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Title: A Phase I/II Study of PI3Kγδ inhibitor Duvelisib in Combination with Nivolumab in Patients with Advanced Unresectable Melanoma who have Progressed on Anti-PD1 Therapy

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i. Abbreviations

AJCC – American Joint Committee on Cancer

ANC – Absolute Neutrophil Count

βhCG – Beta Human Chorionic Gonadotropin

CNS – Central Nervous System

COPD – Chronic Obstructive Pulmonary Disease

CR – Complete Response

CRF- Case Report File

CRS – Clinical Research Staff

CT – Computed Tomography

CTCAE – Common Terminology Criteria for Adverse Events

DLT – Dose Limiting Toxicity

DOR – Duration of Response

DRESS – Drug Reaction with Eosinophilia and Systemic Symptoms

DSMB – Data Safety Monitoring Board

EMR – Electronic Medical Record

HSV – Herpes Simplex Virus

IP – Investigational Product

IRB – Institutional Review Board

MDSC – Myeloid-Derived Suppressor Cells

MI – Myocardial Infarction

MRI – Magnetic Resonance Imaging

MTD – Maximum Tolerated Dose

OS – Overall Survival

PBMC – Peripheral Blood Mononuclear Cells

PD – Progressive Disease

PD1 – Programmed Cell Death Receptor

PDL1 – Programmed Cell Death Ligand 1

PFS - Progression Free Survival

PI3K - Phosphoinositide 3-Kinase

PJP – Pneumocystis jiroveci Pneumonia

PR – Partial Response

RECIST - Response Evaluation Criteria in Solid Tumors

RP2D – Recommended Phase 2 Dose

SAE – Serious Adverse Event

SD – Stable Disease

SJS – Stevens-Johnson Syndrome

TEN – Toxic Epidermal Necrolysis

TIA – Transient Ischemic Attack

TME - Tumor Microenvironment

T-vec - talimogene laherparepvec

ULN – Upper Limit of Normal

UPMC – University of Pittsburgh Medical Center

VZV – Varicella Zoster Virus

WCBP – Women of Child Bearing Age

IRB – Institutional Review Board

ii. Protocol Summary

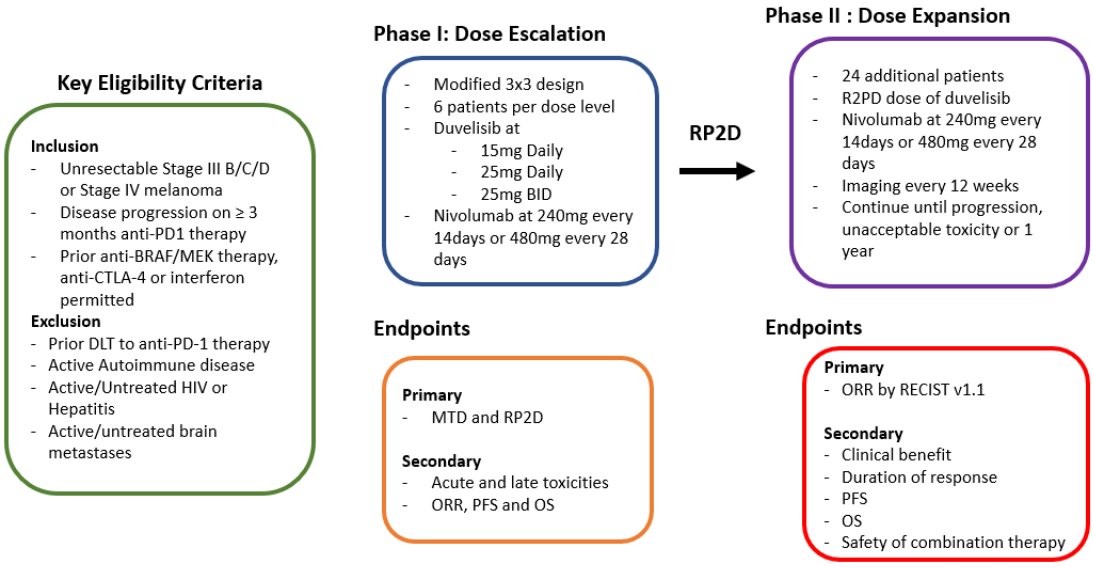
Title	A Phase I/II Study of PI3Kγδ inhibitor Duvelisib in Combination with Nivolumab in Patients with Advanced Unresectable Melanoma who have Progressed on Anti-PD1 Therapy
Short Title	*PI3*γδ inhibition in PD1 Refractory Melanoma
Protocol Number	*20-155*
Phase	Phase I/II
Methodology	Single-arm, open label phase I/II study
Study Duration	We expect to enroll patients over 18 months and complete data analysis by 36 months.
Study Center(s)	UPMC Hillman Cancer Center
Objectives	For the Phase I portion, the primary objective is to determine the recommended phase II dose of duvelisib when combined with nivolumab using dose-limiting toxicity and immunologic parameters, and the secondary objectives are to assess early and late toxicities and the anti-tumor effect of combination therapy. The primary objective for the phase II cohort is to evaluate the anti-tumor effect of the combination of anti-PD1 therapy and duvelisib by comparing disease change using RECIST v1.1 criteria. Our secondary objectives are to assess 1) potential clinical benefit of combination therapy, 2) duration of response, 3) progression-free survival, 4) overall survival, and 5) safety measured by adverse events graded by CTCAE v5.0. A number of exploratory objectives will also be pursued including laboratory correlatives.
Number of Subjects	42

Main Inclusion and Exclusion Criteria	Inclusion criteria*:* Men and women 18 years of age or older with unresectable stage III or stage IV melanoma by AJCC 8th edition who have progressed on anti-PD1 therapy after a minimum of 12 weeks of therapy. Exclusion criteria: Patients with known or suspected symptomatic or progressive CNS metastases; patients with treated CNS disease who are stable on repeat imaging at 2-4 weeks post SRS and neurologically stable are allowed. Patients with active autoimmune disease requiring treatment and patients with uveal or mucosal melanoma are not eligible. Patients with uncontrolled cardiovascular, pulmonary, and certain infectious disease are also excluded.
Investigational Product	Duvelisib is an oral medication that will be administered in doses from 15mg once a day to 25mg BID for dose finding studies. Nivolumab is supplied as a 240mg/24 mL formulation to be administered as an IV infusion at 240mg every 2 weeks, and if tolerated, potentially changed to 480mg once every 4 weeks.
Duration of administration	Both duvelisib and nivolumab will be administered in 4-week cycles until progression of disease, unacceptable toxicity, or 1 year, whichever is longer.
Reference therapy	For patients who have progressed on immunotherapy and targeted agents, there is no current standard of care[1] and clinical trials are the recommended option.
Correlative studies	Patients will have peripheral blood draw and tumor biopsy performed at baseline and after 12 weeks of treatment in both phases of the trial. For the phase I cohort, changes in immune cell populations, particularly CD8+ T cell proliferation, will be used to measure the immunomodulatory effect of increasing doses of duvelisib. Additional studies are planned to characterize T cell phenotype, function, and metabolism as well to evaluate expression of genes involved in autoimmunity and inflammation and to correlate with toxicity. Correlative studies will be used along with toxicity data to inform the phase II dose. Ideally, the dose chosen will have a potent anti-tumor immune profile such as high CD8+ T effector cells, low T regulatory cells, low myeloid-derived suppressor cells.
Statistical Methodology	For the Phase I study, a modified 3+3 dose finding design is used, with 6 patients at each of 3 dose levels of 15mg daily, 25mg daily and 25mg twice daily. For the Phase II expansion, the expected response rate for treatment of patients with anti-PD1 beyond progression is <14% [2]. For this study to be clinically relevant a response rate of at least 20% is sought from the addition of duvelisib. Regimen efficacy will be monitored using a Bayesian method. The trial will be stopped for futility if the posterior probability of response rate is <5% or is >70%. Response rate, progression free survival and overall survival will be analyzed via Kaplan-Meier methods. For safety analyses, a Bayesian monitoring scheme will also be used to monitor the severe adverse event rate.

Safety Evaluations	Patients will be evaluated at clinic visits at least every 2-4 weeks for safety analyses. Blood work will also be tested at these visits to evaluate any adverse effects. For patients with toxicity or other clinical concerns, additional visits and imaging may be warranted at the discretion of the treating physicians and in consultation with a study investigator.
Data and Safety Monitoring Plan	The Data Safety Monitoring Board consists of investigators, regulatory staff, CRS management, clinical research coordinators, data managers and clinic staff, and these will meet regularly at least monthly to discuss trial concerns and study data. The DSMB includes individuals not involved in study design or implementation. Information to be reviewed includes serious adverse events, safety issues, recruitment, accrual, protocol deviations and unanticipated problems. The protocol and investigators will also comply with IRB policy for reporting risk to subjects.

iii. Study Design Schematic

A Phase I/II Study of PI3Kγδ inhibitor Duvelisib in Combination with Nivolumab in Patients with Advanced Unresectable Melanoma who have Progressed on Anti-PD1 Therapy



1.0 Background and Study Rationale

Melanoma is an aggressive form of skin cancer with historically poor outcomes, especially prior to the advent of modern checkpoint blockade and targeted antitumor agents. Immunotherapy has changed the field of melanoma considerably in the last 5 years. In the Checkmate-066 trial, patients with metastatic melanoma who received single agent nivolumab had a 1-year overall survival of 72.9%, compared to 42.1% with the prior standard of care, dacarbazine [3]. While these results are promising, only 31% patients with locally advanced or metastatic melanoma have a durable progression free survival at 4 years with the remainder progressing or relapsing [4]. The potential mechanisms by which patients are refractory to or develop resistance to immunotherapy are numerous and include loss of the antigenic target, T-cell exhaustion, and development or enhancement of an immunosuppressive tumor microenvironment (TME) [5]. Sensitizing these patients to immunotherapy is the focus of current drug development and ongoing clinical trials.

The phosphoinositide 3-kinase (PI3K) signaling pathway functions at many stages of cancer biology including cell division, differentiation, motility and metabolism [6]. Inhibitors downstream of the PI3K pathway are active in some solid tumors, including everolimus in neuroendocrine tumors[7] and everolimus with exemestane in breast cancer[8]. While these therapies have clinical benefit, the toxicities of inhibiting such pervasive pathways are often significant[9]. A more targeted approach to PI3K inhibition may be useful for immune modulation in malignancies treated with immunotherapy.

PI3K has four subunits that are differentially expressed by cell type: α, β, γ and δ. While α and β are present in the majority of cell types, the PI3K γ and δ isoforms are expressed primarily in hematopoietic cells [10]. Duvelisib is a potent inhibitor of both γ and δ isoforms and is FDA approved for relapsed refractory CLL/SLL and follicular lymphoma based on the DUO and DYNAMO trials [11],[12],[13]. Tumor biopsies and peripheral blood cytokine analyses from lymphoma patients treated with duvelisib demonstrated shifts to a pro-inflammatory (anti-tumor) phenotype[14].

In pre-clinical tumor models of anti-PD1 resistance, PI3Kγ inhibition in combination with anti-PD1 therapy was able to restore anti-PD1 activity as demonstrated by a reduction in tumor size [15]. In xenograft tumor models treated with PI3Kγ inhibition, the TME demonstrated lower proportions of suppressive M2 macrophages and T-regulatory cells [15]. In a mouse model of head and neck squamous cell carcinoma (HNSCC), the combination of PI3Kγ inhibition and anti-PD1 blockade lead to a decrease in tumor growth and increased survival compared to mice treated with either agent alone [16]. These mice were noted to have increased activation and recruitment of CD8+ T cells to tumor sites [16]. Duvelisib also demonstrated anti-tumor effects in a distinct mouse model of HNSCC, with increased CD8+ T cell infiltration and less suppression by tumor-infiltrating myeloid-derived suppressor cells[17]. Mice treated with both duvelisib and anti-PDL1 demonstrated increased survival and decreased rates of tumor growth compared to mice treated with anti-PDL1 alone[17].

Despite promising preclinical data, there is limited data on the use of PI3K isoform inhibitors in solid tumors. Shifts to a pro-inflammatory TME were observed in patients receiving a PI3Kδ inhibitor in

combination with anti-PD1 in a phase 1b trial of patients with advanced solid tumors[18]. However, data regarding safety and efficacy in patients with melanoma is lacking. Taken together, these studies present duvelisib as an immunomodulator of the tumor microenvironment and a potentially effective treatment when combined with anti-PD1 therapy.

Our study will explore duvelisib as a means to overcome anti-PD1 resistance in human metastatic melanoma patients. We will test the safety and efficacy of the combination of duvelisib and nivolumab (anti-PD1) therapy in patients who have shown progression of disease on anti-PD1 therapy alone. We hypothesize that duvelisib will act as an immunomodulator, to shift the TME from an immunosuppressive to an immunostimulatory setting, helping to overcome acquired resistance in anti-PD1 treated patients. The phase I portion of our study is uniquely designed to find the ideal dose of duvelisib as an immunomodulator, which we suspect to be lower than the previously determined maximum tolerated dose (MTD) of duvelisib in lymphoma studies. In the absence of clinical dose-limiting toxicities (DLTs), immunologic parameters measured in blood and tumor samples will be used to determine dosing for the phase II portion of the study. Further, our translational correlative studies on peripheral blood and tumor biopsies will help elucidate mechanisms of resistance and the role of duvelisib in PD1 refractory settings. This is a promising area with the potential for great clinical benefit in multiple solid tumors.

2.0 Study Objectives

2.2 Primary Objectives

- Phase I:
    - To determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of duvelisib when combined with anti-PD1 therapy nivolumab by immunologic profiling and toxicity data.
- Phase II:
    - To assess the anti-tumor activity of the combination of duvelisib and nivolumab therapy, comparing disease change documented in CT measurements 12 weeks after initiation of therapy to baseline scans, and every 12 weeks thereafter.

2.3 Secondary Objectives

- Phase I:
    - To assess early (within 4 weeks) and late toxicities (after 4 weeks) of combination duvelisib and nivolumab
    - To assess the anti-tumor activity of the combination of duvelisib and nivolumab therapy, comparing disease change documented in CT measurements 12 weeks after initiation of therapy to baseline scans, and every 12 weeks thereafter.

- Phase II:
    - To assess the potential antitumor response of the combination of duvelisib and anti-PD1 therapy
    - To assess the duration of response with this combination
    - To assess progression-free survival and overall survival
    - To assess the safety of the combination of duvelisib and anti-PD1 therapy
    - To evaluate differences in response between certain pre-specified subsets of melanoma patients, including those who progressed on anti-PD1 therapy within 3 months (early progressors) and those who progressed after 3 months (late progressors), as well as by BRAF mutation status

2.4 Exploratory Objectives

- To evaluate how immune cell populations change by duvelisib dose, to help inform recommended phase II dosing
- To evaluate the effects of duvelisib on the tumor microenvironment (TME)
- To explore mechanism of anti-PD1 resistance and the role of duvelisib in overcoming this resistance

3.0 Investigational Plan

3.1 General Study Design

This trial is a phase I/II, dose-escalation and dose-expansion, open-label, single-arm trial in which duvelisib will be studied in combination with nivolumab.

3.1.1 Screening of Subjects

Patients will be identified during evaluation by their oncologist. Once identified, patients will meet with clinical research staff to determine eligibility, perform screening and discuss consent.

3.1.2 Study Intervention

Once consented patients should begin protocol treatment within 28 days. Treatment delays should be discussed with the Principal Investigator. If protocol is not initiated as specified, the patient's registration for the study may be cancelled.

3.1.3 Follow-Up Phase

Patients who discontinue study participation will be evaluated as determined by the treating physician regardless of the reason(s) for discontinuation (patient withdrawal, disease progression, toxicity). Patients will be followed for a minimum of 1 month after discontinuation of the study to complete data collection regarding safety. Patients may be contacted for survival follow-up for up to 5 years. Survival follow-up will be performed at approximately 3-month intervals. Patients discontinuing the study for adverse events will be followed until resolution or stabilization of the adverse event, with a minimum of 1 month follow-up.

3.1.4 Allocation to Interventional Group

The study is a single arm trial, and all patients will be allocated to the interventional group. The study coordinator at UPMC will be responsible for enrolling patients at each dose level and assigning appropriate doses.

3.2 Study Endpoints

3.2.1 Primary Endpoints

- Phase I
    - RP2D of duvelisib when used in combination with nivolumab, as determined by immunomodulatory effect in peripheral blood and TME, toxicity, and any early efficacy signals.
    - Maximum-tolerated dose of duvelisib in combination with nivolumab.

- Phase II
    - Overall response rate of the combination of anti-PD1 therapy and duvelisib as measured by overall antitumor response (defined as complete response + partial response) based on RECIST v1.1 criteria initially assessed at 12 weeks after initiation of the combination, compared to baseline imaging obtained immediately prior to initiating combination, and subsequently at 12 week intervals until progression.

3.2.2 Secondary Endpoints

Several secondary endpoints will be analyzed as follows:

- Acute and late toxicities rates throughout treatment, as graded by CTCAE v5.0 in patients at each dosing interval and in the expansion cohort
- Clinical benefit of combination therapy, defined as complete response, partial response and stable disease as assessed by RECIST v1.1, initially assessed at 12 weeks after initiation of therapy and subsequently at 12-week intervals until progression

- Duration of response defined by time at which measurement criteria are first met for complete response or partial response until the first time at which progressive disease is objectively documented
- Progression-free survival defined as time at start of treatment and first date of documented progression or death due to any cause
- Overall Survival defined as the time of start of treatment and the date of death due to any cause. Patients who are alive will be censored at the time of the last follow-up. Patients will be followed for survival for 5 years.
- Safety of the combination of anti-PD1 and duvelisib measured by adverse events graded by CTCAE v5.0. Adverse events will be captured during treatment and 100 days after discontinuing treatment. We will continuously for DLTs as defined in section 8.1 that are possibly, probably or definitely related to treatment. If the adverse event rate exceeds acceptable limits, the study will be modified or discontinued.
- Subset analysis will be performed to determine how certain disease characteristics affect response to the combination, including prior time prior to progression while on anti-PD1 therapy, presence of CNS disease, radiated CNS disease and tumor BRAF mutation status.

4.0 Study Population and Eligibility

4.1 Inclusion Criteria

- AJCC 8th edition criteria for unresectable stage IIIB, stage IIIC, stage IIID or stage IV melanoma who have received at least 3 months of prior treatment with an anti-PD1 or anti-PDL1 antibody and who have progressed on this treatment. Patients who have received a combination anti-PD1 and anti-CTLA4 therapy who exhibit progression at this interval are also permitted. There are no restrictions regarding time since last anti-PD1 treatment, or number of therapies after anti-PD1.
- Age ≥ 18 years;
- ECOG performance status ≤ 2 or Karnofsky ≥ 60%
- Patients must have normal organ and bone marrow function as defined below:

Lab Test	Criteria
Hemoglobin	≥9.0 g/dL
Absolute neutrophil count	≥1500 cells/µL
Platelets	≥100,000 cells/µL
Total bilirubin	≤ 1.5 x institutional upper limit of normal (ULN). Patients with Gilbert's syndrome must have normal direct bilirubin
AST/ALT	≤2.5x ULN in subjects with liver metastasis, must be within normal limits for those without liver metastasis
Creatinine	< 1.5 mg/dL

- For patients with actionable BRAF mutations, treatment with BRAF and MEK inhibitors prior to initiation on trial is recommended, unless patients are intolerant of therapy or choose not to pursue BRAF targeted therapy.
- Patients must have measurable disease, defined as at least one tumor lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥10mm with CT scan, MRI or by calipers if documented on clinical exam. If patients have a single lesion, the lesion must be amenable to biopsy without interfering with radiographic assessment as determined by one of the co-PIs.
- Duvelisib and nivolumab therapy may be harmful for a developing fetus. Women of child bearing potential (WCBP) must have a negative urine or serum β human chorionic gonadotropin (βhCG) pregnancy test within 7 days before starting treatment. WCBP and men must agree to use highly effective contraception (pharmacologic birth control, barrier methods or abstinence) prior to study entry and for the duration of study participation through 5 months after the last dose of study medication. Should a woman become pregnant while she or her partner are participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use highly effective contraception prior to the study, for the duration of study participation and 12 weeks following the last dose.
- WCBP defined as a sexually mature woman who as not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months for women >55 years of age
- Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

4.2.1 Target disease

- Patients with known or suspected CNS metastases are excluded, unless the following criteria are met:
    - Subjects have controlled brain metastasis, defined as metastases without radiographic progression for at least 4 weeks following treatment with stereotactic radiation and/or surgical treatment
    - Subjects must be off steroids without symptoms of CNS disease for at least 2 weeks prior to treatment
    - Subjects with signs or symptoms of brain metastasis are not eligible unless brain metastasis is ruled out by computed tomography or magnetic resonance imaging
- Patients with uveal or mucosal melanoma are excluded

4.2.2 Medical comorbidities

- Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders such as vitiligo, alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll

- Subjects with history of chronic liver disease, veno-occlusive disease, active alcohol abuse or illicit drug use other than marijuana or its derivatives
- Uncontrolled or significant cardiovascular disease including but not limited to the following
    - Myocardial infarction (MI) or stroke/transient ischemic attack (TIA) within the 6 months prior to consent
    - Uncontrolled angina within the 3 months prior to consent
    - Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, or poorly controlled atrial fibrillation)
    - History of other clinically significant cardiovascular disease (i.e., cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, poorly controlled deep venous thrombosis, etc)
    - Cardiovascular disease-related requirement for daily supplemental oxygen
    - Subjects with history of myocarditis, regardless of etiology
    - Baseline left ventricular ejection fraction (LVEF) <45%. ECHO/MUGA not required at screening unless history of significant cardiac history.
    - QTc prolongation > 500 msec
- Uncontrolled or significant pulmonary disease including but not limited to the following
    - Obstructive or restrictive lung disease requiring home oxygen
    - Hospitalization with chronic obstructive pulmonary disease (COPD) exacerbation within the last 6 months
    - History or concurrent condition of interstitial lung disease of any severity
    - Prior history of pneumonitis of grade II or higher, regardless of cause
    - Patients with diagnosis of obstructive sleep apnea (OSA) who are compliant with prescribed therapy (nocturnal O2, CPAP or BiPAP) are allowed on study
- Uncontrolled or significant infectious disease including but not limited to the following
    - Ongoing treatment for systemic bacterial, fungal or viral infection at screening
    - Subjects are not excluded for antimicrobial, antifungal or antiviral prophylaxis if other inclusion/exclusion criteria are met
    - Active cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection (i.e., subjects with known history of detectable viral load)
    - Infection with hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or human T-lymphotropic virus type 1

- Subjects with a positive hepatitis B surface antigen [HBsAg] or hepatitis C antibody [HCV Ab] will be excluded, unless documented treatment and resolution of hepatitis C treatment
    - Subjects with a positive hepatitis B core antibody (HBcAb) must have negative hepatitis B virus (HBV) deoxyribonucleic acid (DNA) assay to be eligible, must receive prophylaxis with entecavir (or equivalent) concomitant with duvelisib treatment, and must be periodically monitored for HBV reactivation by institutional guidelines. If unable to receive prophylaxis, then case will be discussed with investigators to determine eligibility.
- History of tuberculosis treatment within 2 years prior to enrollment

- Patients with history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent
- Ongoing chronic treatment with immunosuppressants (e.g. cyclosporine) or systemic steroids > 10mg of prednisone or equivalent once daily. Topical and inhaled steroids are allowed.
- Subjects with other uncontrolled medical conditions or other illnesses, laboratory findings or other factors that would, in the investigator's judgment, increase the risk to the subject associated with his or her participation in the study.

4.2.3 Prior therapies

- Patients who are receiving other investigational therapies will be excluded
- Patients who had a history of life-threatening toxicity related to prior immune therapy (e.g. anti-CTLA-4, anti-PD1 or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are well controlled an unlikely to be an issue with standard countermeasures (e.g. endocrine disorders managed by hormone replacement).
- Subjects with a history of grade II or greater immune-mediated colitis. Patients whose toxicity was clearly attributable to anti-CTLA-4 treatment (tolerated anti-PD1 after receiving anti-CTLA4) may still be allowed on trial.
- Subjects with a history of grade II or greater pneumonitis or transaminitis.
- Prior treatments with PI3K inhibitors
- Subject has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone therapy with curative intent, or treated in situ cervical cancer for which there is appropriate ongoing surveillance
- Subject had therapy with radiation, surgery or chemotherapy within 4 weeks prior to time of consent and/or has not recovered from adverse events to due to prior therapy. Subjects

should be adequately recovered from all toxicities, complications, or acute illnesses prior to starting investigational therapy.

- A maximum of three patients who have received talimogene laherparepvec (T-vec) as prior therapy will be allowed to enroll in the Phase II portion of the study. However, study-related biopsies must be performed at a disease site that was not injected with T-vec or adjacent to a T-vec injection site.

4.2.4 Other exclusion criteria

- Subjects who are unable or unwilling to take prophylaxis for Pneumocystis jirovecii, human simplex virus (HSV) or herpes zoster (VZV) at time of screening
- Subjects with known hypersensitivity to duvelisib and/or its excipients: Microcrystalline cellulose and magnesium stearate
- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness
- Subjects who are unable or unwilling to comply with restrictions and prohibited activities and treatments
- Subjects who are unable or unwilling to undergo venipuncture or tolerate venous access
- Subjects with prior surgery and/or chronic gastrointestinal dysfunction that may affect drug absorption, such as gastric bypass, gastrectomy, malabsorption, inflammatory bowel disease, chronic diarrhea
- Concurrent administration of medications or foods that are strong inhibitors of inducers of cytochrome p450 3A (CYP3A) within 2 weeks prior to study intervention. Duvelisib can increase exposure to CYP3A4 substrates: consider dose reduction of such substrates and monitor for signs of toxicities of co-administered sensitive CYP3A substrates See appendix A for list of example medications

4.3 Subject Recruitment

Participants will be enrolled at the UPMC Hillman Cancer Center . The trial will be advertised in weekly clinical trials bulletins to community oncologists who are a part of the UPMC Network, which includes over 60 locations in Pennsylvania and Ohio. Clinical staff at Hillman Cancer Center will be educated to identify potential participants. Each participant will be assigned to a clinical research coordinator (CRC) who will aid in ensuring study criteria are met and will serve as a point of contact for the participant.

4.4 Subject Withdrawal or Termination

4.4.1 Termination of Study Participation

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

- Disease Progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgement of the investigator
- Patient non-compliance
- Pregnancy
    - All WCBP will be instructed to contact the investigator immediately if they suspect pregnancy at any time during study participation
    - The investigator must immediately notify the IRB in the event of a confirmed pregnancy in a patient participating in the study
- Termination of the study by sponsor
- Loss of access to one or both investigational agents
- The maximum planned duration treatment of 12 months has been completed.

4.4.1 Duration of Follow Up and Retreatment

The period of acute toxicity and DLT evaluation is 28 days. Beyond that, AEs that arise while on treatment and within 4 weeks (+ 2 weeks) after discontinuation of treatment will be considered late toxicities

Patients will be evaluated by the treating physician after trial discontinuation, regardless of reason for discontinuation. Patients will be seen for an additional visit 4 weeks (+ 2 weeks) after study discontinuation to evaluate for additional adverse events and will continue to be followed until all adverse events have resolved or stabilized. The investigator and treating physician are responsible to ensure, within reason, that the patients receive appropriate treatment for their malignancy after trial discontinuation. Patients may be contacted for survival follow-up for up to 5 years. Survival follow-up will be performed approximately every 3 months. Patients terminated from the trial for adverse events will be followed until resolution or stabilization of the adverse event. Patients will have regular lab work and need documentation of CD4 T-cell subset >200 cells/µL prior to stopping PJP prophylaxis. We anticipate 3 years of data collection to determine duration of response.

4.4.2 Withdrawal of consent

Patients who request to discontinue study treatment will remain on the study and must continue to be followed for protocol-specified follow-up procedures and visits. A patient may elect to withdraw consent for further contact by study personnel, in which case he or she will be exempt from study procedures. Patients should notify investigator of such decisions in writing, whenever possible. The withdrawal of consent will be described in detail in the medical records, to clarify withdrawal from treatment and/or study procedures and/or post-treatment study follow-up.

4.4.3 Lost to Follow Up

Lost to follow-up describes inability to reach a subject after a minimum of 3 months of effort to contact such patient has been made. This includes documented phone calls, faxes, emails and also at least one registered mail letter during the 3-month period. Attempts to contact patients will be documented in the EMR. If a patient has died, permissible local information can be used to determine date and cause of death. Publicly available information may be used throughout the trial and the survival follow up period to determine survival status, in accordance with local law.

5.0 Clinical Trial Processes and Procedures

5.1 Study Site

The study will be conducted at the UPMC Hillman Cancer Center in Pittsburgh, Pennsylvania.

5.2 Screening and Pretreatment Evaluations

Screening and pretreatment evaluation will take place within 28 days from study initiation. The evaluation includes the assessments in the table below

Table 5.2 Screening and Pretreatment Evaluations

Evaluation	Description
Informed consent	A subject is only considered enrolled when an IRB/IEC approved informed consent form is signed and dated.
Medical Record Review	The patient will be interviewed and medical history will be reviewed in the EMR. Details of risk factors for potential events such as pulmonary or infectious complications should be evaluated. Toxicities from prior treatments and allergies will also be reviewed.
Inclusion/exclusion criteria	Criteria will be reviewed as well as compared with the medical record.
Pre-treatment tumor biopsy	Should be performed within 4 weeks of treatment, see laboratory manual for further details.

Vital signs	Includes height (at screening only), weight, blood pressure, temperature, heart rate, oxygen saturation, respirations, body mass index (at screening only).
Physical Examination	Physical exam should be performed at screening and within 3 days of treatment initiation.
Performance status	ECOG performance status will be evaluated and recorded.
Laboratory tests	See section 6.4 for tests to be performed at screening and at time of drug initiation. Labs are performed locally and may be collected within 3 days prior to dosing.
Pregnancy test	Urine or serum pregnancy test should be performed in all WCBP prior to study initiation.
Contraceptive use	Men and women will be evaluated for and counseled about highly effective contraceptive use.
Concomitant medications	Medication review will take place at screening and at each subsequent visit.
Assessment of signs and symptoms	Evaluation will be performed at screening and at each subsequent visit.
Monitor for adverse events	AEs are collected from the start of treatment including SAEs.
Diagnostic imaging	CT with contrast is the preferred modality and should include chest/abdomen/pelvis as well as other body areas based on the patients' disease. CT without contrast or MRI is also permitted.
Brain imaging	For patients with a history of brain metastases or concerning symptoms, brain imaging should be performed within 4 weeks of treatment. Brain MRI is preferred, but CT is also permitted. Brain MRI/CT will be required for all patients at screening.

5.3 Diagnostic Plan

Patients will be evaluated for safety and efficacy at regular intervals. Initial visits will begin 2 weeks after starting duvelisib to evaluate labs and for drug tolerance and will continue on 2 week intervals for 4 cycles. After this time if minimal/no toxicity is noted, visits may be spaced to every 4 weeks. Additional visits are permissible at the discretion of the treating physician. For example, additional visits for monitoring an AE or for concerns of clinical deterioration may be performed. Additionally, imaging for efficacy analyses will be performed at 12-week intervals. The first imaging evaluation may be performed before 12 weeks if there is clinical concern for deterioration or progression.

5.4 Procedure for Registration of Subjects

Registration will be conducted at UPMC Hillman Cancer Center. Patients will be enrolled at UPMC Hillman Cancer Center.

6.0 Trial Treatments, Evaluations, and Measurements

6.1 Medical Record Review

The medical record will be reviewed at screening for the following variables.

- Date of birth
- Height
- Weight
- Any history of disease, comorbidities
- Surgical history
- Pathology reports for melanoma diagnosis and any subsequent pathology
- Oncology history and treatment including disease response, and all toxicity

6.2 Medical History and Physical Examination

Describe the baseline evaluations including the medical history, physical examination, demographic characteristics (age, gender, race) and other information that will be collected.

- Demographics (screening only) – Age, gender (male, female, non-binary), race
- Medical history (screening only) – Comorbidities, surgical history
- Social history(screening only) – Alcohol, tobacco, recreational drugs,
    - For WCBP contraceptive use will be reviewed at each visit
- Physical exam (each visit) – Based on disease and signs and symptoms

6.3 Vital Signs

Vital signs will be measured at each visit. Vitals will be taken on digital machine and repeated manually when appropriate

- Weight – Recorded on digital scale in plain clothes, without shoes and jackets
- Height – Recorded on screening visit only, measured by stadiometer
- Blood pressure – Taken seated, using digital blood pressure cuff. Can be repeated with manual cuff if clinician feels necessary
- Heart rate – Taken when seated with digital heart rate monitor
- Respirations – Manually observed
- Temperature
- Oxygen saturation – Measured by digital pulse oximeter
- Body mass index – Calculated from height and weight

6.4 Laboratory Evaluations

Blood sampling will be performed with the laboratory tests below at each visit, with exceptions noted below:

6.4.1 Table: Clinical Laboratory Tests

Category	***Tests***
Hematology	Hemoglobin, hematocrit, platelet count, WBC with differential. CD4+ T cell subsets will be checked at screening and at study discontinuation and monthly until CD4+ threshold is reached.

Serum chemistries	Sodium, potassium, chloride, Co2, BUN, creatinine, calcium, glucose, LDH
Liver function tests	SGOT/AST, SGPT/ALT, total Bilirubin, alkaline phosphatase, albumin
Endocrine tests	TSH with free T4, T3 as applicable; Cortisol and ACTH if clinician concerned for hypophysitis
Infectious disease	HIV, Hepatitis C Ab, Hepatitis B Surface Ag, Hepatitis B Surface Ab, Hepatitis B Core Ab on screening only
Pregnancy test	Serum or urine βhCG testing on screening only

6.5 Pregnancy Testing

Women of childbearing potential (WCBP) is defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months. WCBP should have a urine or serum pregnancy test with minimum sensitivity of 25IU/L of either total hCG or βhCG. WCBP and all men will be counseled on highly effective contraceptive methods while on study. Contraceptive use will be reviewed at each study visit. If any concern for or chance for pregnancy, study drugs will be held until pregnancy test is performed. Patients will also be advised to stop study drug and discuss with treating team if concern for pregnancy.

6.6 Efficacy Evaluations

Efficacy evaluations will be based on tumor response on radiographic imaging, preferably CT scans. Baseline imaging will be obtained within 28 days prior to starting the trial. The same imagining modality will be used for subsequent imaging evaluation. Imaging will be reviewed by investigators for measurements. Measurements will be performed according to RECIST v1.1 [19] criteria for size response. Further details on imaging modalities allowed, performing measurements, definition of lesions and evaluation of response are available in section 12.0.

6.7 Safety Evaluations

Will be conducted according to the table below.

Table 6.7.1: Schedule of Study Procedures

Study Stage	**Screening**	**Intervention**								**Safety Follow-up**
Visit Number		**1**	**2**	**3**	**4-6**	**7**	**8-9**	**10**	**11-15**	**16+**
Study Days (+/- 1 week) For cycles 1-4, visits every 14days, then every 28 days	**-28 to 0**	**1-14**	**15-28**	**29-42**	**43-**	**85-98**	**99-126-168**	**169-196**	**197-364**	**365+**
Cycle Number		**C1D1 and 15**	**C2D1 and 15**	**C3D1 and 15**	**C4-6 Day 1 and C4D15**	**C7D1**	**C8-9D1**	**C10D1**	**C11-15D1**	**C16+D1**
Informed Consent/Assent	X									
Review Inclusion/Exclusion Criteria	X									
Demographics/Medical History	X									
Physical Examination	X	X	X	X	X	X	X	X	X	X
Vital Signs: BP, HR, RR, Temp O2	X	X	X	X	X	X	X	X	X	X
Height and BMI	X									
Weight	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X									
Assess contraceptive use	X	X	X	X	X	X	X	X	X	X
EKG	X									
Prior/Concomitant Medications – including PJP and VZV prophylaxis	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluation	X	X	X	X	X	X	X	X	X	X
Peripheral blood for correlatives (week 0, 4*, 12, at progression) *For phase I		X	X		X Cycle 4 only					
Diagnostic imaging (every 12 weeks +/- 7 days)	X				X		X		X	
Biopsy for correlatives (baseline, 12 weeks +/- 2 weeks)		X			X Cycle 4 only					
Dispense Investigational Product (IP)		X	X	X	X	X	X	X	X	
IP Compliance		X	X	X	X	X	X	X	X	
Adverse Events and Unanticipated Problems Assessment		X	X	X	X	X	X	X	X	X

6.8 Prophylactic Medications

In addition to the study drug, patients will be required to start PJP prophylaxis after registration and prior to initiation of duvelisib. Prophylaxis will be determined by the treating physician, but examples include trimethoprim-sulfamethoxazole, pentamidine, dapsone. Prophylaxis should start before cycle 1 of treatment. For patients with history of recurrent or recent HSV or VZV infections, antiviral prophylaxis may be considered, at the discretion of the treating physician.

7.0 Study Drug Supply and Administration

In this study, duvelisib and nivolumab are considered the study drugs. Information regarding handling and dispensing when applicable is provided below for clarification. Institutional protocols for nivolumab should be followed unless otherwise specified.

7.1 Drug Inventory Records

Study drug will be shipped to the investigational pharmacies and inventory will be performed by pharmacy staff upon receipt of drug. Discrepancies in initial inventory will be immediately documented and discussed with the shipping party SecuraBio. Study drugs will not be returned, and any unused, expired or damaged products will be destroyed on site per pharmacy protocol. Inventory will also be performed when the last subject has discontinued study drugs

7.2 Description

Duvelisib

Duvelisib is a white powder encapsulated in a gelatin capsule and is available as 15mg and 25mg capsules. It is packaged in an opaque high-density polyethylene bottle with induction sealed child resistant caps or thermoform blister strips with push through lidding packaged into wallets.

Nivolumab

Nivolumab is commercially available and supplied as single dose vials. Nivolumab solution contains mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate and water.

7.3 Packaging

Duvelisib will be supplied in 32-count blister cards containing either 15mg or 25mg capsules and will be labelled as such. The investigational medicinal product will be labeled with a single panel label which specifies protocol number, product name, contents of blister card, required storage conditions and manufacturer.

7.4 Receiving, Storage, Dispensing, and Return

7.4.1 Receipt of Drug Supplies

Duvelisib will be shipped from SecuraBio to UPMC Hillman Cancer Center Investigational Pharmacy under the direction of Brian Miller, PharmD to the address below.

Brian M. Miller, PharmD
UPMC Hillman Cancer Center
Manager, Investigational Drug Service
Ground Floor, AG40.3
5115 Centre Avenue
Pittsburgh, PA 15232
Phone: 412-623-3381
Fax: 412-623-0337
Pager: 412-958-1586
Email: millerbm2@upmc.edu

7.4.2 Storage

Duvelisib

The drug product blister cards should be stored at room temperature (15 to 30°C). The capsules are intended for oral administration.

Caution is required when handling duvelisib. Personnel dispensing duvelisib should follow standard procedures for the handling of investigational drugs, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, the individual should be treated for physical exposure (skin washing) or inhalation (move to fresh air, as necessary), and, if needed, seek medical advice.

When duvelisib capsules are dispensed for self-administration, they should only be handled by the study subject. After handling capsules, the subject should wash his or her hands thoroughly. If someone who is not enrolled in a duvelisib clinical trial swallows a capsule or inhales drug powder from a broken capsule, he or she should contact the relevant Investigator to determine whether safety monitoring is necessary. The Investigator should report the incident to Secura Bio, securabio@parexel.com . Capsules should always be stored in the container provided to the study subject.

Nivolumab

Nivolumab will be stored on site per package insert recommendations and in accordance with Hillman Cancer Center. Vials will be stored in refrigeration at 2C - 8C. Vials are protected from light until time of use by storing in original packaging.

7.4.3 Dispensing of Study Drug

Duvelisib

Study patients will receive a 4-week supply of duvelisib upon initiation of therapy and at each return visit until discontinuation of investigational agents. Pill counts will be performed at each 4-week visit. Patients will also be provided a pill drug diary (see Appendix B) to record pills taken, missed pills, damaged pills or other issues. This will be reviewed by the CRC at each visit.

Nivolumab

Nivolumab will be stored in the outpatient pharmacy and prepared by oncology pharmacy at the time of infusion. Nivolumab is stored as a clear to opalescent, colorless to pale-yellow solution in a single-dose vial at a concentration of 10mg/mL. It is diluted with either 0.9% sodium chloride solution or 5% dextrose for a final concentration not to exceed 10mg/mL or less than 1mg/mL in a volume less than or equal to 160mL. Dilutions will be made within 8 hours of infusion. Nivolumab will be administered by infusion over 30 minutes using a non-pyrogenic, low protein binding-in line filter.

7.4.4 Return or Destruction of Study Drug

Duvelisib

At each cycle, patients will return any unused duvelisib. Blister packs with unused duvelisib will have their contents destroyed on site per investigational pharmacy procedures

Nivolumab

Nivolumab is regularly stocked at the UPMC Hillman Cancer Center and Winship Cancer Institute and managed according to current pharmacy protocols.

7.5 Treatment Regimen

Duvelisib

Duvelisib is available in 15mg and 25mg dose capsules. Based on information provided in the Investigators Brochure from SecuraBio, in Phase I trials with duvelisib as monotherapy for lymphoma, the maximum tolerated dose of duvelisib was 75mg BID[20]. After further evaluation 25mg BID was chosen to be the preferred therapeutic dose in an effort to minimize toxicity without compromising efficacy. Given that duvelisib acts primarily as an immunomodulator, as opposed to being directly cytotoxic to tumor, doses were chosen to maximize T cell proliferation according to pre-clinical data[21]. These data suggest that doses lower than even 25mg BID may result in serum drug concentrations able to optimize T cell proliferation. Thus, doses lower than 25mg BID may be ideal for both maximizing immune changes in the TME and reducing patient toxicities. If significant toxicity is noted in the first 3 patients of each/any dose level, subsequent patients may be treated with a 2 week lead-in of duvelisib as monotherapy prior to the addition of nivolumab.

Dosing for the dose escalation phase will be as follows:

Table 7.5 Duvelisib Dose levels

Dose Level	Duvelisib Dose
Level I	15mg Daily
Level II	25mg Daily
Level III	25mg BID

Nivolumab

Nivolumab will be administered at a flat dose of 240mg every 2 weeks for the first 4 cycles, thereafter it then may be switched to 480mg every 4 weeks (+/- 1 week allowed without study deviation) if deemed appropriate by the treating physician in consultation with a given patient and his/her caretakers. Patients changed to the every 4 weeks schedule for nivolumab will continue to undergo close monitoring by the study team for potential toxicities, as deemed necessary and appropriate by the treating physician.

7.6 Dose Adjustments and Adverse Reaction Management

Dose adjustments for toxicity of duvelisib and nivolumab are detailed below and are excerpted from the duvelisib package insert and the nivolumab package insert[11,22]. Where appropriate, management guidelines for immune-related adverse events in patients receiving immune checkpoint therapy, from the American Society of Clinical Oncology (ASCO) Practice Guidelines has been included[23]. The table below is not comprehensive and clinicians should refer to the ASCO Practice Guidelines for more detailed management recommendations. When possible, biopsies should be pursued to help determine the study drug(s) responsible for a given toxicity.

Table 7.6 Dose Adjustments for Toxicity

Toxicity	**Adverse Reaction Grade**	**Recommended Management**
Nonhematologic Adverse Reactions		
Infections	Grade 3 or higher infection	**Duvelisib** - Withhold duvelisib until resolved - Resume at the same or reduced dose **Nivolumab** - Withhold nivolumab until resolved - Resume at same dose
	Clinical CMV infection or viremia (positive PCR or antigen test)	**Duvelisib** - Withhold duvelisib until resolved - Resume at the same or reduced dose - If duvelisib is resumed, monitor patients for CMV reactivation by PCR or antigen test at least monthly

Toxicity	Adverse Reaction Grade	Recommended Management
		Nivolumab - Withhold nivolumab until resolved - Resume at same dose
	PJP	**Duvelisib** - For suspected PJP, withhold duvelisib until evaluated - For confirmed PJP, discontinue duvelisib **Nivolumab** - Withhold nivolumab until resolved
Non-infectious diarrhea or colitis	Mild/moderate diarrhea (Grade 1-2, up to 4 stools per day over baseline) and responsive to antidiarrheal agents, OR Asymptomatic (Grade 1) colitis	**Duvelisib** - No change in dose - Initiate supportive therapy with antidiarrheal agents as appropriate - Monitor at least weekly until resolved **Nivolumab** **-** Continue nivolumab or hold until symptoms resolve
	Mild/moderate diarrhea (Grade 1-2, up to 6 stools per day over baseline) and unresponsive to antidiarrheal agents	**Duvelisib** - Withhold duvelisib until resolved - Initiate supportive therapy with systemic steroids - Monitor at least weekly until resolved - Resume at a reduced dose - Gastroenterology consultation, recommend endoscopy and biopsy **Nivolumab** - Withhold nivolumab until resolved - Resume at same dose - Support with systemic steroids, gastroenterology consultation, recommend endoscopy and biopsy
	Abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, OR Severe diarrhea (Grade 3, >6 stools per day over baseline)	**Duvelisib** - Withhold duvelisib until resolved - Initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids - Monitor at least weekly until resolved - Resume at a reduced dose

Toxicity	Adverse Reaction Grade	Recommended Management
		- For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue duvelisib **Nivolumab** - Withhold nivolumab until resolved - Resume at same dose - Systemic steroids, gastroenterology consultation and biopsy - If no improvement in 3-5 days, consider addition of infliximab
	Life-threatening, grade 4	**Duvelisib** - Discontinue duvelisib **Nivolumab** - Permanently discontinue nivolumab - Systemic steroids, gastroenterology consultation and biopsy - If no improvement in 3-5 days, consider addition of infliximab
Cutaneous reactions	Grade 1	**Duvelisib** - No change in dose - Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids - Monitor closely **Nivolumab** - Continue nivolumab - Support with topical emollients and/or mild-moderate potency topical corticosteroids
	Grade 2	**Duvelisib** - Consider holding duvelisib, restart at same dose - Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids - Monitor closely **Nivolumab** - Consider holding nivolumab until resolved - Resume at same dose once improved to grade 1

Toxicity	Adverse Reaction Grade	Recommended Management
		- Support with topical emollients and/or mild-moderate potency topical corticosteroids - Consider systemic steroids at 1mg/kg and taper over 4 weeks - Consider skin biopsy
	Grade 3	**Duvelisib** - Withhold duvelisib until resolved - Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids - Monitor at least weekly until resolved - Resume at reduced dose - If severe cutaneous reaction does not improve, worsens, or recurs, discontinue duvelisib **Nivolumab** - Hold nivolumab until resolved - Resume at same dose once improved to grade 1 - Support with topical emollients and high-potency steroids, dermatology consultation - Systemic steroids at 1-2mg/kg and taper over 4 weeks - Consider dermatology consultation - Skin biopsy recommended
	Grade 4	**Duvelisib** - Discontinue duvelisib **Nivolumab** - Hold nivolumab - Dermatology consultation to determine if appropriate to resume upon resolution - Systemic steroids administered IV -Skin biopsy recommended
	SJS, TEN, DRESS (any grade) or life-threatening skin toxicity	**Duvelisib** - Discontinue duvelisib **Nivolumab** - Discontinue nivolumab

Toxicity	Adverse Reaction Grade	Recommended Management
Pneumonitis without suspected infectious cause	Grade 1 – asymptomatic. If repeat imaging with progression	**Duvelisib** - Withhold duvelisib - If pneumonitis recovers to Grade 0 or 1, duvelisib may be resumed at same dose - If no improvement should treat as grade 2 **Nivolumab** - Withhold nivolumab until resolved - Resume at same dose - If no improvement, treat as grade 2
	Moderate (Grade 2) symptomatic pneumonitis	**Duvelisib** - Withhold duvelisib - Treat with systemic steroid therapy - If pneumonitis recovers to Grade 0 or 1, duvelisib may be resumed at reduced dose - If non-infectious pneumonitis recurs or patient does not respond to steroid therapy, discontinue duvelisib **Nivolumab** - Withhold nivolumab until resolved to grade 0-1 - Resume at same dose - Prednisone 1-2mg/kg/d, with long taper - Consider pulmonology consultation, bronchoscopy and biopsy, empiric antibiotics - Monitor closely, if no improvement in 2-3 days treat as grade 3
	Severe (Grade 3) or Grade 4life-threatening pneumonitis	**Duvelisib** - Discontinue duvelisib - Treat with systemic steroid therapy **Nivolumab** - Permanently discontinue nivolumab - Treat with high dose IV steroids, consider infliximab, empiric antibioitics - Pulmonary and infectious disease consultations and biopsy if able
ALT/AST elevation	3 to 5 × upper limit of normal (ULN) (Grade 2)	**Duvelisib** - Maintain duvelisib dose - Monitor at least weekly until return to < 3 x ULN

Toxicity	Adverse Reaction Grade	Recommended Management
		Nivolumab - Withhold nivolumab until resolved to grade 1 - Resume at same dose - Consider steroids if abnormality persists and clinical symptoms
	> 5 to 20 × ULN (Grade 3)	**Duvelisib** - Withhold duvelisib and monitor at least weekly until return < 3 x ULN - Resume duvelisib at same dose (first occurrence) or at a reduced dose for subsequent occurrence **Nivolumab** - Permanently discontinue nivolumab - Start steroids with methylprednisolone at 1-2mg/kg/d - Consider liver biopsy
	> 20 × ULN (Grade 4)	**Duvelisib** - Discontinue duvelisib - Systemic steroid treatment **Nivolumab** - Permanently discontinue nivolumab - Start steroids with methylprednisolone at 1-2mg/kg/d - Avoid infliximab - Hepatology consultation, consider liver biopsy
Hematologic Adverse Reactions		
Neutropenia	Absolute neutrophil count (ANC) 500 to 1000 cells/µL	**Duvelisib** - Maintain duvelisib dose - Monitor ANC at least weekly **Nivolumab** - Withhold nivolumab until resolved if it is felt to contribute to the neutropenia, and otherwise continue nivolumab as previously - Resume at same dose
	ANC less than 500 cells/µL	**Duvelisib** - Withhold duvelisib

Toxicity	Adverse Reaction Grade	Recommended Management
		- Monitor ANC until > 500 cell/uL - Resume duvelisib at same dose (first occurrence) or at a reduced dose for subsequent occurrence **Nivolumab** - Withhold nivolumab until resolved if it is felt to contribute to the neutropenia, and otherwise continue nivolumab as previously - Resume at same dose *If concern for auto-immune neutropenia, then hold nivolumab and follow practice guidelines
Thrombocytopenia	Platelet count 25K to < 50K cells/µL (Grade 3) with Grade 1 bleeding	**Duvelisib** - No change in dose - Monitor platelet counts at least weekly **Nivolumab** - Withhold nivolumab until resolved - Resume at same dose
	Platelet count 25K to < 50K cells/µL with grade 2 bleeding OR platelet count <25K cells/µL (Grade 4)	**Duvelisib** - Withhold duvelisib - Monitor platelet count until > 25K cells/uL and resolution of bleeding if applicable. - Resume duvelisib at same dose (first occurrence) or resume at a reduced dose for subsequent occurrence **Nivolumab** - Withhold nivolumab until resolved - Resume at same dose *****If concerned for autoimmune thrombocytopenia, hold nivolumab and follow practice guidelines

Table 7.7 Dose Reductions for Duvelisib

Initial Dose	Decreased Dose
15mg Daily	None

25mg Daily	15mg Daily
25mg BID	25mg Daily

Note: If patient is on dose level 1, 15mg daily and has a dose interruption, duvelisib will be resumed at same dose. If patient subsequently requires another dose interruption at this level for the same toxicity, duvelisib should be discontinued. No more than 2 dose reductions for the same side effect are allowed for any patient, irrespective of starting dose.

7.7 Method of Subject Assignment to Treatment Groups

The study is a single arm, non-randomized trial. Patients will first be allocated to Phase I dose escalation cohorts at each dose level listed in Table 7.5. Patients will be enrolled and allotted to the next available opening for each dose cohort as specified. For the Phase II dose expansion cohort, all patients will be enrolled at the recommended phase II dose.

7.8 Preparation and Administration of Study Drug

Duvelisib

Duvelisib is provided in capsules with no additional preparation. The drug will be stored at the investigational pharmacy and dispensed to the patient. The medication can be taken with or without food. If a dose is missed by less than 6 hours, the dose should be taken immediately. If it has been more than six hours, the dose will be skipped and the next dose will be taken at the scheduled time.

Nivolumab

Nivolumab will be prepared per package insert by pharmacy staff. Nivolumab vial is diluted with either 0.9% sodium chloride solution or 5% dextrose for a final concentration not to exceed 10mg/mL or less than 1mg/mL in a volume less than or equal to 160mL. Dilutions will be made within 8 hours of infusion. Nivolumab will be administered by infusion over 30 minutes using a non-pyrogenic, low protein binding-in line filter.

7.9 Subject Compliance Monitoring

Compliance with duvelisib will be monitored with pill count at each 4-week visit. Patients will also be provided a pill drug diary (see Appendix B) to record pills taken, missed pills, damaged pills or other issues. This will be reviewed by the CRC at each visit. If there is significant non-compliance across multiple visits that is not due to adverse effects or other reasonable events, patient will be discontinued from the study. This will ultimately be at the discretion of the investigator (in discussion with the treating physician as appropriate).

7.10 Prior and Concomitant Therapy

7.10.1 Prohibited and/or Restricted Treatments

- Duvelisib is metabolized by CYP3A4
    - Medications and foods that are strong CYP3A inducers will decrease the area under the curve (AUC) of duvelisib and should therefore be avoided.
    - Medications that are strong CYP3A inhibitors will increase the AUC of duvelisib and should be avoided. If unavoidable, the investigator may permit dose reduction of duvelisib to 15mg BID in cases when there is no alternative to a concurrent CYP3A inhibitor.
    - Medications that are substrates for CYP3A that are co-administered with duvelisib should also be avoided as the exposures to these medications may increase in presence of duvelisib. Investigator should consider decreasing doses of these substrates as appropriate.
    - Ultimately dose adjustments and medication adjustments are at the discretion of the investigator.
    - See Appendix A for a list of medications
- Immunosuppressive agents unless they are utilized to treat an AE
- Concurrent administration of any anticancer therapies (investigational or approved) with the exception of subjects in the survival period of the study
- Use of allergen sensitization therapy
- Use of recreational drugs other than alcohol or tobacco. Marijuana for medical use is permitted.
- Palliative radiation treatment is not recommended while on combination therapy. If radiation is deemed necessary, duvelisib should be held for 1 week prior and 2 weeks after therapy. Any radiation-related AEs should resolve to grade 1 or less prior to resuming treatment.

7.10.2 Permitted therapy

- Inactivated influenza vaccination is permitted.
- Topical, ocular, intra-articular, intranasal and inhalational corticosteroids are permitted.
- Oral corticosteroids for premedication prior to scans are permitted.
- Systemic corticosteroids are permitted for treatment of AEs.
- Use of growth factors are permitted.
- Palliative care evaluation for symptom control can be offered to any patient on trial.
- For patients requiring surgery other than treatment-related biopsies, duvelisib should be held for 2 weeks before and after if possible. Duvelisib may be restarted sooner than 2 weeks, in consultation with the attending surgeon if the subject recovers and surgery-related AEs have decreased to grade 1 or baseline.

7.11 Blinding of Study Drug

This study consists of a single treatment arm, and therefore will not be blinded.

8.0 Safety and Adverse Events Assessing, Recording, and Reporting

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with study participation whether or not considered related to the investigational product.

The causal relationship to both/either study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

- Unrelated: There is no temporal relationship to study drug; there is a reasonable causal relationship to another drug product, concurrent disease, or circumstance.
- Unlikely related: There is only a temporal relationship to study drug, but not a reasonable causal relationship between the investigational product and the AE.
- Possibly related: There is a reasonable possibility that the drug caused the adverse event. The investigator can provide a rationale or evidence to suggest a causal relationship between the study drug and the adverse event other than just a temporal relationship.
- Probably related: There is a reasonable causal relationship between the study drug and the AE, and/or the event responds to dechallenge.
- Definitely related: There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible.

8.1 Dose Limiting Toxicities

Acute dose limiting toxicities (DLTs) are defined as any of the following AEs and laboratory abnormalities considered possibly, probably, or definitely related to study treatment that occur any time from the initial dose of duvelisib in combination with nivolumab through day 28 of treatment. Toxicities occurring from day 29 through 28 days after completion of treatment will be considered late toxicities. Only acute DLTs will be considered for decisions to continue enrollment at the current dose level or proceed to the next dose level. Acute and late toxicities will be considered when deciding on the RP2D and will be discussed in monthly Data Safety Monitoring Board (DSMB) meetings. See Section 15.0 for further details.

Severity of adverse events will be graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). A goal of ≤ 33% DLTs at each dose level will be considered acceptable.

Whenever possible, biopsies are recommended if they can be done safely to help determine between immune-related and other etiologies of toxicity, particularly for rash and colitis. Biopsies for elevated liver enzymes and/or for pneumonitis should be considered if deemed feasible and safe in the context of risk:benefit evaluation. General criteria for consideration of biopsy:

- Diarrhea/colitis
    - Biopsy proven grade ≥3 immune-related colitis
    - Diarrhea of grade ≥3 that does not respond to treatment with steroids within 5 days
- Pneumonitis
    - Immune-related pneumonitis grade ≥2

  - Any grade ≥3 pneumonitis
- Hematologic abnormalities
  - Neutropenia grade 4 despite holding duvelisib for 7 days
  - Thrombocytopenia grade ≥3 with bleeding
  - Thrombocytopenia grade 4
- Other immune-related toxicities
  - Any grade ≥3 toxicity that does not respond to treatment within 5d
- For the remainder of non-hematologic toxicities, grade ≥3

8.2 Serious Adverse Events

8.2.1 SAE Definitions

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above. (Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event.

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE (e.g. contamination of drug product). Although pregnancy, overdose, new cancers, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE (see below for reporting details).

The following hospitalizations will not be considered SAEs in this study:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission, unless otherwise deemed an important medical or life-threatening event
- Elective surgery, planned prior to signing study consent
- Admissions as per protocol for a planned medical/surgical procedure

- Routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- Medical/surgical admission not intended to remedy ill health and/or planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

8.2.2 Serious Adverse Event Collection and Reporting

All events meeting the definition of a serious adverse event should be reported according to the departmental SAE checklist and SAE form. SAEs will be collected from a subject's first dose of study medication until 100 days after the last dose of study medication. The initial SAE form should be sent to the following within 24 business hours / 1 business day of the Principal Investigator becoming aware:

1. John M. Kirkwood: kirkwoodjm@upmc.edu
2. crssafetysubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met.
4. SecuraBio, securabio@parexel.com and dlitwak@securabio.com

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections B and C of the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drugs
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up reports:

Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or by creating supplemental summary information and submitting it as follow-up along with a copy of the original departmental SAE form.

8.4 Nonserious Adverse Events

A nonserious adverse event is an AE not classified as serious. The collection of non-serious AE information should begin upon initiation of study drugs. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, and/or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment, as appropriate.

8.5 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE Case Report Form (CRF) page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that whenever possible, the clinical rather than laboratory term will be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

8.6 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with study agent, the participant will immediately be discontinued from the study therapy, and followed for safety and efficacy evaluation as possible. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The pregnancy will be recorded on the case report form (CRF) and reported by the Investigator to the Institutional Review Board (IRB).

Any pregnancy that occurs during a clinical study with an investigational medicinal product must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, and/or any pregnancy- or childbirth-related and/or newborn complications. The pregnancy should be recorded on a case report form (CRF) and reported by the Investigator to Secura Bio. Pregnancy follow-up should be reported using the Pregnancy Follow up Form. Any SAE experienced during pregnancy must be reported.

The Investigator should counsel any pregnant subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Additionally, the pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Monitoring of the subject should continue at least until delivery or until the pregnancy has terminated.

If, while on study treatment a male study participant's sexual partner becomes pregnant by said study participant, the pregnancy and pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

8.7 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.

8.8 Potential Drug Induced Liver Injury

Whenever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria below, must be reported as SAEs (see Section 8.1.1 for reporting details).

Potential drug induced liver injury is defined as:

- AT (ALT or AST) elevation > 3 times upper limit of normal (ULN) AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.0 Safety Information: Sponsor and Investigator Responsibilities

9.1 Review of Safety Information: Sponsor Responsibilities

The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from domestic and foreign regulatory authorities and reports of domestic and foreign commercial marketing experience.

Note : The requirements of the manufacturer for the reporting of suspected adverse drug reactions to the FDA differ from the requirements of the sponsor Investigators (see below and Investigator Responsibilities on the O3IS website) for the reporting of adverse events. Sponsor-investigators of IND applications are subject to compliance with both the adverse reaction reporting requirements of the Sponsor and the adverse event reporting requirements of the Investigator.

9.2 IND Safety Reports

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under Sections 9.2.1 to 9.2.4 below. In each IND safety report, the sponsor must identify all IND

safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

9.2.1 Serious and unexpected suspected adverse reaction

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.
-

9.2.2 Findings from other studies

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under section 1.5.1), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

9.2.3 Findings from animal or in vitro testing

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

9.2.4 Increased rate of occurrence of serious suspected adverse reactions

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

9.3 Submission of IND safety reports

The sponsor must submit each IND safety report in a narrative format or on Form FDA 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). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a Form FDA 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. 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 or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor 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.

9.3.1 Unexpected fatal or life-threatening suspected adverse reaction reports

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

9.3.2 Reporting format or frequency

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

9.3.3 Investigations of marketed drugs

A sponsor of a clinical study of a drug marketed and/or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements.

9.3.4 Reporting study endpoints

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under Section 1.7 third bullet of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between a study drug and the event (e.g., death from anaphylaxis), such event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

9.4 Follow-up

The sponsor must promptly investigate all safety information it receives.

Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, eg., "Follow-up IND Safety Report."

If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under IND safety reporting guidelines is, in fact, so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after such determination is made.

9.5 Disclaimer

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

9.6 Reporting Adverse Events to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) associated with the investigational drug or study treatment(s); 2) serious; and 3) unexpected. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) possibly, probably or definitely attributed to the investigational drug(s) or study treatment(s); 2) fatal or life-threatening; and 3) unexpected, will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

9.7 Other Safety Considerations

Any significant worsening of condition noted during interim or final physical examinations, electrocardiograms, radiologic exams, or any other assessment required or not required by protocol should be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

10.0 Data Safety Monitoring Plan

10.1 Study Oversight

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events

- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

Minutes from the disease center DSMB meetings are made available to those who are unable to attend in person.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria Version 5.0. All study treatment associated adverse events that are serious, at least possibly related to study drugs, and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue or close the trial to accrual are also to be discussed during DSMB meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission, and the study may be terminated.

All study data reviewed and discussed during DSMB meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed bi-annually.

Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

10.2 Data Handling and Record Keeping

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. Source Data are the clinical findings and observations, laboratory and test data, and other information contained in Source Documents. Source Documents are the original records including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation

checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

11.0 Management of Adverse Events with Duvelisib

Management of adverse events often depends on clinical context. From prior experience, suggestions regarding duvelisib toxicities are below per product insert and investigator's brochure. Please refer to section 7.6 for information on managing AEs with nivolumab and duvelisib. Please also refer to published guidelines from ASCO for management of immune-related adverse events[23].

11.1 Infections

Duvelisib carries a black box warning regarding infection risk, most often URI and pneumonia. The median time to infection was 3 months, with the majority occurring prior to 6 months. For any grade 3 or higher infection, duvelisib must be held. For patients with suspected PJP, duvelisib should be held and permanently discontinued if PJP is confirmed. PJP prophylaxis is required for all patients and should continue until CD4+ T cell count is > 200 cells/µL or for 14 days after last dose of duvelisib. For patients with CMV reactivation or infection, drug should be held until resolved. If resumed, patients should be monitored at least monthly for reactivation and prophylaxis should be considered. For other infections, recommended dose reductions are listed in Table 7.5.

11.2 Diarrhea/Colitis

Diarrhea and colitis were also seen frequently. Median time to onset was 4 months, with the majority of cases occurring before 8 months, and symptoms could be prolonged (median duration 0.5 months). For grade 1-2 diarrhea or asymptomatic colitis, initiate supportive care with antidiarrheal agents, continue medication and monitor weekly until resolution. If unresponsive to antidiarrheals then duvelisib should be held and enteric steroids such as budesonide should be started. Duvelisib may then be restarted at a reduced dose as deemed clinically appropriate by the treating physician.

For subjects with abdominal pain, stools with mucus or blood, or severe diarrhea, hold duvelisib and start systemic or enteric steroids. If possible, a colonoscopy and work-up for immune-mediated colitis should be performed. Restart duvelisib at a reduced dose upon resolution of symptoms to less than or equal to CTCAE Grade 1. For recurrent events, duvelisib should be permanently discontinued.

11.3 Cutaneous Reactions

Cutaneous reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) occurred with duvelisib. Median time to onset was 3 months with a median event duration of 1 month. Patients often presented with pruritic, erythematous or maculo-papular rash. Subjects should report rashes, sores, ulcers on skin, lips, mouth, blisters, rash, fevers promptly. Subjects with Grade 1-2 reactions should continue duvelisib at the current dose, supported with

emollients, anti-histamines, topical steroids and close monitoring. If reaction is more severe, duvelisib should be held, and steroids (topical and systemic) and antihistamines should be given. Patients should be monitored at least weekly. Duvelisib should be discontinued if cutaneous reactions recur. If subjects experience, SJS, TEN, or DRESS of any grade, discontinue duvelisib.

11.4 Pneumonitis

Serious cases of pneumonitis occurred with duvelisib. Median time to onset of any grade was 4 months with the majority of cases occurring prior to 9 months and with a mean duration of event of 1 month. Subjects should report new cough or shortness of breath. Patients who have pulmonary signs and symptoms such as cough, dyspnea, hypoxia, radiologic changes, or decline of >5% in oxygen saturation should have duvelisib held and be evaluated. Infectious etiologies should be treated as above. Systemic steroids should be considered. For moderate disease, reduced duvelisib doses can be considered. If non-infectious pneumonitis recurs or does not respond to steroid therapy, discontinue duvelisib. For severe or life-threatening pulmonary disease, duvelisib should be permanently discontinued.

11.5 Neutropenia

Patients with hematologic conditions treated with duvelisib frequently developed neutropenia. CBC with differential should be checked at least every 2 weeks during cycle 1, and more frequently for those with ANC < 1000 cells/µL. Withhold duvelisib if ANC < 500 cells/µL, monitor weekly and resume at same dose of the first occurrence or at a decreased dose for subsequent occurrence. Duvelisib can be resumed when ANC>100 is reached in the absence of signs of infection. G-CSF may be used per ASCO guidelines.

12.0 Assessment of Disease

Patients will be evaluated for response every 12 weeks while on study. If clinicians have clinical concerns, evaluation by imaging may be done as there is clinical or subjective evidence of progression before 12 weeks, with imaging resumed on a Q 12-week imaging cycle. Assessments for response and progression will be carried out according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 [19] which are reproduced and paraphrased in the sections below. Following RECIST criteria, changes in the largest diameter of the tumor lesions and the shortest diameter for malignant lymph nodes will be used.

12.1 Definitions

- Evaluable for toxicity – All patients are evaluable for toxicity upon initiating treatment of nivolumab and duvelisib. For the phase I portion, patients should have taken 75% of duvelisib pills according to pill diary and pill counts.
- Evaluable for objective response – Patients who have measurable disease at baseline and have their disease re-evaluated at 12 weeks of therapy will be evaluable for response. Patients who

exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

- Evaluable non-target disease response – Patients who have baseline lesions that are evaluable but do not meet the definitions of measurable disease have received at least one cycle of therapy and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

- Measurable disease – Tumor lesions that can be accurately measured by the longest diameter in the plane of measurement with a minimum size of 10mm by CT scan, 10mm caliper measurement on clinical exam, 20mm by chest x-ray. CT scan thickness should be no greater than 5mm. Tumor measurements must be recorded in mm or decimal fractions of centimeters.

- Malignant lymph nodes – To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when measured by CT scan. Only the short axis will be measured and followed.

- Non-measurable disease – All other lesions, including small lesions < 10mm and lymph nodes < 15mm are considered non-measurable disease. Other non-measurable disease examples include ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly that don't correlate to CT or MRI, bone lesions, inflammatory breast disease.

- Target lesions – When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (max two per organ) representative of all involved organs should be recorded and measured at baseline. If only 2 organs are involved, the maximum number of target lesions is four. Target lesions should be selected based on lesions with the longest diameter, be representative of involved organs, and should lend themselves to repeated measurements. If lesions do not fulfill these requirements, the next largest lesion that can reproducibly be measured should be selected.

  A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then only the short axis will be added. The baseline sum will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- Non-target lesions – All other lesions or sites of disease including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as present, absent or unequivocal progression.

Other considerations

- Lesions that meet radiographic criteria for simple cysts should not be considered malignant lesions, because 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, they are preferred for selection as target lesions.

- Lesions situated in a previously irradiated area, or an area subjected to other loco-regional therapy, are usually considered non-measurable unless there has been demonstrated progression in the lesion.

12.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in the metric system using ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions - Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- Conventional CT and MRI – CT is the preferred modality for evaluating lesions. By RECIST, the measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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).

  MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Ideally, the same type of scanner should be used and the same image acquisition protocol should be followed as closely as possible across all scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT - The low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of sufficiently comparable diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- FDG-PET - While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
    - No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
    - FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the radiographic protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that such approaches may lead to false positive CR's due to limitations of FDG-PET resolution/sensitivity.
- Ultrasound – Ultrasound examinations are not reliably reproduced for review and are operator dependent. As such, it cannot be guaranteed that the same techniques and measurements are taken on each evaluation, and ultrasound should not be routinely used as a method of lesion measurement. If new lesions are identified by ultrasound, they should be verified by another modality as described above.
- Cytology and Histology - These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.3 Response Criteria

12.3.1 Evaluation of target lesions

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

- Partial response (PR) – At least a 30% decrease in the sum of 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).

  Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
- Stable disease (SD) - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.3.2 Evaluation of non-target lesions

- Complete response (CR) – Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
- Non-CR/Non-PD – Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive disease (PD) – Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

12.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence. The reference for progressive disease is the smallest measurement since treatment initiation. The best response assignment will depend on the achievement of both measurement and confirmation criteria, as seen in the tables below, excerpted from the RECIST v1.1 manuscript [19].

For patients with measurable disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document objective progression even after discontinuation of treatment.

For patients with non-measurable disease (i.e. non-target disease)

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

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

12.3.4 Duration of response

- Duration of overall response – The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented. The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

12.3.5 Progression-Free survival

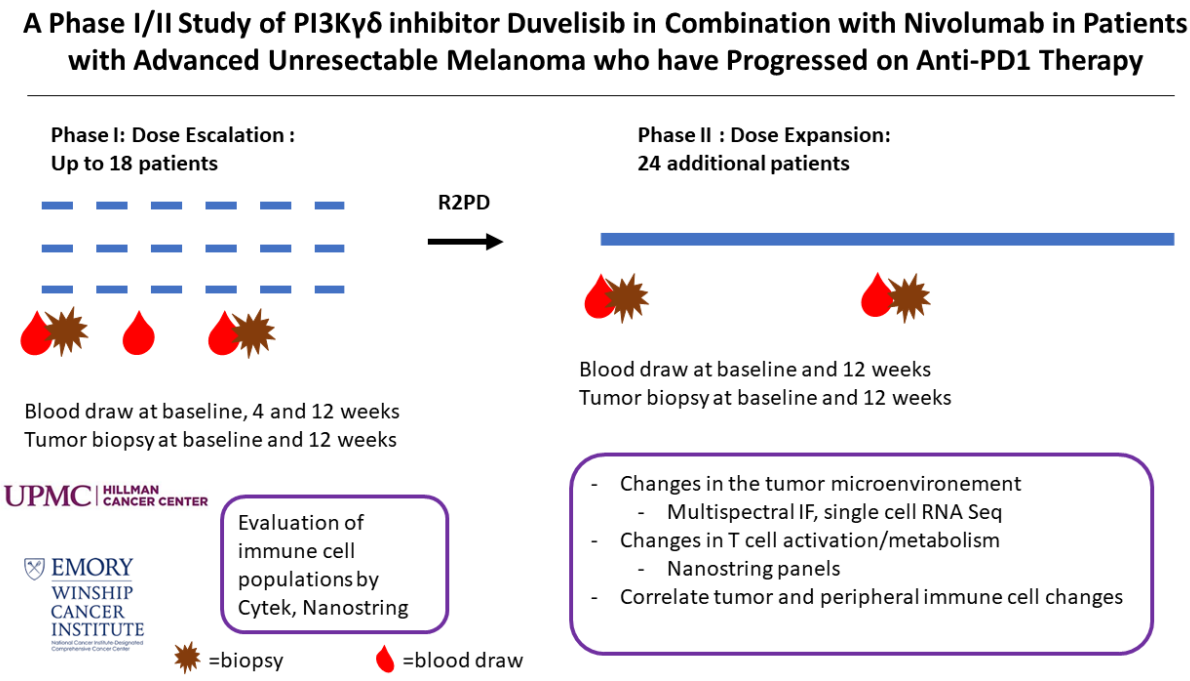
- Progression-free survival defined as the time between the date of first treatment and the date of first documented progression or death due to any cause, whichever occurs first.

12.3.6 Overall survival

- Overall survival is defined as the time between the date of first treatment and the date of death due to any cause. Patients who are alive will be censored at the time of the last follow-up.

13.0 Tissue and Blood Collection and Biomarker Studies

Correlative studies will be carried out at UPMC Hillman Cancer Center by Dr. Tullia Bruno and at Emory Winship Cancer Institute in the laboratory of Dr. Edmund Waller. The majority of samples will be processed at and preserved at UPMC. All samples will be banked at UPMC as the central site of the study. See schema below regarding time of patient samples:



13.1 Phase I Correlative Studies

For the phase I dose escalation study, patients will have blood drawn and tumor biopsies at baseline and again after 12 weeks of treatment. These time points were chosen based on prior experience with checkpoint inhibitors and duvelisib, as well as for patient convenience (monthly visits) and to correlate

with efficacy evaluations (every 12 weeks). We will also conduct a peripheral blood draw at 4 weeks. Previous analysis of peripheral blood samples in melanoma patients being treated with checkpoint inhibitors have demonstrated expansion of CD8+ T cells detectable as early as 4 weeks[24]. Further, changes in peripheral cytokine levels have been seen as early as day 8 in lymphoma patients treated with duvelisib[14]. While evaluation at 4 or 12 weeks may not capture the "peak" of change with this therapy, we anticipate alterations attributable to therapy will be observed and can be correlated with outcomes in a clinically meaningful way.

We will use CyTek flow cytometry to evaluate peripheral blood mononuclear cells (PBMCs) and tumor-infiltrating cells from patients treated with each dose level of duvelisib. Several of the immune cell types that correlate with anti-tumor response, including CD8+ T cells, B cells and MDSCs, have been shown to be altered with PI3Kγ or PI3Kγδ inhibition [15],[14]. In particular, CD8+ T cells are often cytotoxic to tumor cells, and increased CD8+ TILs correlate with improved survival in patients with melanoma[25]. Proliferation of intratumoral CD8+ T cells after immunotherapy was shown to correlate with anti-tumor response[24]. The ideal RP2D will demonstrate proliferation and activation of CD8+ TILs. We will also examine CD8+ and CD4+ T cell subsets, and markers of activation and exhaustion by flow cytometry. Additional cell types of importance in the tumor microenvironment will also be queried, including T regulatory cells, B cells and monocyte precursors in peripheral blood and tumor biopsies.

Further, we will use RNA from PBMCs to evaluate the immune profile of patients prior to and on therapy with duvelisib with the Nanostring platform. This includes a panel of 770 genes associated with inflammation and autoimmune disease. Nanostring signatures will be correlated with any clinical toxicities observed, as a way to evaluate possible biomarkers of toxicity.

Along with toxicity data from the clinical portion of the phase I trial, this data will also help inform the recommended phase 2 dose of duvelisib. Ideally, the chosen dose will minimize patient toxicity while maximizing anti-tumor immune profile (high T effector cells, low T regulatory cells, low myeloid-derived suppressor cells). Observations from this portion of the study will be used to focus studies in the Phase II portion of exploratory analysis.

13.2 Phase II Correlative Studies

Patients enrolled in the phase II cohort will have blood draws at baseline and 12 weeks on treatment. Tumor biopsies will be performed at baseline and after 12 weeks on treatment. For the phase II correlative studies, we will use a multi-level approach to evaluate the interplay of the immune system with the tumor microenvironment (pre-treatment, post-treatment with duvelisib, and at progression). Studies will be focused on answering several questions pertinent to the mechanism of action of duvelisib and resistance to PD1 therapy.

First, we will characterize T cell responses to duvelisib. In combination with data from flow cytometry in Phase I studies, and we will add more detailed studies to characterize T cell activation through functional assays. We will also use Cytek to evaluate markers of T cell exhaustion, including LAG3, TIM3, TIGIT, CD38, bcl2 and HLA-DR. This data will be corroborated with a Nanostring T cell characterization panel which evaluates RNA expression of pathways involved in T cell activation, exhaustion, persistence, and metabolism. T cell metabolism will also be evaluated by an assay for mitochondrial mass.

Second, we will evaluate changes in the tumor microenvironment while on duvelisib using tumor biopsy samples. We will use flow cytometry to evaluate immune populations within tissues and evaluate whether these reflect changes in the periphery. Multispectral immunofluorescence will be used to evaluate the spatial relationship and interplay between immune populations, particularly between pro-inflammatory and anti-inflammatory populations. Presence and alterations of B cells in biopsy samples are of particular interest, given the known activity of duvelisib on B cells and the prognostic implications of B cells and tertiary lymphoid structures.

Finally, global changes in the tumor microenvironment will be evaluated by single cell RNAseq. For these studies, fresh tissue from 9 patient's tumors with matched peripheral blood samples will be used. In addition to providing important data regarding alterations associated with duvelisib, these samples will also be informative regarding acquired resistance to anti-PD1 therapy.

The following techniques will be used:

Single cell RNAseq: We will perform single cell RNAseq on patient PBL and TIL pre and post treatment to assess effects on all immune populations for 9 patients who demonstrate a standard pattern of anti-PD1 resistance. This will generate a robust data set that could give us information on differences that would not be detected by the above methods. Further, because we will utilize the 10x 5' system, we could ideally get both RNA signatures as well as paired TCR and BCR sequences from these patients.

Cytek Aurora (26 parameter flow cytometry): Via the UPMC Hillman Cancer Cytometry Facility, we will utilize the Cytek Aurora to analyze changes in immune cells pre and post therapy. We will be able to analyze samples with three comprehensive, 26 parameter panels which will assay general changes in the immune infiltrate (unbiased, analyzing all populations) as well as specific changes in CD8+ T cells, Tregs, macrophages and B cells, given the specific effects of this therapeutic regimen described in the literature.

Multispectral IF: We will pair our above flow cytometric analyses with locational studies on the immune infiltrate via Vectra Polaris multispectral IF (7 colors in total). Further, we will expand our panels to an Akoya CODEX system able to assay 30+ biological correlates on a single piece of paraffin embedded tissue.

In vitro functional assays: The Bruno lab has developed micro-sized functional assays that can assess CD8+ T cell, Treg, macrophage and B cell function pre and post treatment, which will be used to analyze Study specimens.

Nanostring: RNA Analysis of 770 gene panel for evaluation of multiple aspects of T cell biology, including activation, metabolism and exhaustion will be employed. A separate panel will be used to evaluate RNA signatures in toxicity which includes genes involved in inflammation and autoimmunity.

14.0 Statistical Methods

This clinical trial includes a phase I dose-finding study and a phase II efficacy study. The phase I portion requires up to 18 patients. The phase II portion needs an additional 24 patients (6 carried over from phase I using the RP2D level) for a study total of up to 42 patients and a phase II total of 30 patients. With 2 centers, each accruing 1-2 patients per month, we anticipate completing enrollment in 18 months.

14.1. Phase I Portion of the Study

14.1.1. Study Design

The primary objectives of the phase I portion are to determine the maximum tolerated dose (MTD) of duvelisib when combined with anti-PD1 therapy nivolumab, and to decide on its recommended phase II dose (RP2D). Dose escalation will follow the decision rule in the following table, using the three dose levels defined in Section 7.5 (i.e., 15mg Daily, 25mg Daily, and 25mg BID), starting from the lowest dose. The MTD is defined to be the highest dose level at which no more than 1 of 6 treated patients experiences a DLT (DLT is defined in Section 8.1). Cohorts of three to six patients each will be treated at a dose level. Patients should have taken 75% of pills to be included in analysis of their respective cohort, as assessed through pill counts and pill diary. Only toxicities observed during the first treatment cycle will affect dose escalation. Late toxicities observed will be discussed at monthly data safety monitoring boards to determine if dose adjustments should be made.

After MTD is determined, we will decide on RP2D based on an overall consideration of DLT data, as well as immune cell profiling with laboratory correlatives. For this purpose, our decision rule in the following table is a slight modification of the standard “3+3” to make sure 6 patients will be accrued at each safe dose in order to have enough patients for laboratory evaluations. RP2D should not be higher than MTD. If the MTD is not reached, R2PD will be decided based on safety data from acute and late toxicities as well as immune cell profiling data by the investigators (see section 13.1).

DECISION RULES FOR DOSE LEVEL ESCALATION

No. of patients with DLT's at this dose level	No. of patients treated at this dose level	Action
≤1	3	Treat 3 more patients at this dose level.
≤1	6	Treat 3 patients at the next higher dose level (or if at the highest level, stop the trial, and declare the dose at this level to be the MTD).

>1	3 or 6	Stop dose escalation. The previous dose is defined as MTD.

Cohorts need not be completed if clear decisions can be made on the basis of an incomplete cohort. For example, if the first two patients in an intended cohort of three experience DLT's, escalation can be stopped without accruing the third member of the cohort.

14.1.2. Sample Size/Accrual Rate

The number of patients accrued to the study will depend on the MTD. No more than 18 evaluable patients will be treated in the phase I portion. An evaluable patient is defined as one who either a) receives at least one dose the study drug and/or suffers DLT, or b) completes a treatment cycle and has no DLT observed during this cycle.

14.2. Phase II Portion of the Study

The study primary endpoint will be analyzed once the last patient on treatment is on study for 18 weeks.

14.2.1. Study Populations:

Safety population: patients who received any amount of the study regimen.

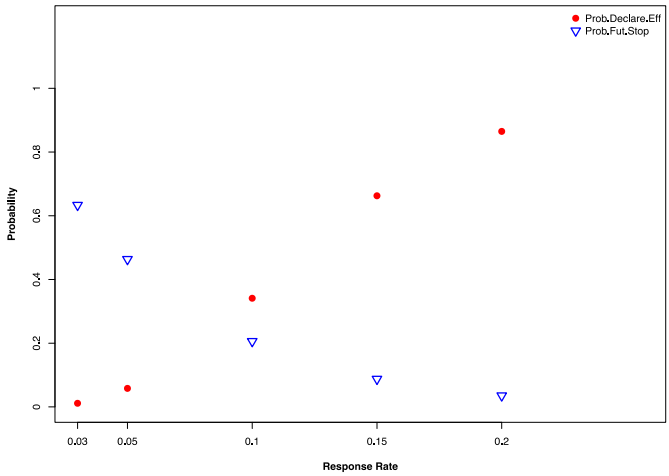
Efficacy population: patients who received at least one cycle of the treatment and at least one efficacy evaluation.

14.2.2. Study Design and Interim Analysis

The primary objective of this study is to evaluate the overall response rate to the combination of anti-PD1 therapy and duvelisib. We would consider the combination futile and not worth further study if the response rate is 5% or lower. We will monitor the efficacy of the regimen using a Bayesian method. We will consider the trial futile and propose stopping if the posterior probability that response rate is <5% given the observed data is >70%. A non-informative prior of Beta (0.5, 0.5) is used for the true response rate and the cohort size is set to be 5. The futility early stopping boundaries are given in the following table:

# Patients (inclusive)	# Responses (inclusive) are considered futile	Actions
5	Never stop with this many patients	
10	Never stop with this many patients	
15	0	Early stopping
20	0	Early stopping
25	0	Early stopping

Therefore, if none of the first 15 patients responds to the combination, the study will be stopped early for futility. Otherwise, the study will continue to recruit all 30 patients. By the end of the study, we will consider the study combination effective and worth further study if the posterior probability that the response rate is >5% given the observed data is 90% or higher (in our case, if we observe >3 responses in 30 evaluable patients). The following figure demonstrated the simulation results of the operating characteristics of our study design, under the assumption of various true response rates. As shown, when the response rate is 5% or lower, the probability of early stop is higher (>0.46) and probability of declaring efficacy (i.e. "type I error") is low (<0.06). When the response rate is 20% or higher, the probability of early stopping is less than 3.5% and the probability of declaring efficacy (i.e. "power") is over 86%.



The simulation is performed using the web tool for Bayesian Efficacy Monitoring Via Posterior Probability (http://www.trialdesign.org/one-page-shell.html#BEMPO).

14.2.3. Analysis of Primary and Secondary Endpoints

14.2.3.1. Analysis of Tumor Response:

Overall Response Rate (**primary endpoint**) will be estimated by the proportion of patients with a best response of complete response (CR) or partial response (PR) by RECIST 1.1 criteria, with corresponding exact 95% confidence limits being reported. The response rate will also be compared between pre-

specified subsets of melanoma patients with Fisher's exact tests. These comparisons will be done in an exploratory manner.

The distribution of response duration (defined in Section 12.3.4) will be characterized by median and quartiles, with the corresponding Kaplan-Meier estimate being made of PFS among patients responding to treatment. To the extent possible from the available data, proportional hazards models will be used to assess whether the rate of disease progression varies materially among the three subgroups of disease response: CR, PR, and SD.

14.2.3.2. Analysis of Progression Free Survival (PFS) and Overall Survival (OS):

PFS and OS (defined in Section 12.3.5 and 12.3.6 respectively) will be estimated by the Kaplan-Meier method. The corresponding median survival times (with 95% confidence limits) will be determined, as will the cumulative percentage of patients remaining progression-free (and the cumulative percentage-alive) at selected time points after initial treatment (e.g., 6,12, 18 months).

14.2.3.3. Stopping Rule for Excessive Toxicity

We will use a Bayesian monitoring scheme to continuously monitor the dose limiting toxicity rate of the study combination at 30%. The DLT is defined generally as grade 3 and 4 toxicity, see section 8.1 for more detailed definitions. Again, a non-informative prior of Beta (0.5, 0.5) for the DLT rate will be used. We will hold patient recruitment if the posterior probability Pr(SAE rate>30% is $\geq$0.7, and the study committee and the PI will then decide whether to modify or discontinue the study. The stopping boundary for toxicity is given in the following table:

Number of SAEs >=	in Number of Patients =
2	3-5
3	6-7
4	8-10
5	11-13
6	14-16
7	17-19
8	20-22
9	23-26
10	27-29
11	30

We simulate the operating characteristics under various assumed true toxicity ratesratesrates (see the following table):

Scenario	Prob.Of.Tox	Prob.Early.Stop
1	0.1	0.0885
2	0.2	0.3332
3	0.3	0.6727
4	0.4	0.9128

14.2.3.4. Analysis of Safety (for both the phase I portion and the phase II portion)

We will consider a toxicity event to be an adverse event (evaluated by CTCAE 5.0) that is possibly, probably, or definitely related to treatment. Toxicity will be considered attributable to both study drugs, unless investigator determines one of the drugs is a more likely culprit (e.g. CMV due duvelisib). The maximum grade of toxicity for each category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. These will also be done for early toxicities (within 4 weeks) and late toxicities (after 4 weeks) separately.

14.2.3.5. Analysis of exploratory endpoints

The effect of duvelisib dose on marker expression will be exploratively analyzed with generalized linear models, where baseline marker value, duvelisib dose and measurement time are explanatory variables. Also, pre- and post- treatment marker expression values will be compared with paired t-tests or Wilcoxon signed rank tests as appropriate.

15.0 Study Management, Agreement and Ethical Considerations

This study will be managed in the UPMC Melanoma Center which has considerable experience in managing clinical trials. Screening, registration, safety and efficacy evaluations are described in detail above. The study funding will come predominantly from Secura Bio, Inc the manufacturer of duvelisib. Study design, operations and procedures were designed independently by the co-investigators and were compliantly reviewed by appropriate experts on the Secura Bio clinical/scientific team.

Without a standard of care option for anti-PD1 refractory disease, clinical trials are a preferred treatment according to NCCN guidelines [1]. Our trial is a reasonable option for patients who have progressed on anti-PD1 therapy and who have exhausted BRAF targeted therapy, which is ultimately the majority of patients with advanced melanoma. Toxicities with duvelisib were observed in heavily pre-treated patients with hematologic malignancies [12]. Patients with melanoma are less immuno- and myeloid suppressed and should tolerate duvelisib with fewer toxicities. Studies with duvelisib in other solid tumors are also being planned.

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17.0 Appendices

17.1 Appendix A: Medications with CYP3A interactions

Table 17.1 Inhibitors and Inducers of CYP3A

Potent CYP3A Inhibitors	
Antibiotics or antifungals	Clarithromycin, erythromycin, telithromycin
Anti-emetic	Aprepitant
Antifungals	Itraconazole, ketoconazole, voriconazole, posaconazole
Antiretrovirals	Ritonavir, idinavir, nelfinavir, boceprevir, cobicistat, elvitegravir, paritaprevir, telaprevir, tipranavir
Calcium channel inhibitors	Diltiazem, verapamil
Foods	Grapefruit juice
Antidepressant	Nefazodone
Tyrosine Kinase Inhibitor	Imatinib
Potent CYP3A Inducers	
Anti-epileptics	Carbamazepine, phenobarbital, phenytoin
Antibiotics	Rifampin
Antiretrovirals	Efavirenz, etravirine
Supplements	St John's wort
CYP3A Sensitive Substrates	
Analgesic/Benzodiazapine	Alfentanil, midazolam, naloxegol, triazolam,
Aldosterone receptor antagonist	eplerenone
Anti-arrhythmic	dronedarone
Anticholinergic	darifenacin
Antihistamine	ebastine
Anti-retroviral	Darunavir, indinavir, maraviroc, saquinavir, tipranavir,
Antidepressant/antipsychotic	Buspirone, lurasidone, quetiapine
Calcinineurin / mTor inhibitors	Everolimus, sirolimus, tacrolimus
Calcium channel blockers	Nisoldipine, felodipine
CONTINUED…	

Platelet aggregation inhibitor	ticagrelor
Phosphodiesterase inhibitor	avanafil, sildenafil, vardenafil
Statin/lipid lowering agents	Lomitapide, lovastatin, simvastatin
Steroid	Budesonide
Triptan	Eletriptan
Tyrosine kinase inhibitor	dasatinib, ibrutinib
Vaptans	Conivaptan, tolvaptan

References: [26],[27]

UPMC | HILLMAN CANCER CENTER

17.2 Appendix B: Drug Diary

Participant: _____

Your MD _____ Phone _____

Your RN _____ Phone _____

DOSING LOG

Duvelisib Dose ____ Cycle: ___

For each AM dose take: 1 pill

For each PM dose take: 1 pill

	Date	Amount Taken		Comments
		AM dose	PM dose	
Ex:	6/1/2019	8 am - 1	7:30 pm - 1	vomited PM pill
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				

Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Day 22				
Day 23				
Day 24				
Day 25				
Day 26				
Day 27				
Day 28				

Please bring any unused study drug, all empty containers, and your diary to the next clinic visit

FOR STUDY TEAM USE ONLY Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

UPMC | HILLMAN CANCER CENTER

SUMMARY OF CHANGES

Protocol dated 4-27-22

Page 1	Version date **changed from** 3-11-22 to 4-27-22
Page 1 - 2	**Removed** references to Emory University
Page 8	Table ii. Protocol Summary, Methodology, **Removed** "multi-center"
Page 8	Table ii. Protocol Summary**, Removed** reference to Emory Winship Cancer Institute
Page 14	Section 3.1, General Study Design, **Removed** "multi-center study to be conducted at Winship Cancer Institute at Emory University"
Page 17	Section 4.2, Exclusion Criteria, 1st bullet**, Removed** "with"
Page 20	Section 4.3, Subject Recruitment, 1st sentence, R**emoved** "Emory Winship Cancer Institute"
Page 23	Section 5.4, Procedure for Registration of Subjects, **Removed** "Winship Cancer Institute of Emory University;
Page 22	Section 5.1, Study Site, Removed "Winship Cancer Institute"
Page 28	Section 7.4.1, Receipt of Drug Supplies, **Removed** "Winship Cancer Institute"
Page 30	Table 7.6, Dose Adjustments for Toxicity, **Updated** recommended management for Neutropenia
Page 37	Section 7.7, **Removed** references to Emory