients with NSCLC naïve to checkpoint inhibitor therapy, NSCLC progressed on prior checkpoint inhibitor therapy considered primary refractory, NSCLC progressed on prior checkpoint inhibitor therapy considered acquired resistance, and thymic carcinoma.
- Phase II: To evaluate the efficacy as measured by response to the combination nivolumab and vorolanib in patients with refractory NSCLC naïve to checkpoint inhibitor therapy, NSCLC progressed on prior checkpoint inhibitor therapy considered primary refractory, NSCLC progressed on prior checkpoint inhibitor therapy considered acquired resistance, small cell lung cancer, and thymic carcinoma as compared to historical controls.

Secondary Objectives:

- Phase II: To assess the effects of tumor PD-L1 status and tumor mutation burden (TMB) on the response to combinatorial treatment vorolanib and nivolumab.

Exploratory Objectives:

- To assess the effects of combinatorial treatment on specific pharmacodynamic and pharmacogenetic biomarkers.

3.2. Endpoints

Primary Endpoints:

- Phase 2 recommended combination dose will be determined when >1/3 or >2/6 dose limiting toxicities measured using CTCAE criteria version 5.0
- Phase 2 best response will be measured by RECIST v1.1 at end of cycle 1 and confirmed at cycle 2

Secondary Endpoints:

- Phase II progression free survival at six months and one year intervals, duration of response, disease control rate, overall survival at one year, and objective response rate (ORR) as related to PD-L1 status measured as <1%, 1-49%, and >50%.

Exploratory Endpoints:

- To measure the effects of this novel combination on the immune system, we will use mass cytometry of peripheral blood that can distinguish 30 markers per individual cell to measure components of the immune system before, two weeks after initial treatment, at the end of the first cycle, and at time of progression and correlate these changes with response to therapy as determined by RECIST v1.1.
- To determine if the presence or spatial location of CD4, CD8, Foxp3 Tregs, B cells and macrophages in pre-treatment tumor biopsy correlate with response we will perform multiplex immunofluorescence.
- To assess effects of the novel combination on circulating CSF1 and VEGF concentrations we will perform ELISA on pretreatment and posttreatment peripheral blood.

4. PATIENT SELECTION

Questions regarding patient eligibility must be addressed and resolved by the investigator in consultation with the sponsor-investigator or designee prior to enrollment.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Signed and dated written informed consent.
2. Male or female ≥ 18 years of age.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Having progressed on at least one prior line of therapy, or refused chemotherapy, histologically or cytologically confirmed diagnosis of one of the following:

   Dose Escalation and Expansion Cohorts:

- Checkpoint Inhibitor Naïve Non-Small Cell Lung Cancer patients must have progressed on front-line cytotoxic chemotherapy or have refused chemotherapy and may have received up to three prior treatment regimens for stage IV disease provided no regimens included an anti-PD1 or PD-L1 agent or an oral VEGF TKI. Prior bevacizumab or ramucirumab is allowed.
- Progressed on Checkpoint Inhibitor Non-Small Cell Lung Cancer patients must have progressed on front-line or second checkpoint inhibitor therapy and may have received up to three prior treatment regimens for stage IV disease provided no regimens included an oral VEGF TKI. Prior bevacizumab or ramucirumab is allowed.
- Patients with EGFR, ALK, ROS1 and BRAF NSCLC must have progressed on an oral TKI and may have received an unlimited number of prior regimens.
- Thymic carcinoma patients must not be eligible for surgical resection at the time of enrollment and may have received any number of prior lines of therapy provided no regimens included an anti-PD1 or PD-L1 agent or an oral VEGF TKI. Prior bevacizumab or ramucirumab is allowed.
- Small Cell Lung Cancer patients must have progressed on platinum-based chemotherapy and may have received up to three prior lines of therapy for stage IV disease provided no prior regimen included an oral VEGF TKI; prior regimens can include an anti-PD-1 or PD-L1 agent.

5. At least one measureable lesion as defined by RECIST 1.1 which can be followed by CT or MRI.
6. Adequate organ function prior to first dose of protocol-indicated treatment, including:
    - Absolute neutrophil count (ANC) ≥ 1,500/μL
    - Platelets ≥ 100,000/μL
    - Hemoglobin ≥ 9.0 g/dL
    - Serum creatinine ≤ 1.5 times institutional upper limit of normal (ULN), or calculated creatinine clearance ≥ 40 mL/min (per the Cockcroft-Gault formula)
    - Total bilirubin ≤ 1.5 x ULN
      (except subjects with Gilbert Syndrome, who must have total bilirubin < 3.0 mg/dL)
    - Alanine aminotransferase and aspartate aminotransferase ≤ 2.5 x ULN, (≤ 5.0 x ULN with documented liver metastases)
7. Women must not be breastfeeding.
8. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 24 hours prior to receiving first dose of protocol-indicated treatment.
    - WOCBP is defined as any female who has experienced menarche who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal.
    - Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 years of age in the absence of other biological or physiological causes.
    - If menopausal status is considered for the purpose of evaluating childbearing potential, women < 55 years of age must have a documented serum follicle stimulating hormone (FSH) level within laboratory reference range for postmenopausal women, in order to be considered postmenopausal and not of childbearing potential.

9. Women of childbearing potential must agree to follow instructions for acceptable contraception Appendix 5 from the time of signing consent, and for 23 weeks after their last dose of protocol-indicated treatment.
10. Men not azoospermic who are sexually active with WOCBP must agree to follow instructions for acceptable contraception (Appendix 5), from the time of signing consent, and for 31 weeks after their last dose of protocol-indicated treatment.

4.2. Exclusion Criteria

Patients meeting any of the following criteria will not be permitted to enter the trial:

1. ≤ 28 days before first dose of protocol-indicated treatment:
    - Anti-cancer treatment with bevacizumab.
    - Major surgery requiring general anesthesia or significant traumatic injury.
2. ≤ 14 days before first dose of protocol-indicated treatment:
    - Anti-cancer therapy with an approved or investigational agent (including chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or biological therapy).
    - Radiosurgery or radiotherapy. (Note: A tumor lesion situated in a previously irradiated area is considered a measureable/target lesion only if subsequent disease progression has been documented in the lesion.)
    - Initiation of a new erythropoietin, darbepoietin, and/or bisphosphonate therapy. (See Section 9.3.)
    - Minor surgery. (Note: Placement of a vascular access device is not considered minor or major surgery.)
    - Serious or uncontrolled infection.
    - Infection requiring parenteral antibiotics. (Note: Patients with a non-serious infection under active treatment and controlled with oral antibiotics initiated at least 10 days prior to initiation of protocol-indicated treatment are not excluded – e.g. urinary tract infection controlled with oral antibiotics.)
    - Unexplained fever > 38.0 ºC.
3. ≤ 7 days before first dose of protocol-indicated treatment:
    - Receipt of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF). (See Section 9.3.)
4. Concurrent use of any medications or substances (e.g. herbal supplement or food) known to be a strong inhibitor or strong inducer of CYP3A4.
    - Although corticosteroids are considered to be strong inducers of CYP3A4, physiologic replacement doses of corticosteroids ≤ 10 mg daily prednisone or equivalent are allowed (Section 9).

5. Inadequate recovery from toxicity attributed to prior anti-cancer therapy.

    - With the exception of alopecia, fatigue, or peripheral neuropathy, patients must have recovered to ≤ Grade 1 (NCI-CTCAE v5.0) residual toxicity prior to first dose of protocol-indicated treatment.
    - Patients requiring replacement therapy (e.g. prednisone or thyroid replacement therapy) for endocrine disorders from prior checkpoint inhibitor therapy are allowed

6. Known history of allergy or intolerance which, in the opinion of the investigator, was an unacceptable adverse reaction attributed by the investigator to any prior anti-neoplastic therapy specifically targeting vascular endothelial growth factor or the VEGF receptor.

7. Known history of allergy or intolerance which, in the opinion of the investigator, was an unacceptable adverse reaction attributed by the investigator to any prior anti-neoplastic therapy specifically targeting T-cell costimulation or immune checkpoint pathways – i.e. nivolumab (OPDIVO), pembrolizumab (KEYTRUDA), atezolizumab (TECENTRIQ), ipilimumab (YERVOY), etc.

8. Non-healing wounds on any part of the body.

9. Known or suspected clinically significant active bleeding.

10. Inability to swallow oral medication; or the presence of a poorly controlled gastrointestinal disorder that could significantly affect the absorption of oral study drug – e.g. Crohn's disease, ulcerative colitis, chronic diarrhea (defined as > 4 loose stools per day), malabsorption, or bowel obstruction.

11. NSCLC patients with radiographic evidence of major airway or blood vessel invasion by cancer, radiographic evidence of intra-tumor cavitation, or gross hemoptysis (≥ one teaspoon) within the preceding 2 months.

12. Significant cardiovascular disease or condition including:

    - Congestive heart failure (CHF) that is uncontrolled on current therapy.
    - Class III or IV cardiovascular disease according to the New York Heart Association (NYHA) Functional Criteria.
    - Uncontrolled arrhythmia.
    - Severe conduction disturbance (e.g. 3rd degree heart block).
    - Unstable angina pectoris (i.e. last episode ≤ 6 months prior to first dose of protocol-indicated treatment).
    - Uncontrolled (per investigator judgment) hypertension.
    - Myocardial infarction within 6 months prior to starting trial treatment.
    - QTcF >450 ms in men, or >470 ms in women.

13. Deep vein thrombosis or pulmonary embolism ≤ 4 weeks before first dose of protocol-indicated treatment, unless adequately treated and stable.

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

14. Patients with active interstitial lung disease and non-infectious pneumonitis or a history of active interstitial lung disease or pneumonitis requiring treatment with steroids or that may interfere with the detection or management of suspected drug-related pulmonary toxicity. Patients with lung cancer with a remote history (> 3 months ago) of pneumonitis following chemo-radiation treatment that has resolved are allowed.

    - Note: Patients with Chronic Obstructive Pulmonary Disease (COPD) whose disease is controlled (per investigator judgment) at trial entry are not excluded.

15. CNS metastasis, unless asymptomatic and stable with no change in CNS disease status for at least two (2) weeks prior to initiating protocol-indicated treatment.

    - Anticonvulsant and/or corticosteroid prophylaxis (≤ 10 mg/day prednisone or equivalent daily) will be allowed if patient is on a stable or decreasing dose of such treatment for at least 14 days prior to initiating protocol-indicated treatment.

16. Any condition requiring systemic treatment with either corticosteroids (> 10 mg/day prednisone or equivalent daily) or other immunosuppressive medications within 14 days prior to initiating protocol-indicated treatment.

    - In the absence of active autoimmune disease: Subjects are permitted the use of corticosteroids with minimal systemic absorption (e.g. topical, ocular, intra-articular, intranasal, and inhalational) ≤ 10 mg/day prednisone or equivalent daily; and physiologic replacement doses of systemic corticosteroids ≤ 10 mg/day prednisone or equivalent daily (e.g. hormone replacement therapy needed in patients with hypophysitis).

17. Active, known or suspected autoimmune disease.

    - Subjects with type I diabetes mellitus; hypothyroidism; or endocrine disorders requiring hormone replacement even if due to prior immunotherapy; skin disorders such as vitiligo, psoriasis or alopecia not requiring systemic treatment; or conditions not expected by the investigator to recur in the absence of an external trigger are permitted to enroll.

18. Uncontrolled (per investigator judgment) type I or type II diabetes mellitus.

19. Known positive test for Human Immunodeficiency Virus (HIV) or known Acquired Immunodeficiency Syndrome (AIDS).

20. Any active Hepatitis B or Hepatitis C infection.

    - Hepatitis B and C testing required ≤ 28 days prior to initiating protocol-indicated treatment, including at least: Hepatitis B surface antigen (HBV sAg); and Hepatitis C virus antibody (HCV Ab) or Hepatitis C virus RNA (HCV RNA).

21. Solid tumor transplantation

22. Immunization with any attenuated live vaccine within 1 week prior to initiating protocol-indicated treatment.

23. Active second malignancy or history of a previous second malignancy within the last 2 years that could in the opinion of the investigator interfere with their assessment of study treatment.

    - Exceptions include the following permitted conditions – provided a complete remission was achieved at least 2 years prior to initiating protocol-indicated treatment AND no additional therapy (with the exception of allowable anti-estrogen/androgen

therapy or bisphosphonates) is ongoing or required during the trial period: non-melanoma skin cancers (e.g. basal or squamous cell); superficial bladder cancer; or carcinoma *in situ* of the prostate, cervix, or breast.

24. Known psychiatric condition, social circumstance, or other medical condition reasonably judged by the investigator to unacceptably increase the risk of study participation; or to prohibit the understanding or rendering of informed consent or anticipated compliance with and interpretation of scheduled visits, treatment schedule, laboratory tests and other study requirements.

4.3. Inclusion of Underrepresented Populations

Women and men of all races and ethnic groups are eligible for this trial. There is no bias towards gender, age, or race in the clinical trial outlined.

4.4. Number of Patients and Replacement of Patients Who Discontinue Early

Up to 177 patients [approximately 9-18 evaluable patients in Dose Escalation; and about 159 evaluable patients in five Dose Expansion cohorts, consisting of Checkpoint Inhibitor naïve Non-Small Cell Lung Cancer (n=39), Non-Small Cell Lung Cancer primary refractory to prior checkpoint inhibitor therapy (n=21), Non-Small Cell Lung Cancer adaptive resistance to prior checkpoint inhibitor therapy (n=21), Small Cell Lung Cancer progressed on platinum-based chemotherapy (n=37), and Thymic carcinoma (n=41)] are anticipated to enroll in this study at Vanderbilt University Medical Center and other study sites.

In general, it is intended that patients will be treated until confirmed disease progression or intolerable toxicity. The criteria for patient discontinuation are listed in Section 8.4.

For purpose of ensuring appropriate opportunity to determine the recommended combination dose (RCD) of vorolanib in combination with nivolumab, a subject who is withdrawn from the study before completion of the first 28 days after initiating protocol-indicated treatment on Cycle 1, Day 1 for a as reason other than a DLT will be replaced.

Additionally, if a patient discontinues protocol treatment for reasons clearly not related to protocol treatment (in the judgement of the sponsor-investigator), after completing less than 75% of scheduled oral doses of vorolanib or less than 2 planned infusions of nivolumab over the first 28 days after initiating protocol-indicated treatment on Cycle 1, Day 1, then that patient will be considered not evaluable for response to overall protocol-indicated treatment and may be replaced with a new patient.

5. ENROLLMENT PROCEDURES

5.1. Registration Procedures

The Vanderbilt-Ingram Cancer Center (VICC) Multi-Institutional Coordinating Office will coordinate enrollment onto the study.

Guidelines for VICC and Participating Institutions

Prior to registration, a copy of the IRB approval at the site will be requested and kept on file at the Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center. Eligible participants will be entered on study centrally at the VICC Coordinating Center. All sites should email the Coordinating Center at [redacted] to verify slot availability prior to enrollment.

All patients MUST be registered with the VICC prior to the start of protocol treatment. Registration can only be conducted during the business hours of 8AM – 5PM Central Standard Time Monday through Friday.

1) All sites must email the VICC CTSR Coordinating Center at Coordinating.Center@vumc.org to notify of upcoming registration and ensure slot availability. The following information should be included in your email:

    - Study number
    - Patient initials
    - Disease type
    - Anticipated consent date
    - Anticipated start date

2) If a subject ID number is required prior to patient enrollment (i.e. at screening due to sample collection requirement), the site must submit the following documents with their email notification to the Coordinating Center:

    - Copy of the patient's signed and dated Informed Consent including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form)
    - VICC Patient Enrollment Form

The Coordinating Center will then provide a subject ID number via email.

3) Email the following documents to the Coordinating Center for eligibility review and patient enrollment ([redacted]

    - Copy of the patient's signed and dated Informed Consent, including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form)
    - VICC Patient Enrollment Form
    - Eligibility supporting documents such as pathology reports, laboratory tests, etc. *or* EMR access. Note: all source documents should be de-identified and screening/subject ID number added prior to sending.
    - Tissue Registration Form (if applicable – see **Lab Manual**)
    - Signed and completed Eligibility Checklist. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.**

Note: All study documents should be received 24-48 hours prior to the patient's anticipated start date. Same day treatment registrations will only be accepted with prior notice and discussion with the Coordinating Center. Please email the Coordinating Center if enrollment is needed sooner.

Upon satisfactory review of eligibility documents submitted, the Coordinating Center will approve enrollment and issue a subject ID number if one was not issued at screening. Once

registration/enrollment confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned Clinical Research Associate (CRA) once the study is activated.

Issues that would cause treatment delays should be discussed with the sponsor-investigator or designee
Any requests for eligibility exceptions and/or deviations must be approved in writing by the Protocol Chair and the VICC DSMC. Changes to the protocol will not be implemented without agreement from the sponsor-investigator, except where necessary to eliminate an immediate hazard to the patient.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after the consent date.

5.2. Screen-Failures

A patient found not eligible for the trial after giving informed consent is considered a screening-failure. The enrollment form and eligibility checklist must be completed and sent to the sponsor-investigator or designee to confirm the outcome of the screening process.

Re-screening and re-enrollment of a subject who has discontinued the study as a pre-treatment failure (i.e. subject has not received protocol-indicated treatment) is permitted.

A consented patient previously reported to the coordinating center as pre-treatment failure must be re-consented prior to undergoing re-screening.

6. SCHEDULE OF ASSESSMENTS

6.1. Study Calendar

Protocol Activities *1 Cycle = 8 weeks (56 days)*	Screening (Day -28 to Day -1)	CYCLE 1-2						CYCLE 3+		Post-Treatment	
		Day 1 (± 3d)[15]	C1D8[23]	Day 15 (± 3d)[15]	C1D22[23]	Day 29 (± 3d)[15]	Day 43 (± 3d)[15]	Day 1 (± 3d)[15]	Day 29 (± 3d)[15]	EOT (≤10d after decision to end treatment)[19]	Follow-Up (after last study dose)[21] Short-term: 28d + 7d Long-term: 100d + 7d
Clinical Assessments											
Consent, Baseline Characteristics & Eligibility[1]	X										
Physical Examination	X	X[12]		X		X	X	X	X	X	X
ECOG Performance Status	X	X		X		X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X
Vital Signs & O_2 Saturation[2]	X	X	X	X	X	X	X	X	X	X	X
Review of Con Meds & Adverse Events[3]	X	X	X	X	X	X	X	X	X	X	X
DLT Evaluation (dose-escalation only)[4]		X	X	X	X	X		X	X		
Laboratory Assessments											
Hematology and Blood Chemistry[5]	X	X[12]	X	X	X	X	X	X	X	X	X
Thyroid Function Testing[6]	X	X[6]				X[6]		X[6]	X[6]	X	X
Serum Amylase & Lipase	X	X[12]						X			
Hepatitis Testing[7]	X										
12-lead ECG[8]	X									X	X
Urinalysis[9]	X	X[12]				X		X	X	X	X
Pregnancy Test[10]	X										
Disease Assessments											
CT/MRI Scans[11]	X	X						Every 8 wks prior to D1[11]		X[20]	X[20]
Follow-Up											X
Biospecimen Collections											
Archival / Fresh Tumor Tissue (optional)[13]	X										

Pharmacogenetic/Pharmacodynamic Blood[14]		X[14]				X[14]				X[14]	
Treatment											
Vorolanib oral administration[16]		Continuous once daily oral dosing									
Nivolumab infusion[17]		X[18]		X[18]		X[18]	X[18]	X[18]	X[18]		

Notes:

1. Informed consent must be obtained before any study-specific screening assessments are performed. Screening assessments are to be performed within 28 days prior to Day 1 of Cycle 1 unless otherwise noted. Assessments performed as standard of care within the screening window may be used for screening. Baseline characteristics include but are not limited to: demographics, medical and surgical history, extent of disease, prior anti-cancer treatment, and tumor histology.

2. Vital Signs and Oxygen Saturation. (If on day of nivolumab administration, then both measurements to be done at least pre-dose, prior to initiation of nivolumab infusion, with any additional time points per local institutional standard / treating physician discretion). Vital Signs to include: blood pressure (BP), heart rate (HR) and temperature. Oxygen saturation by pulse oximetry to be done at least *at rest*, with any additional recordings per local site's standard of care / treating physician discretion. (Note: If additional recordings of pulse oximetry follow patient *exertion*, then the extent of exertion preceding measurement of oxygen saturation should be based on the judgment of the patient's study physician, and should remain consistent for each individual subject throughout the study.)

3. Review and capture of all concomitant medications will be performed as indicated. Concomitant medications include prescription medications and over-the-counter preparations used by a patient within at least 14 days prior to first dose of protocol-defined treatment and continuing through at least the 28-day Follow-Up study visit. After signing informed consent, adverse events will be collected as detailed in protocol Section 12. All adverse events will be followed at least until 28 days after a patient's final protocol-directed treatment with vorolanib or nivolumab (whichever occurs last) or until initiation of another anti-cancer therapy – whichever occurs first.

4. For dose-escalation only: Dedicated surveillance and expedited reporting of Dose Limiting Toxicity (DLT) required for 28 days after initiating protocol-indicated treatment. On Day 29, satisfactory completion of the physical exam and safety labs is required to help detect evidence of past or present DLT as having occurred during the first 28 days of protocol-indicated treatment. If intolerable delayed toxicity attributable (per sponsor-investigator judgement) to protocol treatment is detected past Day 28, then the 28-Day DLT window may possibly be extended. See protocol Section 10.1 for definition of DLT and toxicities which, if experienced during the first 28 days after initiating protocol-indicated treatment, shall be considered dose limiting.

5. Hematology includes white blood cell count with differential, hemoglobin, hematocrit, and platelet count. Blood Chemistry to include sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, and total protein.

6. Thyroid stimulating hormone (with additional free T3 and free T4, if TSH is abnormal) to be done at Screening and every 4 weeks; and at the end of treatment (EOT) and Follow-up visits. Testing will be performed on Day 1 of each cycle (except cycle 1 as was done at screening) and day 29 of each cycle.

7. Hepatitis B and C testing at Screening (≤ 28 days prior to initiating protocol-indicated treatment), including at least: Hepatitis B surface antigen (HBV sAg); and Hepatitis C virus antibody (HCV Ab) or RNA (HCV RNA).

8. One standard 12-lead electrocardiogram (ECG) using local site equipment during Screening; and at EOT and Follow-up visits. Additional ECGs as clinically indicated per patient's study physician.

9. Macroscopic urinalysis to include specific gravity, pH, glucose, protein, ketones, and blood. Increased frequency of urinalysis and urine microscopics (e.g. RBC, WBC, casts, and crystals) as clinically indicated per patient's study physician.

10. For women of childbearing potential: Serum pregnancy test required during Screening. A woman of childbearing potential is defined as any female who has experienced menarche who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

    Postmenopausal status in females < 55 years of age should be confirmed with a serum follicle-stimulating hormone level within laboratory reference range for postmenopausal women (if the patient's postmenopausal status is considered for childbearing potential and study-required contraception – Appendix 5).

11. Baseline evaluation of disease status by CT or MRI within 28 days prior to initiating protocol treatment on Cycle 1, Day 1. Baseline and subsequent scans to include imaging of the chest and abdomen. Additional sites of known or suspected disease (e.g. pelvis) should be imaged during screening and subsequent scans. *Re-scanning to occur every 8 weeks* (± 7 days) after initiating protocol treatment on Cycle 1, Day 1. (The ± 7 day scan window is intended to facilitate flexibility in scheduling re-scans *during Week 8 of each 56 day cycle*, prior to initiation of treatment on Day 1 of every new cycle.)

    Patients with known or suspected CNS metastasis must have imaging of the head by CT or preferable MRI during screening (and thereafter, while on-study, at least every 3 months ± 7 days since prior head imaging, if a CNS lesion is detected on baseline imaging).

    Scanning on the same day as infusion with nivolumab is discouraged but allowed, provided scan results receive appropriate RECIST review prior to initiating a new cycle of study treatment (e.g. first re-scan is discouraged, but permitted on Cycle 2, Day 1, prior to nivolumab infusion later that same day). Additional disease evaluations or increased scan frequency may be performed according to the medical judgment of the patient's study physician, in accordance with the following: In the event of suspected Progressive Disease, a CT/MRI is to be performed as soon as possible. In the event of a Complete or Partial Response, a confirmatory CT/MRI is to be performed no earlier than 28 days after the first assessment of CR/PR.

12. On Cycle 1, Day 1: Physical exam, Hematology and Blood Chemistry, serum lipase and amylase, and Urinalysis need not be repeated if already completed ≤ 7 days prior to first dose of protocol-indicated treatment.

13. Requesting FFPE sample from either a standard of care biopsy performed within 28 days prior to Cycle 1, Day 1 or archival tissue if available to confirm histologic subtype, progression of disease, and for correlative studies (sample optional and not required for study participation).

14. Pharmacogenetic/Pharmacodynamic blood collection. In Cycle 1 blood will be collected on Day 1, Day 29, and End of Therapy for correlative studies. To accommodate scheduling, may occur within - 3 days but blood collection is requested to take place prior to infusion of nivolumab on the day treatment.

15. Beginning with Cycle 1, Day 43 (i.e. beyond the DLT assessment period intended for conclusion with the Day 29 visit): In order to accommodate scheduling, visits and procedures may occur with flexibility of ± 3 days. (Note that a minimum of 12 days is required between successive nivolumab infusions.)

16. All patients are scheduled to receive oral vorolanib once daily (QD) on a continuous dosing schedule. The study will provide vorolanib to the site.

17. All patients are scheduled to receive nivolumab every 2 weeks, as a 30 minute intravenous infusion on Days 1, 15, 29, and 43 of each 56 day (8 week) cycle. The study will provide nivolumab to the site.

18. After the first 16 weeks (2 cycles), if a patient in any cohort has not experienced disease progression (non-PD response), patients with continued clinical benefit can switch to treatment with 480 mg nivolumab every 4 weeks on Days 1 and 29 of each 56-day cycle.

19. Reasonable effort should be made to complete EOT procedures on the day it is decided a patient will no longer receive protocol-indicated treatment. These procedures must be completed subsequent to and not later than 14 days after investigator decision to permanently discontinue protocol-indicated treatment with vorolanib or nivolumab (whichever treatment occurs last) and prior to any subsequent anti-cancer therapy.

20. At End-of-Treatment, CT/MRI required only if the previous CT/MRI was done > 28 days before. At the 28 day Follow-Up visit, CT/MRI scan required only if disease progression not already documented by CT/MRI done at or before the prior EOT visit. If a patient discontinues the study for reason other than progressive disease confirmed by CT or MRI (e.g. adverse event), then CT or MRI scans involving sites of known or suspected disease must be continued every 8 weeks (± 7 days) until disease progression is confirmed by imaging.

21. Follow-up clinic visit to be completed 28 days (+7 days) after patient's final protocol-indicated treatment with vorolanib or nivolumab (whichever occurs last). Documented attempt(s) should be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities.

    Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed for at least 100 days (+7 days) after the last dose of study drug administration. The extended safety follow-up may be performed either via a clinic visit or telephone call with a subsequent site visit requested in case any concerns are noted during the telephone call.

22. Cycle 1 Day 8 and 22 visits in Phase I (Dose Escalation) ONLY.

6.2. Screening Visit Assessments

Prior to performing any study-based procedures, patient informed consent must be obtained.

The following procedures must be completed ≤ 28 days prior to a patient's first dose of protocol-indicated treatment:

- Baseline evaluation of disease status by CT or MRI; to include at least the chest and abdomen, with additional sites of known or suspected disease (e.g. pelvis) as clinically indicated per patient's study physician.
- For patients with known or suspected CNS metastasis: Baseline imaging of the head by CT or preferable MRI.
- Hepatitis B and C testing: Hepatitis B surface antigen; and Hepatitis C virus antibody or RNA.
- Requesting FFPE sample from either a standard of care biopsy performed within 28 days prior to Cycle 1, Day 1 or archival tissue if available to confirm histologic subtype, progression of disease, and for correlative studies (sample optional and not required for study participation).
- Medical history and Demographics.
- Physical exam.
- ECOG performance status.
- Weight.
- Vital Signs: blood pressure, heart rate and temperature.
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication (prescription and over-the-counter drugs taken at least 14 days prior to intended Cycle 1, Day 1 dosing) and Adverse Event review.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Serum amylase and lipase.
- Thyroid stimulating hormone (with additional free T3 and free T4, if TSH is abnormal).
- 12-lead ECG (single recording on local equipment), with additional ECGs as clinically indicated, per patient's study physician.
- Macroscopic Urinalysis, including specific gravity, pH, glucose, protein, ketones, and blood. (Microscopic analysis only if clinically indicated per patient's study physician.)
- Serum Pregnancy Test in women of childbearing potential (as defined in Section 7.13).

6.3. Cycle 1, Day 1 Assessments

On Cycle 1, Day 1, the following procedures must be completed, unless previously completed ≤ 7 days prior to a patient's first dose of protocol-indicated treatment:

- Physical Exam.
- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Serum amylase and lipase
- Macroscopic Urinalysis, including specific gravity, pH, glucose, protein, ketones, and blood. (Microscopic analysis only if clinically indicated per patient's study physician.)

On Cycle 1, Day 1, the following procedures must be completed, unless previously completed ≤ 3 days prior to a patient's first dose of protocol-indicated treatment.

- Peripheral blood for pharmacogenetics and pharmacodynamics analysis

On Cycle 1, Day 1, the following procedures will be completed:

- ECOG performance status.
- Weight.
- Vital Signs: blood pressure, heart rate and temperature.
  (To be done at least prior to initiation of nivolumab infusion, with any additional recordings per local site's standard of care / treating physician discretion.)
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, prior to initiation of nivolumab infusion, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.
- Surveillance for and expedited reporting of Dose Limiting Toxicity– see Section 10.1 for DLT definition.
- Initiate once daily oral vorolanib.
- Nivolumab infusion.

6.4. Cycle 1, Day 8 Assessments (Phase I - Dose Escalation ONLY)

- Weight.
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, prior to initiation of nivolumab infusion, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.

- Surveillance for and expedited reporting of Dose Limiting Toxicity (DLT) – see Section 10.1 for DLT definition.
- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Continue once daily (QD) oral vorolanib.

6.5. Cycle 1, Day 15 Assessments

- Physical Exam.
- ECOG performance status.
- Weight.
- Vital Signs: blood pressure, heart rate and temperature.
  (To be done at least prior to initiation of nivolumab infusion, with any additional recordings per local site's standard of care / treating physician discretion.)
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, prior to initiation of nivolumab infusion, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.
- Surveillance for and expedited reporting of Dose Limiting Toxicity– see Section 10.1 for DLT definition.
- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Continue once daily oral vorolanib.
- Nivolumab infusion.

6.6. Cycle 1, Day 22 Assessments (Phase I - Dose Escalation ONLY)

- Weight.
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, prior to initiation of nivolumab infusion, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.
- Surveillance for and expedited reporting of Dose Limiting Toxicity – see Section 10.1 for DLT definition.

- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Continue once daily oral vorolanib.

6.7. Cycle 1, Day 29 Assessments

In order to properly evaluate the DLT period, the Cycle 1, Day 29 visit should occur 28 days after Cycle 1, Day 1.

- Physical Exam.
- ECOG performance status.
- Weight.
- Vital Signs: blood pressure, heart rate and temperature.
  (To be done at least prior to initiation of nivolumab infusion, with any additional recordings per local site's standard of care / treating physician discretion.)
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, prior to initiation of nivolumab infusion, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.
- Surveillance for and expedited reporting of Dose Limiting Toxicity – see Section 10.1 for DLT definition.
- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Thyroid stimulating hormone (with additional free T3 and free T4, if TSH is abnormal).
- Macroscopic Urinalysis, including specific gravity, pH, glucose, protein, ketones, and blood.
  (Microscopic analysis only if clinically indicated per patient's study physician.)
- Peripheral blood samples will be drawn for pharmacogenetics and pharmacodynamics studies.
- Continue once daily oral vorolanib.
- Nivolumab infusion.

6.8. Cycle 1, Day 43 Assessments

In the absence of delayed dosing (e.g. due to an adverse event), every reasonable effort should be made to remain on a consistent schedule of 8 Week (56-day) cycles; but for purpose of accommodating holidays, scheduling limitations, etc., subsequent protocol activities beginning with

Cycle 1, Day 43 may occur with permissible scheduling flexibility (unless otherwise noted by protocol) of up to every ± 3 days.

  - Physical Exam
  - ECOG performance status
  - Weight
- Vital Signs: blood pressure, heart rate and temperature.
  (To be done at least prior to initiation of nivolumab infusion, with any additional recordings per local site's standard of care / treating physician discretion.)
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, prior to initiation of nivolumab infusion, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.
- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Continue once daily oral vorolanib.
- Nivolumab infusion.

6.9. Cycle 1, Day 56 Assessments

CT/MRI re-scanning:

- Ideally performed on Cycle 1, Day 56, but for purpose of scheduling flexibility: Scan completion permitted anytime during Week 8 of Cycle 1 (i.e. during Days 50-56 of Cycle 1); or alternatively as late as prior to nivolumab treatment on overall Day 57 (i.e. Cycle 2, Day 1), provided such scan results receive appropriate RECIST review prior to initiating nivolumab in the new cycle.
- Evaluation of disease status by CT or MRI to include at least the chest and abdomen, with additional sites of known or suspected disease (e.g. pelvis) as clinically indicated per patient's study physician.

6.10. Cycles 2+, Day 1 and Day 29 Assessments

For patients that continue beyond Cycle 1, the following assessments will occur on Day 1 and Day 29 of each additional cycle:

- Physical Exam
- ECOG performance status.
- Weight.
- Vital Signs: blood pressure, heart rate and temperature.

(To be done at least prior to initiation of nivolumab infusion, with any additional recordings per local site's standard of care / treating physician discretion.)

- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, prior to initiation of nivolumab infusion, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.
- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Day 1 only: Serum amylase and lipase.
- Macroscopic Urinalysis, including specific gravity, pH, glucose, protein, ketones, and blood. (Microscopic analysis only if clinically indicated per patient's study physician.)
- Thyroid stimulating hormone (with additional free T3 and free T4, if TSH is abnormal).
- Continue once daily oral vorolanib.
- Nivolumab infusion.

6.11. Cycles 2+, Day 15 and Day 43 Assessments

For patients that continue beyond Cycle 1, the following assessments will occur on Day 15 and Day 43 of each additional cycle:

- Physical Exam
- ECOG performance status
- Weight
- Vital Signs: blood pressure, heart rate and temperature.
  (To be done at least prior to initiation of nivolumab infusion, with any additional recordings per local site's standard of care / treating physician discretion.)
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, prior to initiation of nivolumab infusion, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.
- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Continue once daily oral vorolanib.
- Nivolumab infusion.

- **Of note**: If the patient has not exhibited evidence of disease progression (non-PD) and is undergoing treatment in cycles 3+, then nivolumab infusion will be NOT be administered on Day 15 or Day 43.

6.12. Cycles 2+, Day 56 Assessments

CT/MRI re-scanning:

- Ideally performed on Cycle x, Day 56, but for purpose of scheduling flexibility: Scan completion permitted anytime during Week 8 of each cycle (i.e. during cycle Days 50-56); or alternatively as late as prior to nivolumab treatment on Cycle x, Day 1, provided such scan results receive appropriate RECIST review prior to initiating nivolumab in the new cycle.
- Evaluation of disease status by CT or MRI to include at least the chest and abdomen, with additional sites of known or suspected disease (e.g. pelvis) as clinically indicated per patient's study physician.
- Additional disease evaluations or increased scan frequency may be performed according to the medical judgment of the patient's study physician, in accordance with the following: In the event of suspected Progressive Disease, a CT/MRI is to be performed as soon as possible. In the event of a Complete or Partial Response, a confirmatory CT/MRI is to be performed no earlier than 28 days after the first assessment of CR/PR.
- Regarding brain scans, please note patients with known or suspected CNS metastasis must have baseline imaging of the head by CT or preferable MRI during screening; and thereafter, while on-study, at least every 3 months ± 7 days since prior head imaging – if a CNS lesion was detected on baseline imaging.

6.13. End-of-Treatment / Withdrawal Assessments

Reasonable effort should be made to complete End-of-Treatment / Withdrawal procedures on the day it is decided that a patient will no longer receive protocol-indicated treatment.

The following EOT procedures must be completed subsequent to and not later than 14 days after investigator decision to permanently discontinue protocol-indicated treatment with vorolanib / nivolumab (whichever treatment occurs last) and prior to any subsequent anti-cancer therapy:

- Physical Exam.
- ECOG Performance Status.
- Weight.
- Vital Signs: blood pressure, heart rate and temperature.
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.
- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].

- Peripheral blood will be drawn for pharmacogenetic and pharmacodynamics testing.
- Thyroid stimulating hormone (with additional free T3 and free T4, if TSH is abnormal).
- 12-lead ECG (single recording on local equipment), with additional ECGs as clinically indicated, per patient's study physician.
- Macroscopic Urinalysis, including specific gravity, pH, glucose, protein, ketones, and blood. (Microscopic analysis only if clinically indicated per patient's study physician.)
- Disease evaluation by CT/MRI (only if the previous CT/MRI was done > 28 days before).

6.14. Follow-Up Visit Assessments (28-Day and 100-Day)

Documented attempt(s) should be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities.

A Follow-up clinic visit is to be completed 28 days (+7 days) after patient's final protocol-indicated treatment with vorolanib or nivolumab (whichever occurs last), in order to undergo the following assessments:

- Physical Exam.
- ECOG Performance Status.
- Weight.
- Vital Signs: blood pressure, heart rate and temperature.
- Oxygen Saturation by pulse oximetry.
  (To be done at least at rest, prior to initiation of nivolumab infusion, with any additional measurements per local site's standard of care / treating physician discretion.)
- Concomitant medication and Adverse Event review.
- Complete Blood Count with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein].
- Thyroid stimulating hormone (with additional free T3 and free T4, if TSH is abnormal).
- 12-lead ECG (single recording on local equipment), with additional ECGs as clinically indicated, per patient's study physician.
- Macroscopic Urinalysis, including specific gravity, pH, glucose, protein, ketones, and blood. (Microscopic analysis only if clinically indicated per patient's study physician.)

If a patient discontinues the study for reason other than progressive disease confirmed by CT or MRI (e.g. adverse event), then CT or MRI scans of the chest and abdomen (and any additional sites of known or suspected disease) must be continued not later than every 8 weeks (± 7 days) until disease progression is confirmed by imaging.

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 100 days (+7 days) after the last dose of study drug.

7. STUDY PROCEDURES

7.1. Informed Consent

Informed consent must be obtained before any study-specific screening assessments are performed. Screening assessments are to be performed within 28 days prior to Day 1 of Cycle 1 unless otherwise noted. Assessments performed as standard of care within the screening window may be used for screening. Baseline characteristics include but are not limited to: demographics, medical and surgical history, extent of disease, prior anti-cancer treatment, and tumor histology.

7.2. Physical Examination

Physical examinations to be performed within 28 days prior to initiating protocol treatment; on Day 1 (unless previously completed ≤ 7 days prior to a patient's first dose of protocol-indicated treatment) and Day 15, Day 29, and Day 43; and at the End-of-Treatment or 28-day Follow-Up visit.

7.3. Performance Status

Eastern Cooperative Oncology Group performance status to be recorded during Screening; on Days 1, 15, 29 and 43 of each cycle; and at the EOT and Follow-up visits.

7.4. Vital Signs, Body Weight, and Oxygen Saturation

Vital Signs to include: blood pressure, heart rate and temperature.

Oxygen saturation by pulse oximetry to be done at least at rest, with any additional recordings per local site's standard of care / treating physician discretion. (Note: If additional recordings of pulse oximetry follow patient exertion, then the extent of exertion preceding measurement of oxygen saturation should be based on judgment of the patient's study physician, and should remain consistent for each individual subject throughout the study.)

On days of measurement occurring on day of nivolumab administration, then Vital Signs, weight and Oxygen Saturation to be done at least pre-dose (i.e. prior to initiation of nivolumab infusion), with any additional time points per local institutional standard / treating physician discretion).

7.5. Review of Concomitant Medications and Adverse Events

Review and capture of all concomitant medications will be performed at each visit as indicated in Section 6. Concomitant medications include prescription medications and over-the-counter preparations used by a patient within at least 14 days prior to first dose of protocol-defined treatment and continuing through at least the 28-day Follow-Up study visit. After signing the informed consent, adverse events will be collected as detailed in protocol Section 12. All adverse events will be recorded at least until 28 days after a patient's final protocol-directed treatment with vorolanib or nivolumab (whichever occurs last) or until initiation of another anti-cancer therapy – whichever occurs first.

7.6. Surveillance and Expedited Reporting of Dose Limiting Toxicity

For dose-escalation only: Dedicated surveillance and expedited reporting of Dose Limiting Toxicity are required for 28 days after initiating protocol-indicated treatment. On Cycle 1, Day 29, satisfactory completion of the physical exam and the safety labs is required to help detect evidence of past or present DLT as having occurred during the first 28 days of protocol-indicated treatment. If intolerable delayed toxicity attributable (per sponsor-investigator judgement) to protocol treatment is detected past Day 28, then the 28-Day DLT window may possibly be extended. See protocol Section 10.1 for definition of DLT and toxicities which if experienced during the first 28 days after initiating protocol-indicated treatment shall be considered dose limiting.

7.7. Complete Blood Count with Differential

Hematology includes white blood cell count with differential, hemoglobin, hematocrit, and platelet count.

7.8. Blood Chemistry

Local blood chemistry results to include sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein.

7.9. Thyroid Function Testing

Thyroid stimulating hormone (with additional free T3 and free T4, if TSH is abnormal) to be done at Screening and every eight weeks; and at the EOT and Follow-up visits.

7.10. Hepatitis Testing

Hepatitis B and C testing at Screening (≤ 28 days prior to initiating protocol-indicated treatment): Hepatitis B surface antigen; and Hepatitis C virus antibody or RNA.

7.11. ECG

Standard 12-lead electrocardiogram, single tracing, using local site equipment during Screening; and at EOT and Follow-up visits. Additional ECGs as clinically indicated per patient's study physician.

7.12. Urinalysis

Macroscopic urinalysis to include specific gravity, pH, glucose, protein, ketones, and blood. Increased frequency of urinalysis and urine microscopics (e.g. RBC, WBC, casts, and crystals) as clinically indicated per patient's study physician.

7.13. Pregnancy Test

Serum pregnancy test for women of childbearing potential required during Screening. Subsequent pregnancy test – either serum or urine – to be done if clinically indicated per study physician.

A woman of childbearing potential is defined as any female who has experienced menarche who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

Postmenopausal status in females < 55years of age should be confirmed with a serum follicle-stimulating hormone level within laboratory reference range for postmenopausal women (if the patient's postmenopausal status is considered for childbearing potential and study-required contraception).

7.14. Disease Assessment by CT/MRI

Baseline evaluation of disease status by CT or MRI within 28 days prior to initiating protocol treatment on Cycle 1, Day 1.

Baseline and subsequent scans to include imaging at least of the chest and abdomen. Additional sites of known or suspected disease (e.g. pelvis) per judgement of patient's study physician should be imaged during screening and subsequent scans.

Re-scanning ideally performed on Cycle x, Day 56, but for purpose of scheduling flexibility: Re-scanning completion permitted anytime during Week 8 of each cycle (i.e. during cycle Days 50-56); or alternatively as late as prior to nivolumab treatment on Cycle x, Day 1, provided such scan results receive appropriate RECIST review prior to initiating nivolumab in the new cycle.

Patients with known or suspected CNS metastasis must have imaging of the head by CT or preferable MRI during screening (and thereafter, while on-study, at least every 3 months ± 7 days since prior head imaging, if a CNS lesion is detected on baseline imaging).

CT/MRI scanning on the same day as infusion with nivolumab is allowed, provided scan results receive appropriate RECIST review prior to initiating a new cycle of study treatment (e.g. first re-scan is permitted as late as Cycle 2, Day 1, prior to nivolumab infusion later that same day).

Additional disease evaluations or increased scan frequency may be performed according to the medical judgment of the patient's study physician, in accordance with the following: In the event of suspected Progressive Disease, a CT/MRI is to be performed as soon as possible. In the event of a Complete or Partial Response, a confirmatory CT/MRI is to be performed no earlier than 28 days after the first assessment of CR/PR.

At End-of-Treatment, CT/MRI required only if the previous CT/MRI was done > 28 days before.

At the 28-day Follow-Up visit, CT/MRI scan required only if disease progression not already documented by CT/MRI done at or before the prior EOT visit.

If a patient discontinues the study for reason other than progressive disease confirmed by CT or MRI (e.g. adverse event), then CT or MRI scans of involving sites of known or suspected disease must be continued every 8 weeks (± 7 days) until disease progression is confirmed by imaging or up to 100 days after last dose.

7.15. Tumor Tissue and Correlative Blood Samples

Biopsy confirming progression of disease and histology is requested to be analyzed for PD-L1 and exploratory endpoints. If biopsy specimen not available at time of progression prior to entry on study, archival tissue is requested to be analyzed for PD-L1 expression and exploratory biologic correlates.

Pharmacodynamic and pharmacogenetics blood samples will be collected at baseline prior to starting therapy, on Days 1 and 29 of Cycle 1 and at End of Therapy. Longitudinal blood samples will be analyzed for exploratory endpoints described above including but not limited to: mass CyTOF measuring changing in the systemic immune milieu, soluble VEGF and CSF1 concentrations, as well as other biomarkers of interest.

7.16. Handling of Biological Samples

All biological samples to be analyzed locally will be collected and handled according to local institutional practices. All biological samples to be analyzed centrally will be collected and handled according to a provided laboratory manual. Retention time for biologic specimens will be specified in the laboratory manual.

Please see the Laboratory Manual for standard operating procedures on collection, documentation, and transfer of materials.

7.17. Specimen Banking

Any leftover study tissue or blood samples may be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. All future use as part of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the Institutional Review Board according to its established policies, whether the specimens are stored in a central site or at a local institution or in a virtual repository.

8. PROTOCOL TREATMENT

8.1. Dose Level Summary

This is a phase 1/2, multi-center trial that will evaluate the safety, tolerability, and preliminary efficacy of vorolanib (an oral angiogenesis inhibitor), in combination with nivolumab (an infusional anti-PD-1 monoclonal antibody) in patients with selected advanced solid tumors.

The primary objective of the phase I component is to determine the Maximum Tolerated Dose (MTD) / Recommended Combination Dose of vorolanib in combination with nivolumab. Dose-escalation in phase 1 will follow a standard 3+3 design. The dose-escalation schema is presented in **Table 2**:

TABLE 2: Dose Escalation Summary

Dose Level	**Vorolanib** Oral continuous once daily (QD)	**Nivolumab** I.V. Days 1, 15, 29, and 43 (each cycle)
-1	100 mg	240 mg
1	200 mg	240 mg

2	300 mg	240 mg
3	400 mg	240 mg

1 cycle = 56 days (8 weeks)

The first cohort of patients will be started at dose level 1. At least 3 patients will be studied at each dose level and evaluated for toxicity. If 0 of 3 patients experience a dose-limiting toxicity, the dose will be escalated. If 1 of 3 patients experiences a DLT, 3 additional patients will be treated. If none of the additional patients develop a DLT, the dose will be escalated, otherwise escalation ceases. If > 2 of 3, or > 2 of 6, patients experience a DLT, the RCD has been exceeded.

In the phase 2 dose-expansion portion of the study, additional patients (about 159 total additional patients) will be split into five cohorts (about 21-41 evaluable patients/cohort), consisting of patients with checkpoint naïve NSCLC, previously progressed on checkpoint inhibitor therapy NSCLC, SCLC previously progressed on platinum based chemotherapy, and thymic carcinoma, who will be treated at the Recommended Combination Dose determined in the phase 1 portion of the study.

8.2. Oral Vorolanib

The study will supply vorolanib to each site.

Patients are scheduled to take an oral dose of vorolanib once each day continuously until development of progressive disease or unacceptable adverse event.

Vorolanib should be taken whole with food, at approximately the same time each day, approximately 24 hours (± 2 hours) apart. Unless as additionally directed by protocol, once daily dosing with vorolanib may occur in the morning, afternoon, or evening. Foods along with medications and herbal supplements that are known modulators of CYP3A4 should not be taken with vorolanib and are listed in Appendix 4.

Missed doses of vorolanib can be made up during the same day as soon as the patient remembers (or, as additionally directed by the clinical team). However, if the previous dose was taken < 6 hours in the past, or if the next scheduled dose is due < 6 hours in the future, then the missed dose should be skipped. Patients with emesis must not take a replacement dose.

Each patient receiving vorolanib will be treated at the assigned dose, unless dose-reduction is necessary as specified in Section 10. There will be no intra-patient dose-escalation of vorolanib.

8.3. Nivolumab Infusion

All patients are scheduled to receive 240 mg of nivolumab by 30 minute intravenous infusion on Days 1, 15, 29, and 43 of each 56 day (8 week) Cycle. The study will supply nivolumab to each site.

Nivolumab will be given every two weeks, with no less than 12 days between successive nivolumab infusions.

Of note: If the patient has not exhibited evidence of disease progression (non-PD) and is undergoing treatment in cycles 3+, then 480 mg of nivolumab by 30 minute intravenous infusion will be administered on Days 1 and Day 29 of each 56 day (8 week) Cycle.

Every effort should be made to target infusion timings to be as close to scheduled duration as possible. But given the variability of infusion pumps, time windows of ± 10 minutes for the duration of scheduled infusions are permitted. (Additionally, prolongation of infusion duration for the purpose of managing suspected or actual adverse event such as infusion reaction will not be considered a protocol deviation.)

Nivolumab will be prepared and administered consistent with the product label:

- Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

- Preparation:

  - Withdraw the required volume of nivolumab and transfer into an intravenous container.
  - Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
  - Mix diluted solution by gentle inversion. Do not shake.
  - Discard partially used vials or empty vials of nivolumab.

- Storage of Infusion:

  - The product does not contain a preservative.
  - After preparation, store the nivolumab infusion either: At room temperature for no more than 8 hours from the time of preparation (this includes room temperature storage of the infusion in the IV container and time for administration of the infusion), or under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.
  - Do not freeze.

- Administration:

  - Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
  - Do not co-administer other drugs through the same intravenous line.
  - Flush the intravenous line at end of infusion.

For all nivolumab infusions, an appropriate dosing history will be recorded, e.g.:

- Total dose and volume administered
- Start and stop time of infusion
- Infusion interruption or termination and reason for such actions.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 10.9.

There are no pre-medications recommended for nivolumab prior to Day 29 of the first cycle (i.e. the intended DLT evaluation period).

Doses of nivolumab may be interrupted, delayed, or discontinued (e.g. Section 10) depending on how well the subject tolerates the treatment.

Dose reductions or dose escalations of nivolumab are not permitted.

8.4. Discontinuation of Protocol-Indicated Treatment

All patients will initiate the study via receipt of vorolanib in combination with nivolumab.

The visit schedule for protocol treatment will apply until vorolanib treatment in combination with nivolumab has been permanently discontinued. Once this has occurred, an End-of-Treatment visit will be performed within 14 days after the decision of permanent discontinuation, prior to any subsequent anti-cancer therapy.

After the EOT visit, the patient will continue to be followed until 28 days (+7 days) after the last dose of protocol-indicated treatment, at which time the Follow-Up visit must be completed.

Reasons for permanent discontinuation of a patient's protocol-indicated treatment include any of the following:

- Inability to tolerate vorolanib in combination with nivolumab. Please note: Within the study, a patient will not receive nivolumab as an exclusive 'single-agent' therapy. Therefore, **a patient must permanently discontinue the study if unable to tolerate vorolanib.**
- Patient withdraws consent to participate.
- Occurrence of an AE considered by the investigator to require treatment discontinuation.
- Toxicity requiring discontinuation as outlined in Section 10.
- Progressive Disease, verified by CT/MRI according to RECIST v1.1.
- Treatment failure not meeting the criteria for PD, but considered by the investigator to require treatment discontinuation (e.g. clinical progression).
- Requirement for a significant surgical procedure. Note: Patients requiring a minor surgical procedure (e.g. port placement, skin abscess drainage) may continue at the investigator's discretion following discussion with the sponsor-investigator or designee. A brief interruption in therapy may be considered.
- An intercurrent illness which, in the opinion of the investigator, would prevent completion of trial-related evaluations.
- The investigator judges it necessary due to medical reasons (e.g. significant deterioration in performance status).
- Required use of a prohibited concomitant medication, as defined in Section 9. Note: subject to discussion with and approval by the sponsor-investigator, inadvertent isolated receipt of a prohibited concomitant medication (e.g. incidental to acute management of an adverse event) does not require permanent discontinuation.
- The patient becomes pregnant during treatment. (Cases of pregnancy that occur during maternal or paternal exposures to study treatment should be reported. Data on fetal

outcome and breast-feeding may be collected for regulatory reporting and drug safety evaluation.)

- Significant deviation from the protocol or eligibility criteria. Such patients will be considered protocol violations and may be discontinued from treatment after discussion with the sponsor-investigator.
- Noncompliance with trial procedures may require discontinuation after discussion with the sponsor-investigator.
- Termination of the trial by the sponsor-investigator or regulatory authority.

8.5. Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.

With written permission from the sponsor-investigator, subjects will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria determined by the investigator:

- Investigator-assessed clinical benefit from protocol-indicated treatment
- Subject is tolerating nivolumab
- Stable performance status.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases).

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

For the subjects who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

For statistical analyses, it is intended that subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-

assessed progressive disease at the time of the initial progression event after having it confirmed on repeat imaging.

8.6. Duration of Follow-Up

In general, it is intended that patients will be treated until disease progression or intolerable toxicity. Criteria for patient discontinuation include those listed in Section 8.4. Patients should be assessed when it is decided the patient will no longer receive protocol-indicated treatment; and assessed again 28 days (+ 7 days) after patient's final protocol-indicated treatment with vorolanib / nivolumab. There will be a 100day follow up visit for all patients.

8.7. Withdrawal from Study

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor-investigator for safety, or behavioral reasons; or the inability of the subject to comply with the protocol-required schedule of study visits or procedures, or an inability to maintain voluntary informed consent. The EOT and the Follow-Up visits should be performed to the extent possible and the Investigator should ensure any serious adverse event (SAE) is followed as described in Section 12.

Reasons for withdrawal from the study might include but are not limited to any of the following:

- The patient withdraws consent to participate in treatment, follow-up, or survival monitoring.
- The investigator judges it necessary due to medical reasons.
- Subject is lost to follow-up.
- Study is terminated for any reason.

9. CONCOMITANT TREATMENT

9.1. Prohibited or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event).
- Systemic corticosteroids >10 mg daily prednisone equivalent (except to treat a drug-related adverse event).
- Other than vorolanib and nivolumab, any other concurrent anti-neoplastic therapy (i.e. chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC, SCLC, or thymic carcinoma).
- Vorolanib is primarily metabolized by CYP3A4 and to a lesser extent by CYP2D6 and CYP2C9 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. A list of medications and foods which are common strong modulators of CYP3A4 and CYP2C9 are included in Appendix 4.
- Hematopoietic growth factors and transfusion support – as per Section 9.3.

- Caution should be used regarding the use of herbal medications as there may be as yet unknown interactions with nivolumab. Discontinuation of the use of herbal medications prior to study enrollment is encouraged.
- Immunization with any attenuated live vaccine. Note: The inactivated seasonal influenza vaccine (intramuscular injection) can be given to patients while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e. pneumovax, varicella, etc.) may be permitted, but must be discussed in writing with the sponsor-investigator and may require a study drug washout period prior to and after administration of the vaccine.
- Drugs that are known to cause hepatictoxicity should be used with caution

9.2. Permitted Therapy

In the absence of active autoimmune disease: Subjects are permitted the use of corticosteroids with minimal systemic absorption (e.g. topical, ocular, intra-articular, intranasal, and inhalational) ≤ 10 mg/day prednisone or equivalent daily; and physiologic replacement doses of systemic corticosteroids ≤ 10 mg/day prednisone or equivalent daily (e.g. hormone replacement therapy needed in patients with hypophysitis).

A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Regular concomitant use of bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in patients with bone metastases is allowed if initiated > 2 weeks prior to first dose of protocol-indicated treatment.

Prior palliative radiotherapy must have been completed > 2 weeks prior to first dose of protocol-indicated treatment.

All concomitant (non-oncological) therapies with the exception of vitamins, appetite stimulants, or nutrient supplements, starting or changing must be recorded in the eCRF during the screening and treatment period, starting from the date of signature of informed consent (to include concomitant medications include prescription medications and over-the-counter preparations used by a patient within at least 14 days prior to first dose of protocol-defined treatment), and ending at the EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported. Trade name, indication, dose and dates of administration will be documented.

Patients may receive their current concomitant medication and any medication considered necessary for the welfare of the patient during trial, except as otherwise restricted or prohibited per protocol (e.g. if con med is restricted by Section 4 Inclusion/Exclusion Criteria, or Section 9.1).

9.3. Hematopoietic Growth Factors and Transfusion Support

- Packed red blood cell and platelet transfusions should be administered only if clinically indicated, and should be avoided during the first 28 days after the start of a patient's first dose of vorolanib / nivolumab.
- Use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) is prohibited unless the patient experiences a hematologic DLT. Per eligibility criteria, G-CSF or GM-CSF should not be administered ≤ 7 days before first dose of protocol-indicated treatment. At the discretion of the treating physician,

patients may receive G-CSF or GM-CSF after the completion of the first 28 days after the start of a patient's first dose of vorolanib / nivolumab if neutropenia occurs. Therapeutic use of G-CSF / GM-CSF should follow standard ASCO guidelines.

- Patients who enter the trial on stable doses (initiated > 14 days prior to initiating trial treatment) of erythropoietin, darbepoietin, and/or bisphosphonates may continue this treatment; and patients may start such treatment during the trial (after the first 28 days of trial treatment) at the discretion of the treating physician if clinically indicated.

9.4. Clarifications about Steroid Use including Hormones

Data indicate that corticosteroids have an adverse effect on T cell function and that they inhibit and damage lymphocytes. Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppression such as with steroids will counteract the intended benefit of the proposed trial treatment. However, studies with anti-CTLA-4 antibodies indicate that short-term use of steroids may be employed without compromising clinical outcomes.

Therefore, allowable steroid use during this trial includes the following:

- Prophylaxis and treatment of toxicities attributed to protocol-indicated treatment [e.g. immune-related adverse events (irAEs)]
- Adrenal replacement steroid doses ≤ 10 mg daily prednisone or equivalent
- Corticosteroids with minimal systemic absorption (e.g. topical, ocular, intra-articular, intranasal, and inhalational) ≤ 10 mg/day prednisone or equivalent daily
- Steroid therapy for contrast reaction prophylaxis
- Hormonal therapy (e.g. Megace) for appetite stimulation
- Hormonal contraceptive therapy
- Hormone replacement therapy for hypophysitis and hypothyroidism.

Other steroid use may be allowed upon discussion with and written agreement from the sponsor-investigator.

9.5. Palliative Local Radiotherapy

The potential for overlapping toxicities with radiotherapy and vorolanib/nivolumab is currently unknown. Per eligibility criteria, prior therapeutic or palliative radiation therapy must be completed > 2 weeks prior to first dose of vorolanib/nivolumab. After beginning trial treatment, palliative radiotherapy is generally not recommended while receiving vorolanib/nivolumab.

However, local radiotherapy of isolated lesions with palliative intent (e.g. bleeding, pain, compression, etc.) is permitted if considered medically necessary by the treating physician. The irradiated area should be as small as possible, and the total dose delivered must be in a palliative range according to institutional standards. Irradiated lesions will be followed for disease progression but will not be accounted for in the evaluation of the response. Radiotherapy other than palliative radiotherapy for symptom control is not allowed concomitantly with the administration of protocol-indicated treatment.

Patients requiring palliative radiotherapy should be assessed for disease progression. If palliative radiotherapy is needed to control pain, the site(s) of disease causing pain should be present at baseline; otherwise, painful lesion(s) requiring radiotherapy should be considered as a sign of disease progression.

Administration of additional vorolanib/nivolumab to patients who experienced PD at the time of palliative radiotherapy should follow guidelines specified in Section 8.5.

If palliative radiotherapy is required, then vorolanib/nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation. Patients should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs considered related to radiotherapy should resolve to Grade ≤1 prior to resuming vorolanib/nivolumab.

If a treatment cycle is interrupted for more than 28 days, the decision to continue will be made by the investigator in agreement with the sponsor-investigator. Continuous interruption of >28 days due to palliative radiotherapy will not be allowed.

Only non-target bone lesions that do not include lung tissue in the planned radiation field may receive palliative radiotherapy while on trial treatment. Details of palliative radiotherapy should be documented in the source records and eCRF. Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs.

10. ADVERSE EVENT MANAGEMENT

Patients should be instructed to notify their study team at the first occurrence of any adverse symptom. In addition to dose delays according to protocol guidance, investigators are encouraged to employ best supportive care according to local institutional clinical practice.

Recognizing that new knowledge will be acquired and unforeseen safety issues may arise in the course of the study, the management guidelines are not exhaustive and do not represent the full spectrum of care or treatment options described.

In general, an adverse event related to study treatment that results in a dose delay should be present on the day of intended study treatment (i.e. a delayed toxicity that develops mid-cycle, but which is no longer present or has resolved to an acceptable grade on the day of intended dosing, generally does not require a delay in treatment – unless, for example, the occasion involves retrospective detection of a prior event of sufficient grade to, regardless of duration, require delay or discontinuation).

In the event of multiple toxicities, treatment delay should be based on the worst toxicity observed.

Even if protocol-indicated dosing is interrupted, tumor scans and other visits, assessments and procedures should continue per protocol (i.e. per timeline in place prior to the dose interruption).

10.1. Definition of Dose-Limiting Toxicity

When classified by the sponsor-investigator as **possibly, probably or definitely related to vorolanib; or to the combination of vorolanib + nivolumab**: any of the following events occurring during the first 28 days after first dose of protocol-indicated treatment will be considered a dose-limiting toxicity (DLT):

1) **Non-Hematologic DLT:**

   - Any ≥ Grade 4 non-hematological toxicity.

- Grade ≥ 3 total bilirubin or hepatic transaminases [ALT (SGPT) or AST (SGOT)] with the following exceptions:
  - Grade 3 elevated ALT/AST lasting for ≤ 7 days, in the absence of elevated direct bilirubin that is both > ULN and more than 35% increased over baseline, will not be considered a DLT.
  - For patients with a Grade 1 hepatic transaminase level at baseline (i.e. ALT or AST), same respective hepatic transaminase level must increase to > 7.5 × ULN to be considered a DLT.
  - For patients with a Grade 2 hepatic transaminase level at baseline (i.e. ALT or AST), same respective hepatic transaminase level must increase to > 10 × ULN to be considered a DLT.
- Grade ≥ 3 of the following:
  - Pneumonitis
  - Adrenal Insufficiency
  - Immune-mediated hepatitis
  - Colitis
- Immune-mediated encephalitis
- Grade 3 other non-hematologic toxicity lasting > 3 days despite optimal supportive care with the exception of:
  - Grade 3 fatigue
  - Grade 3 symptomatic rash that resolves to ≤ Grade 1 within 3 weeks; or a Grade 3 asymptomatic rash
  - Grade 3 tumor flare (defined as local pain, irritation or rash localized at sites of known or suspected tumor)
  - Transient (resolves within 6 hours of onset) Grade 3 infusion-related AE
  - Grade 3/4 elevation in serum amylase and/or lipase not associated with clinical or radiological evidence of pancreatitis.
- Any clinically meaningful (per investigator judgement) Grade 3 non-hematologic laboratory value if:
  - Medical intervention (other than electrolyte repletion) is required to treat the patient, OR
  - The abnormality leads to hospitalization, OR
  - The abnormality persists for >1 week.

2) <u>Hematologic DLT</u>:

- Grade ≥ 3 febrile neutropenia [ANC < 1000 /mm^3 with either a single temperature of > 38.3 ºC (101 ºF), or a sustained temperature of ≥ 38 ºC (100.4 ºF) for > 1 hour].
- Grade 4 neutropenia (ANC < 500 /mm^3) lasting > 5 days.
- Grade 4 anemia lasting > 5 days despite optimum management by transfusions.

- Grade 4 thrombocytopenia (platelets < 25,000 /mm^3) if associated with:
  - — A bleeding event that requires an elective platelet transfusion, OR
  - — A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit.
- Any Grade 5 hematologic or non-hematologic toxicity.

3) **Inability to initiate Cycle 1, Day 29** treatment within protocol-specified allowances due to adverse event that is possibly, probably, or definitely related to protocol-indicated treatment.

Note: Subjects who have experienced a DLT do not automatically require discontinuation of protocol-indicated treatment, unless the nature or severity of the DLT is also an adverse event that would require permanent discontinuation of treatment as elsewhere defined by the protocol. Rather, a patient who has experienced a DLT should be evaluated for consideration of an appropriate dose hold or dose modification which, if consistent with the protocol, would allow continued dosing under revised circumstance.

For purpose of ensuring appropriate opportunity to determine the maximum tolerated dose (MTD) of vorolanib in combination with nivolumab, a subject who is withdrawn from the study prior to completing the DLT assessment window (i.e. first 28 days after initiating protocol-indicated treatment on Cycle 1, Day 1) for reasons other than a DLT will be considered not evaluable for DLT and will be replaced.

Additionally, if a patient discontinues study treatment for reasons clearly not related to protocol-indicated treatment (in the judgement of the sponsor-investigator), after completing less than 75% of scheduled oral doses of vorolanib and/or less than 2 planned infusions of nivolumab over the first 28 days after initiating protocol-indicated treatment on Cycle 1, Day 1, then that patient will be considered not evaluable for response to overall protocol-indicated treatment and may be replaced with a new patient.

10.2. Dose Modifications and Delays of vorolanib

Dose modifications for hematologic and non-hematologic toxicities considered related to vorolanib by the patient's study physician are described below in Sections 10.2.1 and 2.

Vorolanib treatment may be delayed for up to 4 weeks from the last dose. If vorolanib is interrupted for more than 28 days, written permission to continue vorolanib must be obtained from the sponsor-investigator subsequent to consultation with the investigator and study physician.

Vorolanib dose levels are indicated in Section 8.1. Note the lowest dose of vorolanib allowed on study is 100 mg QD. Accordingly, **a patient unable to tolerate vorolanib at a minimum dose of 100 mg QD would be unable to continue the study**.

For each dose reduction of vorolanib, reduce the current vorolanib dose by 100 mg daily.

During the initial 28 days after first dose of protocol-indicated treatment on Cycle 1, Day 1: Dose reductions of vorolanib are to be avoided for patients enrolled in the Phase 1 dose escalation part of the study, and are permitted only by written permission from the sponsor-investigator. (The data from such a dose-reduced patient would normally not be applicable toward dose-escalation decisions.) At other times, dose reductions of vorolanib for adverse events may take place at any time as otherwise consistent with the protocol.

In general and unless otherwise specified by the protocol, dose reductions of vorolanib for management of adverse event(s) within a given patient should be considered permanent: Once the dose of VOROLANIB has been reduced in a given patient, all subsequent cycles in the same patient should be ordinarily administered at the reduced dose level (unless additional dose reduction is required).

Accordingly, intrapatient dose re-escalation of vorolanib in a given patient will not ordinarily be allowed, unless there is discussion and written agreement between the investigator and the sponsor-investigator (e.g. as part of an appropriate evaluation of the combinatorial setting in which, after strategic dose intervention involving one or more particular agent, any potentially overlapping toxicity between vorolanib and nivolumab is ultimately judged best attributed to one individual drug, but unlikely or not related to the other drug).

Note that whereas intrapatient dose *re*-escalation (e.g. following an adverse event) of vorolanib in a given patient will not be ordinarily be allowed, intrapatient dose *escalation* of vorolanib may be allowed by the sponsor-investigator, to the extent that such action involves an early-enrolling patient, who is tolerating treatment and who was assigned to an early vorolanib dose level which was ultimately found to be below the maximum tolerated dose (MTD) level of the vorolanib + nivolumab combination. Once the MTD of vorolanib + nivolumab is established by the study, early patients who initially enrolled at vorolanib dose levels below the MTD, may optionally be dose escalated to the MTD dose level upon written agreement between the patient's treating physician, the local site's principal investigator and the sponsor-investigator.

For purpose of any necessary definition, "baseline value" is defined as the most immediately known value in place prior to patient's first receipt of vorolanib on Cycle 1, Day 1.

In the event of an adverse event deemed by the study physician as *unrelated* to vorolanib, the study physician may nevertheless optionally choose to precautionarily interrupt vorolanib for up to 28 days, but no dose reduction of vorolanib should occur.

If vorolanib is held for adverse event, tolerated treatment with nivolumab should continue as scheduled until vorolanib is permanently discontinued – at which time the patient must also permanently discontinue the study (per Section 8.4: a patient must permanently discontinue the study if unable to tolerate vorolanib; within the study, a patient will not receive nivolumab as an exclusive 'single-agent' therapy.)

1. Vorolanib Dose Adjustments for Hematologic Toxicity

For hematologic adverse events deemed by the patient's study physician as **possibly, probably, or definitely related to vorolanib**, treatment with vorolanib should be held according to **Table 3**, with subsequent monitoring and re-evaluation of ANC and platelets at an interval deemed appropriate by the patient's study physician.

If ANC and/or platelets do not recover to ≤ Grade 2 within 4 weeks, then the patient will be discontinued from the trial unless the treating physician and PI agree that continued treatment at lower doses is in the best interest of the patient, and written permission is obtained from the sponsor-investigator.

TABLE 3: Vorolanib Dose Modifications for Hematologic Toxicities

Severity Grade (CTCAE v5.0)	Description	Specific intervention
NEUTROPENIA (ANC)		
Grade 3	< 1000 – 500 /mm^3	Hold dose until recovery to ANC ≥ 1000 /mm^3 • If recovered in ≤ 7 days, then resume without OR with a dose reduction. (Dose reduction optional per investigator discretion) • If recovered in > 7 days but < 4 weeks, then resume vorolanib at one lower dose level.
Grade 4	< 500 /mm^3	Hold vorolanib until recovery to ANC ≥ 1000 /mm^3, then resume vorolanib at one lower dose level.
THROMBOCYTOPENIA		
Grade 3	< 50,000 – 25,000 /mm^3	Hold vorolanib until recovery to platelets ≥ 75,000 /mm^3 • If resolved in ≤ 7 days, then resume without OR with a dose reduction. (Dose reduction optional per investigator discretion) • If resolved in > 7 days but < 4 weeks, then resume vorolanib at one lower dose level.
Grade 4	< 25,000 /mm^3	Discontinue vorolanib permanently.

2. Vorolanib Dose Adjustments for Non-Hematologic Toxicity

For non-hematologic adverse events deemed by the patient's study physician as **possibly, probably, or definitely related to vorolanib**, treatment with vorolanib should be modified according to the below guidance, with subsequent monitoring and re-evaluation at an interval deemed appropriate by the patient's study physician.

- If a Grade 3 non-hematologic toxicity related to vorolanib is expected to be manageable and reversible with dose reduction occurs, treatment with vorolanib should be held until the toxicity resolves to ≤ Grade 1, then reduce one dose level.
- If a Grade 3 non-hematologic toxicity related to vorolanib lasts > 7 days despite optimal applicable intervention, vorolanib will be permanently discontinued.
- Patients with a Grade 3 non-hematologic toxicity related to vorolanib lasting ≤ 7 days that does not resolve to ≤ Grade 1 within 4 weeks should also be removed from the trial – unless the study physician, investigator, and sponsor-investigator mutually agree in

writing that continued treatment at a reduced dose of vorolanib is in the best interest of the patient.

- If a Grade 4 non-hematologic toxicity related to vorolanib occurs, vorolanib will be permanently discontinued.

- Specific Recommendations for Rash, Nausea, Vomiting and Diarrhea:
  For patients with Grade 3 rash, nausea, vomiting, and/or diarrhea related to vorolanib:
  Vorolanib should be held and supportive care initiated. If the Grade 3 toxicity lasts ≤ 7 days, patients may restart vorolanib at a reduced dose when the toxicity reduces to ≤ Grade 1.

- Specific Recommendations for drug induced Liver Function Test Abnormalities:
  For patients with Grade 3 liver enzyme elevations (i.e. AST/ALT) related to vorolanib:
  Vorolanib should be held until the value(s) recover to ≤ Grade 1. Patients with elevated ALT ≥ 3 x ULN in conjunction with a bilirubin ≥ 2 x ULN may continue vorolanib if a correctable cause of the liver test elevations can be documented as unrelated to vorolanib; otherwise, the patient must permanently discontinue vorolanib.

- Specific Recommendations for the Treatment of Hypertension:
  Treatment of hypertension should be based on the patient, and the patient's clinical status. General recommendations for initial management of hypertension (HTN) include:

  1. For hypertension that is persistent in the judgement of the patient's study physician (e.g. consistent blood pressure readings of > 140/90), consider initiating an ACE inhibitor (e.g. benazepril, lisinopril), an angiotensin II receptor blocker (ARB, e.g. losartan), a thiazide diuretic (e.g. HCTZ), or a dihydropyrimidine calcium channel blocker (e.g. amlodipine). Titrate to BP control with dose escalation of the chosen medication or, if additional agents are needed, choose a second agent from the recommended list.

  2. For patients with blood pressure > 160/90, consider initiating combinatorial therapy with an ACE inhibitor + a dihydropyrimidine calcium channel blocker.

10.3. Dose Modifications of Nivolumab

Dose reductions or dose escalations of nivolumab are not permitted. Nivolumab will be managed by dose holds.

10.4. Criteria for Dose Delays of Nivolumab

Because of the potential for clinically meaningful nivolumab-related adverse events requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories. For example, please see Protocol Appendix 7, regarding guidelines for the management of immune-related adverse events (irAEs).

If deemed by the investigator as **possibly, probably, or definitely related to nivolumab, then nivolumab administration should be delayed for the following:**

- Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:

  - Grade 2 drug-related fatigue or laboratory abnormalities do not require treatment delay.

- Grade 3 skin, drug-related AE.

- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:

  - Grade 3 lymphopenia or leukopenia does not require dose delay.

  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.

  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.

  - Any Grade ≥ 3 drug-related amylase or lipase abnormality not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The sponsor-investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of nivolumab.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

10.5. Criteria to Resume Nivolumab Treatment

Subjects may resume treatment with nivolumab when the AE(s) deemed by the investigator as **possibly, probably, or definitely related to nivolumab treatment** resolve to Grade ≤ 1 or baseline value (i.e. the most immediately known value in place prior to patient's first receipt of nivolumab on Cycle 1, Day 1) with the following exceptions:

- Subjects may resume nivolumab treatment in the presence of Grade 2 fatigue.

- Subjects who have not experienced a Grade 3 nivolumab-related skin AE may resume nivolumab treatment in the presence of Grade 2 skin toxicity.

- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume nivolumab treatment in the presence of Grade 2 AST/ALT OR total bilirubin.

- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 10.6) should have nivolumab treatment permanently discontinued.

- Nivolumab-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before nivolumab treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for nivolumab retreatment at the discretion of the investigator, with written permission from the sponsor-investigator.

- Subjects with nivolumab-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume nivolumab treatment with written permission from the sponsor-investigator.

If nivolumab treatment is delayed for > 6 weeks, the subject must permanently discontinue nivolumab therapy, except as otherwise specified (e.g. Section 10.6, where the delay is due to the need for a prolonged steroid taper in order to manage drug-related adverse events, or the delay is not drug related) and written permission to resume treatment is granted by the sponsor-investigator.

10.6. Criteria to Permanently Discontinue Nivolumab Treatment

If deemed by the investigator as **possibly, probably, or definitely related to nivolumab treatment**, treatment with nivolumab should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.

- Any Grade 2 drug-related AST or ALT > 3 x ULN concurrent with total bilirubin > 2 x ULN.

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity and infusion reactions, and endocrinopathies:

  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, colitis or infusion reaction of any duration **requires** discontinuation.

  - Grade 3 drug-related endocrinopathies, except adrenal insufficiency, adequately controlled with only physiologic hormone replacement **do not require** discontinuation. Patients with grade 3 adrenal insufficiency must permanently discontinue nivolumab.

  - Grade 3 drug-related laboratory abnormalities **do not require** treatment discontinuation except:

    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding **requires** discontinuation.

    - Immune mediated hepatitis or any drug-related liver function test (LFT) abnormality that meets the following criteria **requires** discontinuation:

      - AST or ALT > 8 x ULN.
      - Total bilirubin > 5 x ULN.
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN.

- Immune-mediated encephalitis

- Any Grade 4 drug-related adverse event or laboratory abnormality, **except for the following events** which do not require discontinuation:

- Isolated Grade 4 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.

- Isolated Grade 4 electrolyte imbalances/abnormalities not associated with clinical sequelae and corrected with supplementation/appropriate management within 72 hours of onset.

- Grade 4 neutropenia ≤ 7 days

- Grade 4 lymphopenia or leukopenia.

- Grade 4 drug-related endocrinopathy adverse events (except hypophysitis), such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and written approval from the sponsor-investigator. Occurrence of Grade 4 hypophysitis requires discontinuation.

- Any dosing interruption lasting > 6 weeks **with the following exceptions**:

  - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, written permission must be obtained from the sponsor-investigator. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed.

  - Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved in writing by the sponsor-investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the sponsor-investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

10.7. Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events (AEs) that can differ in severity and duration than AEs caused by other therapeutic classes. In this protocol, nivolumab is considered an immuno-oncology agent. Early recognition and management of AEs associated with an immuno-oncology agent may mitigate severe toxicity.

Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary

- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

For the above events deemed by the patient's study physician to be possibly, probably or definitely related to nivolumab, Management Algorithms are found in Appendix 7.

The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

10.8. Guidelines for the Management of Infusion Reactions

Nivolumab can cause severe infusion reactions, which have been reported in less than 1.0% of patients in clinical trials. In patients receiving nivolumab as a single agent, infusion-related reactions occurred in 6.4% (127/1994) of patients. In patients receiving nivolumab with ipilimumab, infusion-related reactions occurred in 2.5% (10/407) of patients.

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

Discontinue nivolumab in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

Infusion reactions should be graded according to NCI CTCAE 5.0 guidelines.

All Grade 3 or 4 infusion reactions will be evaluated as to whether or not the event is a DLT. All infusion reactions that are serious adverse events (per Section 12) must be rapidly reported as such, via notification procedures described in Section 12.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

- **For Grade 1 symptoms:**
    - Mild reaction; infusion interruption not indicated; intervention not indicated.
    - Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.
- **For Grade 2 symptoms**:
    - Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours.

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate.

- If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

- **For Grade 3 or Grade 4 symptoms:**

  - Severe reaction, Grade 3: prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates). Grade 4: life threatening; pressor or ventilatory support indicated.

  - Immediately discontinue infusion of nivolumab.

  - Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.

  - Subject should be monitored until the investigator is comfortable that the symptoms will not recur. **Nivolumab will be permanently discontinued.** Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

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

11. DRUG FORMULATION, SUPPLY AND STORAGE

11.1. Description of Vorolanib

Vorolanib is an oral multi-kinase vascular endothelial growth factor receptor (VEGFR)/platelet derived growth factor receptor (PDGFR)/colony-stimulating factor 1 receptor (CSF1R)/FMS like tyrosine kinase 3 (FLT3) inhibitor under investigation for the treatment of solid tumors and for the

treatment of pathologic angiogenesis in diseases such as neovascular “wet” age-related macular degeneration (AMD), and von Hippel-Lindau Disease. Binding of vorolanib to its target receptors (VEGF and PDGF) results in angiogenesis inhibition.

11.2. Packaging of Vorolanib

The study will supply vorolanib to each site.

Oral vorolanib drug product was originally formulated as capsules and has more recently been formulated as orange tablets with a dosage strength of 100 mg (oblong tablets) of vorolanib drug substance. The tablets are coated with a colored, nonfunctional, globally accepted film coating. The formulation was changed to improve absorption.

11.3. Handling and Storage of Vorolanib

Vorolanib tablets (100 mg) are packaged in 60 cc round, white HDPE bottles containing a pharmaceutical desiccant canister, closed with a white polypropylene child resistant cap and foil induction inner seal.

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

11.4. Description of Nivolumab

Nivolumab (OPDIVO®) is a programmed death receptor-1 (PD-1) blocking antibody that is currently FDA approved for BRAF V600 wild-type unresectable or metastatic melanoma; BRAF V600 mutation-positive unresectable or metastatic melanoma; unresectable or metastatic melanoma, in combination with ipilimumab; metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy; advanced renal cell carcinoma after prior anti-angiogenic therapy; and classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin .

11.5. Packaging of Nivolumab

The study will supply nivolumab to each site.

Nivolumab is typically available as nivolumab injection: 100 mg/10 mL (10 mg/mL) solution in a single-dose vial.

Nivolumab drug product should be visually inspected for particulate matter and discoloration prior to administration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

11.6. Handling and Storage of Nivolumab

Nivolumab product does not contain a preservative. Nivolumab will be prepared according to the product label. After preparation, nivolumab infusion should be stored either:

- At room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion, or

- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

- Do not freeze.

11.7. Drug Accountability and Compliance Check

The Investigator is responsible for ensuring accountability for vorolanib and nivolumab, including maintenance of adequate drug accountability records.

Drug accountability records should include an appropriate inventory of vorolanib and nivolumab including:

- Confirmation that vorolanib and nivolumab supplied by the study was delivered to the trial site
- Record of each dose of vorolanib and nivolumab dispensed
- Return of unused vorolanib and nivolumab provided by the study to the sponsor-investigator or designee, or documentation of destruction at site (if drug destruction by the site is authorized by sponsor-investigator or designee).

Records should specify relevant dates, quantities, batch numbers, use-by dates and patient numbers, as applicable.

The Investigator, or designee, should maintain records that adequately document:

- That patients were provided the doses specified by the clinical trial protocol, and
- That all vorolanib and nivolumab provided by the study was fully reconciled.

12. SAFETY REPORTING OF ADVERSE EVENTS

12.1. General

Each adverse event will be graded according to the NCI's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, dated November 27, 2017, currently locatable via the following URL:
<https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf >.

For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening, or fatal which respectively correspond to Grades 1, 2, 3, 4, and 5 on the NCI CTCAE, with the following definitions:

- **Mild:** An event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate:** An event not resulting in disability or incapacity but which requires intervention;
- **Severe:** An event resulting in temporary disability or incapacity and which requires intervention;

- **Life-threatening:** An event in which the patient was at risk of death at the time of the event;
- **Fatal:** An event that results in the death of the patient.

Information on all adverse events, whether serious or not, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Reporting period: Adverse events experienced by participants will be collected and reported from initiation of protocol-indicated treatment (to also include events after signing consent but before initiation of protocol-indicated treatment if an adverse event is at least possibly related to a study procedure such as a biopsy, or to the withholding of a medication prohibited by protocol), throughout the study, and within 100 days after the last dose of protocol-indicated treatment. Participants who experience an adverse event related to a study procedure and/or protocol-indicated treatment beyond 100 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

All laboratory test results and vital signs captured as part of the study should be recorded following institutional procedures. Laboratory test results and vital signs that constitute SAEs should be documented and reported as such.

- Any laboratory test result or vital sign considered by the investigator to be clinically significant or meeting the definition of an SAE;
- Any laboratory or vital sign abnormality that required the subject to have protocol-indicated treatment to be discontinued or interrupted;
- Any laboratory or vital sign abnormality that required the subject to receive specific corrective therapy.

Baseline disease-related signs and symptoms which are initially recorded as medical history, will subsequently be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12.2. Risks Associated with Vorolanib

- The most frequent (≥ 10%) drug-related adverse events reported with vorolanib as of 14 Jan 2016 from the first-in-human oncology Phase 1 single-agent study include fatigue, nausea, diarrhea, hair color changes, vomiting, asthenia, rash, and peripheral edema.
- While not a consistent finding, some patients have had decreases in laboratory values (e.g. platelets and hemoglobin). Some patients receiving vorolanib in a study in subjects with age-related macular degeneration (AMD) had increased transaminases. No subjects have met Hy's law criteria. Improvement in transaminases have been documented in all cases, either during a dose pause, permanent drug discontinuation, or with continued dosing.
- A more detailed safety profile of vorolanib is provided in the investigator's brochure (2).

12.3. Risks Associated with Nivolumab

- Most common adverse reactions (≥20%) of nivolumab as a single agent in patients were: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenic conditions, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia.
- A more detailed safety profile of nivolumab is provided in the product labels, currently locatable online via following:

  Nivolumab (OPDIVO):
  < https://packageinserts.bms.com/pi/pi_opdivo.pdf >.

12.4. Adverse Event (AE)

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. Progressive disease will not be considered an adverse event.

An adverse event includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g. invasive procedures such as biopsy).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

12.5. Serious Adverse Event (SAE)

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e. the AE actually causes or leads to death).
- It is life threatening (i.e. the AE, in the view of the investigator or sponsor-investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e. the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product

- It is considered a significant medical event by the investigator or sponsor-investigator based on medical judgment (e.g. may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

Events not considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in an inpatient admission lasting ≥ 24 hours.
- Respite care.

12.6. Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e. start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the investigational treatment (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guidelines:

- **Yes**
  There is a reasonable causal relationship between the investigational treatment and the adverse event. There is a plausible temporal relationship between the onset of the AE and administration of the investigational treatment, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational treatment; and/or the AE abates or resolves upon discontinuation of the investigational treatment or dose reduction and, if applicable, reappears upon re-challenge.

- **No**
  There is no reasonable causal relationship between the investigational treatment administered and the adverse event. Evidence exists that the AE has an etiology other than the investigational treatment (e.g. pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational treatment.

12.7. Expectedness

Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. An adverse event is generally considered expected when it appears in the current adverse event list, investigator's brochure, package insert, protocol; or is included in the informed consent document as a potential risk.

- Unexpected: An adverse event is generally considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the investigator's brochure, package insert, or protocol; or is not listed in the investigator's brochure, package insert, protocol, or informed consent document as a potential risk.

12.8. Attribution

The investigator must attempt to determine if there exists reasonable possibility that an adverse event or serious adverse event is related to the use of the investigational treatment. Attribution of adverse events should be described as unrelated; or unlikely, possibly, probably, or definitely related to the investigational treatment:

Attribution	Description
Unrelated	AE ***is clearly NOT related*** to the intervention.
Unlikely	AE ***is doubtfully related*** to the intervention.
Possible	AE ***may be related*** to the intervention.
Probable	AE ***is likely related*** to the intervention.
Definite	AE ***is clearly related*** to the intervention.

For additional purpose of any applicable binary regulatory reporting, an event should be considered *Unrelated* to study treatment when its attribution is felt by the investigator to be either Unrelated or Unlikely related to investigational treatment. Similarly, an event should be considered *Related* to study treatment, when its attribution is felt to be either Possibly, Probably, or Definitely related to investigational treatment.

12.9. Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations. All adverse events will be captured on the appropriate study-specific electronic case report forms (eCRFs).

12.10. Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

12.11. Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study eCRF.

12.12. Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

12.13. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization ≥ 24 hours or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical

procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions,
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

12.14. Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 23 weeks after the last dose of protocol-indicated treatment. The coordinating center SAE form reporting the pregnancy should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via fax or email. Unless otherwise agreed to and approved by the sponsor-investigator, investigator and the IRB, the patient should discontinue protocol-indicated treatment. Bristol-Myers Squibb will be notified within 24 hours of this knowledge and patient pregnancies monitored.

The investigator or medical designee should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g. an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the coordinating center SAE form.

12.15. Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the informed consent form to immediately inform the investigator if their partner becomes pregnant during the study or within 31 weeks after completing protocol-indicated treatment. Male patients who received study treatment should not attempt to father a child until 31 weeks after stopping study treatment. The coordinating center SAE form reporting the pregnancy should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and faxed or emailed to the sponsor-investigator. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner may be asked to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator or designee will update the coordinating center SAE form with additional information on the course and outcome of the pregnancy. An investigator or medical designee who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

12.16. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

12.17. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or

discontinued study participation if attributed to previous protocol-indicated vorolanib or nivolumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

12.18. Serious Adverse Events

All serious adverse events, regardless of causality to protocol-indicated treatment, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 24 hours of the investigator becoming aware of the event. Events should be reported using the Vanderbilt coordinating center SAE form, located in the packet of supplemental forms. This form must be fully completed and emailed (preferred), faxed, or scanned to:

If SAE documents are faxed, the Coordinating Center must be notified via email as well. Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites as described in FDA guidance only in the case that the event(s) is/are unexpected, and is/are believed to be related (i.e., possibly, probably or definitely) to the study medication. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

The Coordinating Center at Vanderbilt will be responsible for reporting of events to the FDA and study supporters Equinox and Bristol-Myers Squibb as appropriate (outlined below).

12.19. Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications approved by the sponsor-investigator will be provided to the IRB as soon as possible for IRB approval prior to any patient receipt of a revised consent. If an adverse event requires modification to the study protocol, these modifications approved by the sponsor-investigator will be provided to the IRB as soon as is possible.

12.20. Food and Drug Administration (FDA)

In this trial, serious unexpected adverse events suspected by the sponsor-investigator to be possibly, probably, or definitely related to protocol-indicated treatment will be (as determined by the sponsor-investigator) will be reported to the Food and Drug Administration using the MedWatch Form FDA 3500A – Mandatory Reporting form, currently available at:
< http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm >.

Note: Adverse events that do not meet the criteria for reporting in an IND safety report must still be reported in accordance with the periodic reporting regulations, when applicable (e.g., 21 CFR 312.33 IND annual report).

12.21. Expedited 7 and 15 Day Reporting Requirements for

IND

Events meeting the following criteria must be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report

The sponsor-investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and suspected by the sponsor-investigator to be possibly, probably or definitely related to protocol-indicated treatment. The sponsor-investigator must notify the FDA of such events as soon as possible but in no case later than 7 calendar days after the sponsor-investigator's initial receipt of the information.

15 Calendar Day Written Report

The sponsor-investigator is required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event suspected by the sponsor-investigator to be possibly, probably, or definitely related to protocol-indicated treatment. The sponsor-investigator must notify the FDA of such events no later than 15 calendar days after the sponsor-investigator's initial receipt of the information.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the sponsor-investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with analysis of similar events are to be submitted to the FDA and all participating investigators as soon as possible but not later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting.

The sponsor-investigator must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

Each notification to FDA must bear prominent identification of its contents, i.e., "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.

Upon request from FDA, the sponsor-investigator must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

12.22. Xcovery (Equinox Sciences)

If a Vorolanib event originating from any non–Xcovery sponsored study 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 [redacted], 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 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.

12.23. Bristol-Myers Squibb

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 1 Business Day of becoming aware of the event. SAEs and pregnancies must be recorded on the BMS approved coordinating center SAE form and reported to:

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization. Pregnancies will be followed for outcome.

13. DATA SAFETY AND MONITORING

13.1. Data Management and Reporting

Participating institutions will collaborate with Vanderbilt for patient accrual. Data will be collected using a centralized electronic case report form (eCRF) called REDCap.

The Vanderbilt University Office of Research will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) is a secure, web-based application that is flexible enough to be used for a variety of types of research. REDCap provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). In addition to traditional data capture functionality, REDCap's survey capabilities are a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. All data collection projects rely on a thorough, study-specific data dictionary, defined by all members of the research team in an iterative, self-documenting process. This iterative development and testing process results in a well-planned and individualized data collection strategy.

REDCap servers are housed in a local data center at Vanderbilt, and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Vanderbilt researchers by both our Privacy Office and Institutional Review Board. REDCap has been disseminated for local use at more than 940 other academic/non-profit consortium partners in 75 countries. Vanderbilt leads the REDCap Consortium, which currently

supports more than 99,000 projects and 128,000 users. More information about the consortium and system security can be found at [redacted]

Specified members at each participating site will submit all pertinent regulatory documents to the Coordinating Center for storage in a secure location.

The Principal Investigator or designee at each site will inform the Coordinating Center as defined in the Safety and Data Exchange Agreement (SDEA) of any serious adverse event, and will also inform the site's local IRB in accordance with each institution's IRB policy. The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the treating investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs, as detailed in the protocol. If any problem is identified related to the conduct of this research, the VICC Data Safety and Monitoring Committee (DSMC) will be formally asked to review the study and the situation that required DSMC intervention.

13.2. Meetings

This trial will be monitored by the VICC Thoracic Oncology research team. The team is composed of Medical Oncologists, Research Nurses, Data Managers, and Regulatory Specialists. The team meets on a monthly basis to discuss all AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, etc. pertaining to cancer studies conducted by the thoracic team. This particular study will be thoroughly reviewed during these meetings. These monthly meetings are intended to have minutes recorded for review on a monthly basis by the Physician Leader of the thoracic oncology research team.

In addition, monthly teleconferences between participating sites and the Thoracic Oncology research team at Vanderbilt are intended to discuss relevant issues related to the trial (e.g. AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, reviews).

13.3. Monitoring

This trial will be monitored continuously by the study's Protocol Chair and by the Thoracic Oncology research team at Vanderbilt.

Additionally, the Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored, investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

The investigator will allow the VICC-DSMC designee access to all pertinent medical records, as required by federal regulations, in order to allow for the verification of data gathered in the electronic data case report forms (eCRFs) and for the review of the data collection process. The VICC-DSMC designee will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff. The investigator and the investigational site staff

must be available to meet with the VICC-DSMC designee in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the Research Compliance Coordinator.

Additionally, the Coordinating Center has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards to ethics, protocol adherence, integrity, validity of the data recorded on the CRFs, and adherence to regulations regarding Good Clinical Practice (GCP) and the protection of human subjects.

In accordance with applicable regulations, GCP, and Coordinating Center procedures, sites will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Coordinating Center requirements.

During the course of the study, the Coordinating Center will routinely monitor sites for protocol compliance, compare CRFs with individual subjects' original source documents, assess drug accountability, and ensure that the study is being conducted according to the pertinent regulatory requirements. The review of subjects' medical records will be performed in a manner to ensure that subjects' confidentiality is maintained. Monitoring visits will primarily be conducted remotely, and sites are required to provide the appropriate source documentation in order to allow for proper oversight per GCP. Investigators must agree to cooperate with the Coordinating Center to ensure that any problems detected are resolved.

In addition to the above, the FDA may review the conduct or results of the study at the investigational site.

In accordance with HIPAA and associated privacy regulations, a subject's authorization to use personally identifiable health information may be required from each subject before commencement of research activities. This authorization document must clearly specify what parties will have access to a subject's personal health information, for what purpose and for what duration.

13.4. Data Handling and Record Keeping

An electronic case report form (eCRF) is required and must be completed for each included participant. The completed dataset should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Vanderbilt.

To enable evaluations and/or audits from health authorities and Vanderbilt, each site investigator agrees to keep records including: The identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed remotely online. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

14. REGULATORY CONSIDERATIONS

14.1. Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per current institutional standards.

The trial will not be initiated until there is approval by the local IRB of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial. The IRB should be duly constituted according to local regulatory requirements. The investigator will inform the IRB of the progress of the trial at least yearly.

Any changes to the protocol will be made in the form of a written amendment and must be approved by the sponsor-investigator and the local IRB prior to local implementation. All amendments will also be submitted as necessary to the FDA by the sponsor-investigator (or designee).

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform the local IRB; and the sponsor-investigator (or designee), who will communicate as appropriate with the FDA.

The sponsor-investigator (or designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

14.2. Informed Consent

The investigator (or designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

14.3. Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described within:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described within the above and thereby to adhere to the principles of Good Clinical Practice with which the above conform.

14.4. Confidentiality

It is the responsibility of the investigator to insure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms (CRFs) and other documents submitted to regulatory authorities must not contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRFs and any other material submitted to regulatory authorities. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial.

14.5. Study Termination

The sponsor-investigator reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment
- Safety concerns
- Decision by suppliers to modify or discontinue the availability, development or manufacture of protocol-indicated treatment
- A request to discontinue the study by the IRB or FDA.

The sponsor-investigator will promptly notify investigators, the IRB and FDA if the study is terminated for any reason.

15. MULTI-CENTER GUIDELINES

15.1. Pre-Study Documentation

Prior to initiating the trial, the investigator will secure and provide to the Coordinating Center essential documents, including but not limited to:

- A signed FDA Form 1572
- A current curriculum vitae for the Principal Investigator and each sub-investigator listed on the FDA Form 1572
- A copy of the current medical license of the Principal Investigator and each sub-investigator listed on the FDA Form 1572
- A completed Financial Disclosure Form for the investigator and all sub- investigators listed on the FDA 1572

- A letter from the IRB stipulating approval of the protocol, the informed consent document and any other material provided to potential trial participants with information about the trial (e.g. advertisements)
- A copy of the informed consent document approved by both the sponsor and local IRB
- The current IRB membership list for the reviewing IRB
- Current laboratory certification for the reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory.
- A copy of the signed Delegation of Authority Log
- Protocol training documentation for study staff
- The drug destruction SOP for each participating site
- A copy of the fully executed contract must be on record

15.2. Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to local implementation.

The sponsor-investigator (or designee) is responsible for the coordination and development of all protocol amendments. Once approved by the sponsor-investigator, Vanderbilt will disseminate this information to the participating centers.

15.3. Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), each participant's informed consent, enrollment form, eligibility checklist, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below. The participating sites will submit all the research related information (source documents and research records – IRB approval documents, patient registration list, CRF info, toxicity assessments, tumor measurements / responses, etc.) within 2 weeks of the patient's visit to the assigned Coordinating Center Monitor (CRA). The CRA will check if data was entered into REDCap within 1 week of receiving the information. Personnel from the VICC Clinical Trial Shared Resource Coordinating Center will monitor the trial remotely and may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at other sites will allow the monitor to review all source documents used in the preparation of the case reports.

15.4. Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

15.5. Publication

It is understood that any manuscript or releases resulting from the collaborative research must be approved by the sponsor-investigator and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation.

16. STATISTICAL CONSIDERATIONS

16.1. Phase I (Dose-Escalation) Design

The primary objective of the phase I portion of this study is to determine the recommended combination dose (RCD) of the combination of the vorolanib + nivolumab.

At least 3 patients will be studied at each dose level and evaluated for toxicity. If 0 of 3 patients experience a dose-limiting toxicity (DLT), the dose will be escalated. If 1 of 3 patients experiences a DLT, 3 additional patients will be treated. If none of the additional patients develop a DLT, the dose will be escalated, otherwise escalation ceases. If > 1 of 3 or > 2 of 6 patients experience a DLT, the RCD has been exceeded.

For a dose level at which a patient has a high probability to develop a DLT, the intent is for the probability of escalation to a higher dose level to be low. As noted in the summary below, the probability of escalating a certain dose, if the dose level truly has a 10% DLT rate, is about 90%. For a given DLT with a true rate of 10%, 5%, or 1%, the probability of observing at least one such AE in a given cohort of 6 patients is 47%, 26.5%, and 5.8%, respectively.

Underlying DLT Rate	Probability of Observing No DLTs in 3 Patients	Probability of Observing Fewer Than Two DLTs in 6 Patients
0.10	0.73	0.89
0.20	0.51	0.66
0.30	0.34	0.42
0.40	0.22	0.23
0.50	0.13	0.11
0.60	0.06	0.04

It is expected that 2 or 3 dose escalation cohorts will be needed to reach the recommended combinatorial dose (RCD); therefore, approximately 9-18 eligible patients would be required in the dose-escalation portion of the trial, unless it is felt that there might be differences in tolerability based on indication or amount/type of prior therapy. In the latter case, additional patients may be treated to evaluate whether the RCD may be different for these different groups.

16.2. Phase II (Dose-Expansion) Design

In the dose-expansion portion, about 159 patients will be split into four cohorts (20-41 evaluable patients/cohort) and treated at the determined RCD for their corresponding combination regimen:

- **Thymic (n = 41):** A two-stage MinMax design described by Simon will ensure that the number of the total patients exposed to vorolanib + nivolumab is minimized (39). The design is based on assuming an improvement in response rate of 15% or less would not be considered of interest for future study. The design has 80% power to detect the response rate of 35% versus 20% at the 1-sided 10% level. Initially 22 patients will be accrued and assessed for response. If there are less than 5 responses in the first 22 evaluable patients, then accrual to this cohort will be terminated with the conclusion that there is little evidence to suggest that the overall response rate would reach 35%. If there are at least 5 responses in the first 22 patients, the cohort will continue until 41 evaluable patients have been treated. If the study continues past the first stage and 12 or more responses are observed, then this would be considered evidence to consider phase III

study in the future. This design yields a type I error rate of 10% and power of 80% when the true response rate is 35%.

- **NSCLC naïve to checkpoint inhibitor therapy (n = 39):** A two-stage MinMax design described by Simon will ensure that the number of the total patients exposed to the combination nivolumab and X-82 is minimized. Initially, 23 eligible patients will be entered into the study. If there are less than 6 responses in these first 23 patients, the trial will be terminated with the conclusion that there is little evidence to suggest that the overall response rate would reach 45%, i.e., a 20% RR improvement (45% vs. null hypothesis RR = 25%), If there are six or more than six responses in these first 23 patients, the trial will continue until 39 patients have been treated. If there are less than 14 responses in these 39 patients then the NSCLC group will be terminated, otherwise a phase III study may be conducted in the future. This design provides 90% statistical power to detect a difference of 20% (45% vs. 25%) with a significance level less than 0.10 (type I error).

- **NSCLC primary refractory to checkpoint inhibitor therapy (n = 21):** A two-stage MinMax design described by Simon will ensure that the number of the total patients exposed to vorolanib + nivolumab is minimized (39). The design is based on assuming a response rate of 25% improvement or less would not be considered of interest for future study. The design has 90% power to detect the response rate of 40% versus 15% at the 1-sided 10% level, i.e., a 25% RR improvement (40% vs. null hypothesis RR = 15%). Initially 15 patients will be accrued and assessed for response. If there are less than 3 responses in the first 15 evaluable patients, then accrual to this cohort will be terminated with the conclusion that there is little evidence to rule out an improvement in response rate of 25%. If there is at least 3 responses in the first 15 patients, the cohort will continue until 21 evaluable patients have been treated. If the study continues past the first stage and 6 or more responses are observed, then this would be considered evidence to rule out the response rate of 25%. This design yields a type I error rate of 10% and power of 90% when the true response rate is 40%.

- **NSCLC acquired resistance to checkpoint inhibitor therapy (n = 21):** A two-stage MinMax design described by Simon will ensure that the number of the total patients exposed to vorolanib + nivolumab is minimized (39). The design is based on assuming a response rate of 25% improvement or less would not be considered of interest for future study. The design has 90% power to detect the response rate of 40% versus 15% at the 1-sided 10% level, i.e., a 25% RR improvement (40% vs. null hypothesis RR = 15%). Initially 15 patients will be accrued and assessed for response. If there are less than 3 responses in the first 15 evaluable patients, then accrual to this cohort will be terminated with the conclusion that there is little evidence to rule out an improvement in response rate of 25%. If there is at least 3 responses in the first 15 patients, the cohort will continue until 21 evaluable patients have been treated. If the study continues past the first stage and 6 or more responses are observed, then this would be considered evidence to rule out the response rate of 25%. This design yields a type I error rate of 10% and power of 90% when the true response rate is 40%.

- **SCLC progressed on platinum-based chemotherapy (n = 37):** The sample size estimation was completed using the Simon's MinMax design (39). If there are less than 3 responses in the first 18 evaluable patients, the trial will be terminated with the conclusion that there is little evidence to suggest that the ORR would reach 30%, i.e., a 15% ORR improvement (30% vs. null hypothesis ORR = 15%), If there are at least 3 responses in the first 18 evaluable patients, the trial will continue until 37 evaluable patients have been treated. If 9 or more of these 37 patients respond, additional evaluation in this indication may be warranted. This design provides 80% statistical power to detect a difference of 15% with a significance level less than 0.10 (type I error).

16.3. Data Analysis Plan

.

The ORR and DCR will be summarized by binomial response rate and their corresponding two-sided 95% exact Cis using Clopper-Pearson method. For lifetime data analyses, e.g., PFS, Kaplan-Meier product-limit estimates will be prepared. The 95% CIs for the 6-month and 12-month PFS and survival rates will be estimated and reported. Duration of Response (DOR) will also be assessed using KM product-limit method. Median value of Duration of Response (DOR), along with two-sided 95% CI using Brookmeyer and Crowley method will be reported.

As exploratory analysis, the Fisher's exact test as well as the Wilcoxon rank sum test will be applied to examine the correlation between the baseline covariates and toxicities outcomes.

Safety will be examined on an ongoing basis during the study. Data will be listed and/or summarized and tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percents and frequencies for categorical parameters, will be presented.

Adverse events will be tabulated. NCI toxicity Grade 3 and Grade 4 laboratory abnormalities will be listed, and summary statistics will be provided for all laboratory values.

16.4. Anti-Tumor Activity Analyses

Antitumor activity will be assessed by ORR, as well as progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), and 1-year survival. In addition, correlation between the biomarkers and clinical outcomes will be evaluated.

The analyses involving response will be based on definitions of responses according to RECIST v1.1. Data will be listed for all evaluable patients, including by dose level for the dose escalation portion.

Objective response is defined as a complete or partial response, as determined by investigator assessment using RECIST v1.1 and confirmed by repeat assessments > 4 weeks after initial documentation. Disease control is defined as a complete or partial response or stable disease, as determined by investigator assessment. PFS will be defined as the time from study treatment initiation (Cycle 1 Day 1) to the first occurrence of documented disease progression or death from any cause during the study, whichever occurs first. For patients who do not have documented progressive disease or death during the study, PFS will be censored at the day of the last tumor assessment or at time of initiation of subsequent therapy. One-year survival will be evaluated from the first dose of study treatment.

17. REFERENCES

1. Grigg C and Rizvi N. PD-L1 biomarker testing for non-small cell lung cancer: truth or fiction?. Journal for ImmunoTherapy of Cancer. 2016 Aug 16; 4: 48. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27532023

2. Equinox. Vorolanib Investigator's Brochure. 2017.

3. Cetin K, Ettinger DS, Hei YJ, O'Malley CD. Survival by histologic subtype in stage IV nonsmall cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. Clin Epidemiol [Internet]. 2011;3:139–48. Available from:

https://www.ncbi.nlm.nih.gov/pubmed/21607015

4. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol [Internet]. 2015 Jun 20 [cited 2016 Jun 20];33(18):2004–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25897158

5. Yang JC, Hirsh V, Schuler M, Yamamoto N, O'Byrne KJ, Mok TS, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol [Internet]. 2013;31(27):3342–50. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23816967

6. Kwak EL, Bang Y-J, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer. N Engl J Med [Internet]. 2010 Oct 28 [cited 2017 Jul 28];363(18):1693–703. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20979469

7. Kerbel RS. Tumor angiogenesis. N Engl J Med [Internet]. 2008;358(19):2039–49. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18463380

8. Scagliotti G, Govindan R. Targeting angiogenesis with multitargeted tyrosine kinase inhibitors in the treatment of non-small cell lung cancer. Oncologist [Internet]. 2010;15(5):436–46. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20427383

9. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med [Internet]. 2015 Oct 22 [cited 2016 Jun 23];373(17):1627–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26412456

10. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med [Internet]. 2015 Jul 9 [cited 2016 Jun 23];373(2):123–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26028407

11. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–50.

12. Shi S, Wang R, Chen Y, Song H, Chen L, Huang G. Combining antiangiogenic therapy with adoptive cell immunotherapy exerts better antitumor effects in non-small cell lung cancer models. PLoS One [Internet]. 2013;8(6):e65757. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23799045

13. Manegold C, Dingemans AC, Gray JE, Nakagawa K, Nicolson M, Peters S, et al. The potential of combined immunotherapy and antiangiogenesis for the synergistic treatment of advanced NSCLC. J Thorac Oncol [Internet]. 2016; Available from: https://www.ncbi.nlm.nih.gov/pubmed/27729297

14. Rizvi NA, Antonia SJ, Shepherd FA, Chow LQ, Goldman J, Shen Y, et al. Nivolumab (Anti-PD-1; BMS-936558, ONO-4538) Maintenance as Monotherapy or in Combination With Bevacizumab (BEV) for Non-Small Cell Lung Cancer (NSCLC) Previously Treated With Chemotherapy. Int J Radiat Oncol • Biol • Phys [Internet]. Elsevier; 90(5):S32. Available from: http://dx.doi.org/10.1016/j.ijrobp.2014.08.206

15. Margaritora S, Cesario A, Cusumano G, Meacci E, D'Angelillo R, Bonassi S, et al. Thirty-five-year follow-up analysis of clinical and pathologic outcomes of thymoma surgery. Ann Thorac Surg [Internet]. 2010;89(1):245–52; discussion 252. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20103246

16. Rashid OM, Cassano AD, Takabe K. Thymic neoplasm: a rare disease with a complex clinical

presentation. J Thorac Dis [Internet]. 2013;5(2):173–83. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23585946

17. Ried M, Marx A, Gotz A, Hamer O, Schalke B, Hofmann HS. State of the art: diagnostic tools and innovative therapies for treatment of advanced thymoma and thymic carcinoma. Eur J Cardiothorac Surg [Internet]. 2016;49(6):1545–52. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26670806

18. Grassin F, Paleiron N, Andre M, Caliandro R, Bretel JJ, Terrier P, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma. A French experience. J Thorac Oncol [Internet]. 2010;5(6):893–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20521356

19. Thomas A, Rajan A, Berman A, Tomita Y, Brzezniak C, Lee MJ, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. Lancet Oncol [Internet]. 2015;16(2):177–86. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25592632

20. Tomita M, Matsuzaki Y, Edagawa M, Maeda M, Shimizu T, Hara M, et al. Correlation between tumor angiogenesis and invasiveness in thymic epithelial tumors. J Thorac Cardiovasc Surg [Internet]. 2002;124(3):493–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12202865

21. Sasaki H, Yukiue H, Kobayashi Y, Nakashima Y, Moriyama S, Kaji M, et al. Elevated serum vascular endothelial growth factor and basic fibroblast growth factor levels in patients with thymic epithelial neoplasms. Surg Today [Internet]. 2001;31(11):1038–40. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11766079

22. Yokoyama S, Miyoshi H, Nakashima K, Shimono J, Hashiguchi T, Mitsuoka M, et al. Prognostic Value of Programmed Death Ligand 1 and Programmed Death 1 Expression in Thymic Carcinoma. Clin Cancer Res [Internet]. 2016;22(18):4727–34. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27166394

23. Skouras VS, Maragkos C, Grapsa D, Syrigos KN. Targeting Neovasculature with Multitargeted Antiangiogenesis Tyrosine Kinase Inhibitors in Non-small Cell Lung Cancer. BioDrugs [Internet]. 2016;30(5):421–39. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27670779

24. Pietras K, Hanahan D. A Multitargeted, Metronomic, and Maximum-Tolerated Dose “Chemo-Switch” Regimen is Antiangiogenic, Producing Objective Responses and Survival Benefit in a Mouse Model of Cancer. J Clin Oncol [Internet]. 2005 Feb 10 [cited 2017 Jul 28];23(5):939–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15557593

25. Bergers G, Song S, Meyer-Morse N, Bergsland E, Hanahan D. Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. J Clin Invest [Internet]. 2003 May 1 [cited 2017 Jul 28];111(9):1287–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12727920

26. Bristol-Meyers Squibb. Opdivo (nivolumab) Investigator’s Brochure.

27. Garber K. Promising early results for immunotherapy-antiangiogenesis combination. J Natl Cancer Inst [Internet]. 2014;106(11). Available from: https://www.ncbi.nlm.nih.gov/pubmed/25421345

28. Ko JS, Zea AH, Rini BI, Ireland JL, Elson P, Cohen P, et al. Sunitinib mediates reversal of myeloid-derived suppressor cell accumulation in renal cell carcinoma patients. Clin Cancer Res [Internet]. 2009;15(6):2148–57. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19276286

29. Ozao-Choy J, Ma G, Kao J, Wang GX, Meseck M, Sung M, et al. The novel role of tyrosine kinase inhibitor in the reversal of immune suppression and modulation of tumor microenvironment for immune-based cancer therapies. Cancer Res [Internet]. 2009;69(6):2514–22. Available from:

https://www.ncbi.nlm.nih.gov/pubmed/19276342

30. Schalper KA, Kaftan E, Herbst RS. Predictive Biomarkers for PD-1 Axis Therapies: The Hidden Treasure or a Call for Research. Clin Cancer Res [Internet]. 2016 May 1 [cited 2017 Jul 28];22(9):2102–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26957559

31. Hooren L van, Georganaki M, Huang H, Mangsbo SM, Dimberg A. Sunitinib enhances the antitumor responses of agonistic CD40-antibody by reducing MDSCs and synergistically improving endothelial activation and T-cell recruitment. Oncotarget [Internet]. 2016 Aug 2 [cited 2017 Jul 28];7(31):50277–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27385210

32. Dammeijer F, Lievense LA, Kaijen-Lambers ME, van Nimwegen M, Bezemer K, Hegmans JP, et al. Depletion of Tumor-Associated Macrophages with a CSF-1R Kinase Inhibitor Enhances Antitumor Immunity and Survival Induced by DC Immunotherapy. Cancer Immunol Res [Internet]. 2017 Jul [cited 2017 Jul 28];5(7):535–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28536100

33. Huang AC, Postow MA, Orlowski RJ, Mick R, Bengsch B, Manne S, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature [Internet]. 2017 May 4 [cited 2017 Jul 28];545(7652):60–5. Available from: http://www.nature.com/doifinder/10.1038/nature22079

34. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJM, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature [Internet]. 2014 Nov 27 [cited 2017 Jul 28];515(7528):568–71. Available from: http://www.nature.com/doifinder/10.1038/nature13954

35. Stack EC, Foukas PG, Lee PP. Multiplexed tissue biomarker imaging. J Immunother cancer [Internet]. BioMed Central; 2016 [cited 2017 Jul 28];4:9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26885371

36. Hung JY, Horn D, Woodruff K, Prihoda T, LeSaux C, Peters J, et al. Colony-stimulating factor 1 potentiates lung cancer bone metastasis. Lab Investig [Internet]. 2014 Apr 27 [cited 2016 Dec 15];94(4):371–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24468794

37. Zurita AJ, Jonasch E, Wang X, Khajavi M, Yan S, Du DZ, et al. A cytokine and angiogenic factor (CAF) analysis in plasma for selection of sorafenib therapy in patients with metastatic renal cell carcinoma. Ann Oncol Off J Eur Soc Med Oncol [Internet]. Oxford University Press; 2012 Jan [cited 2016 Dec 15];23(1):46–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21464158

38. Panni RZ, Linehan DC, DeNardo DG. Targeting tumor-infiltrating macrophages to combat cancer. Immunotherapy [Internet]. NIH Public Access; 2013 Oct [cited 2016 Dec 15];5(10):1075–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24088077

39. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials [Internet]. 1989 Mar [cited 2017 Aug 3];10(1):1–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2702835

APPENDIX 1
Cockcroft-Gault Formula

Cockcroft-Gault Formula

The following formula may be used for estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula. The use of on-line calculators or formulas which are institution standards for eC_{CR} and differ slightly may also be used. The calculations and results must be filed in the patient's chart.

When serum creatinine is measured in mg/dL;

$$\mathrm{eC_{CR}} = \frac{(140 - \mathrm{Age}) \cdot \mathrm{Mass\,(in\ kilograms)} \cdot [0.85\ if\ Female]}{72 \cdot \mathrm{Serum\ Creatinine\,(in\ mg/dL)}}$$

When serum creatinine is measured in µmol/L;

$$\mathrm{eC_{CR}} = \frac{(140 - \mathrm{Age}) \cdot \mathrm{Mass\,(in\ kilograms)} \cdot \mathrm{Constant}}{\mathrm{Serum\ Creatinine\,(in\ \mu mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

APPENDIX 2
ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX 3

New York Heart Association (NYHA) Functional Classification

APPENDIX 4

Prohibited Medications and Food

The following list describes medications and foods which are common strong inhibitors of CYP3A4. This list should not be considered all-inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A4.

Boceprevir
Conivaptan
Grapefruit juice
Lopinavir
Mibefradil
Posaconazole
Telaprevir
Voriconazole
Ritonavir
Indinavir
Nelfinavir
Saquinavir
Clarithromycin
Telithromycin
Chloramphenicol
Ketoconazole
Itraconazole
Nefazodone
Amprenavir
Aprepitant
Atazanavir
Ciprofloxacin
Darunavir
Diltiazem
Erythromycin
Fluconazole
Fosamprenavir
Imatinib
Verapamil
Avasimibe
Carbamazepine
Phenytoin
Rifampin
St. John's wort

The following list describes medications and foods which are common inhibitors, inducers, and substrates of CYP2C9. This list should not be considered all-inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit or induce CYP2C9.

CYP2C9 Substrates

Major

Celecoxib
Lmoxicam
Diclofenac
Ibuprofen
Piroxicam
Meloxicam
Phenytoin
Fluvastatin
Sulfonylurea
Glibenclamide
Glimepiride
Glipizide
Tolbutamide
Irbesartan
Losartan
Warfarin

Minor

Amitriptyline
Omeprazole
Miconazole
Pitavastatin
Pheylbutazone
Rosiglitazone
Sertraline
Sildenafil
Sulfinpyrazone
Tamoxifen
THC

APPENDIX 5
Acceptable Contraception

Women of childbearing potential must have a negative serum or urine pregnancy test within 24 hours prior to the start of nivolumab. Women must not be breastfeeding.

"Women of childbearing potential" (WOCBP) is defined as any female who has experienced menarche who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal.

Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 years of age in the absence of other biological or physiological causes. If menopausal status is considered for the purpose of evaluating childbearing potential, women < 55 years of age must have a documented serum follicle stimulating hormone (FSH) level within laboratory reference range for postmenopausal women, in order to be considered postmenopausal and not of childbearing potential.

- **Women of childbearing potential (WOCBP) will be instructed to adhere to acceptable contraception from the time of signing consent, and for 23 weeks after their last dose of protocol-indicated treatment.**

- **Men who are not azoospermic and who are sexually active with WOCBP will be instructed to adhere to acceptable contraception from the time of signing consent, and for 31 weeks after their last dose of protocol-indicated treatment.**

These durations have been calculated using the upper limit of the half-life for nivolumab (25 days); and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days, and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days.

Women of child bearing potential (WOCBP) and men able to father children who are sexually active with WOCBP must agree to use acceptable contraception. A study physician or clinical designee shall counsel such participants on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

- **At a minimum, applicable subjects must agree to the use of 2 methods of contraception, with 1 method being highly effective and the other method being either highly effective or less effective, as listed below in Table 4:**

TABLE 4: Methods of Contraception

HIGHLY EFFECTIVE methods of contraception:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®

- Tubal ligation
- Vasectomy
- Complete Abstinence*

  * Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects of childbearing potential must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE methods of contraception:

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.

  * A male and female condom must not be used together.

UNACCEPTABLE methods of contraception:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

APPENDIX 6
Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Measurability of tumor at baseline

Definitions
At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable:

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:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 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). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on “Baseline documentation of target and non-target lesions” for information on lymph node measurement.

Non-measurable:

All other lesions, including small lesions (longest diameter < 10 mm 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.

Special considerations regarding lesion measurability:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable

Cystic lesions

- 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

Lesions with prior local treatment

- Tumor lesions situated in a previously irradiated area, or other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

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 should always be done rather than 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 and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When 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)
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when

biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease.

Tumor response evaluation
To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. Response criteria are listed in **Table 5** and **Table 6**:

TABLE 5: Response Criteria for Evaluation of *TARGET* Lesions

	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 diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of 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 progression)
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

TABLE 6: Response Criteria for Evaluation of *NON-TARGET* Lesions

	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)
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression)

	Evaluation of Non-target Lesions
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Evaluation of Best Overall Response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table 7** provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

TABLE 7: Overall Response Status for Patients with Baseline Measurable 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 evaluated	No	PR
SD	Non-PD or not all evaluated	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

Abbreviation: CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of CR or PR IS NOT required:

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of CR or PR IS required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as shown in **Table 8**.

TABLE 8: Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Abbreviation: CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease

1) If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

APPENDIX 7

Guidelines for the Management of Immune-Related Adverse Events (irAEs)

These general guidelines constitute guidance to the Investigator. The guidance applies to all immuno-oncology (I-O) agents and regimens.

Where applicable the Approved Label should be used in combination with the protocol and IB for guidance around dose modifications and discontinuation.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used

Investigators should refer to the most current version of the IB or Approved Label for current recommendations for management of a specific Adverse Event of interest.