A Phase II Biomarker Trial of Avadomide (CC-122) in Combination with Nivolumab in Advanced Melanoma

NCT03834623

Version 3.7

November 22, 2019

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Protocol Identifying Number: [redacted]

Principal Investigator: [redacted]

Statistician: [redacted]

IND/IDE Sponsor: Moffitt Cancer Center

Funded by: Celgene Corporation

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
LSMEANS	Least Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH	National Institutes of Health
NIH IC	NIH Institute & Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the <NIH IC> Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed of their obligation to meet the above commitments.

Principal Investigator: [redacted]
Print/Type Name

Signed: _____ Date: _____

PROTOCOL SUMMARY

A Phase II Biomarker Trial of CC-122 in Combination with Nivolumab in Advanced Melanoma

Précis:
Preliminary pre-clinical data suggest that the novel immunomodulatory agent CC-122 can restore metabolic function of T-cells and will increase immunosurveillance in melanoma. The synergy of the combination of CC-122 and the anti-PD1 agent nivolumab will enhance reversal of T-cell exhaustion and improve anti-tumor immunity in patients with advanced melanoma. Our goal is to link pharmacodynamic markers to immune mechanism of action and efficacy. In addition, we seek to define sub-populations that may be enriched for response to CC-122 plus nivolumab in melanoma.

Objectives:
Primary: To determine the response rate to combination CC-122 plus nivolumab in both anti-PD1 naïve and anti-PD1 refractory advanced melanoma.
Secondary*: (1)* To assess the toxicity of this combination. *(2)* To determine the progression-free survival and overall survival with this combination. *(3)* Examine blood and tissue-based biomarkers that will further our understanding of the complex interplay between the metabolic needs/changes in the tumor and the immune microenvironment.

Population:
Adults with advanced melanoma who are appropriate for treatment with anti-PD1 therapy or who are appropriate to resume anti-PD1 therapy after prior progression on anti-PD1 therapy with the goal of reversing resistance.

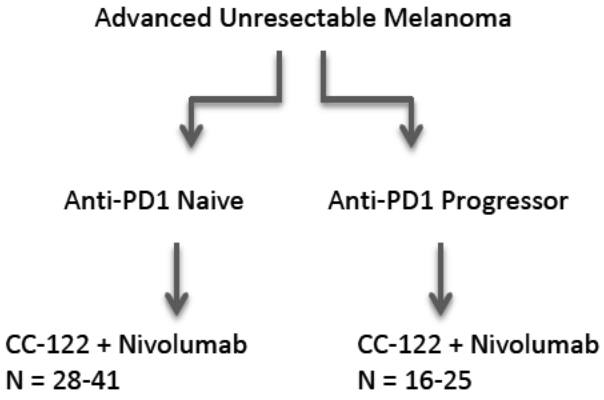
Number of Sites
This study will be conducted at the Moffitt Cancer Center

Study Agent(s) and Administration:
Oral CC-122 at 2mg daily for 5 consecutive days every 7 days, with intravenous nivolumab (240mg) in days 1 and 15 within a 28-day cycle.

Study Duration:
Subjects will receive up to 52 weeks of therapy. Decision to continue beyond this will be made based on response at that time. Based on planned futility analyses and enrollment across cohorts, the total number of subjects is anticipated to be 44-66.

Participant Duration:
Participants to be followed for up to 24 months following completion of study therapy.

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

The advent of immune checkpoint inhibitors against cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death 1 (PD-1), as well as mitogen activated protein kinase (MAPK) targeted therapy has revolutionized the management of advanced melanoma, a disease long associated with therapeutic futility and nihilism. The median survival for patients with metastatic disease treated with a first-line regimen that includes an inhibitor of PD-1 has now approached 36 months, with 3-year overall survival (OS) in excess of 50%.[1] Since 2011, eight new drugs have received regulatory approval in the United States either as single agents or in combination. These include the immune checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab, MAPK targeting agents including vemurafenib, dabrafenib, cobimetinib, and trametinib, and finally intra-lesional oncolytic virotherapy talimogene laherparepvec (T-VEC). While cure may be a distinct possibility for some patients with stage IV melanoma, there are nonetheless 10,000 melanoma deaths annually in the United States.[2] This clearly underscores the ongoing need for further enhancement in melanoma therapeutics.

The PD-1 blocking antibodies, pembrolizumab and nivolumab elicit objective response rates (ORR) between 30% and 40% in metastatic melanoma, with complete response (CR) rates ranging from 5% to 8%.[3,4] In KEYNOTE-001, pembrolizumab was administered at 10 mg/kg every 2 weeks, 10 mg/kg every 3 weeks, or 2 mg/kg every 3 weeks and included both ipilimumab-treated and ipilimumab-naïve metastatic melanoma patients.[5] In a pooled analysis, the ORR was 33% with median OS of 23 months; for therapy-naïve patients these were 45% and 31 months respectively. In KEYNOTE-006, pembrolizumab improved the ORR, progression-free survival (PFS), and overall survival (OS) compared with ipilimumab in advanced melanoma.[3] Remarkably similar results for efficacy and toxicity have been observed with nivolumab as well.[4,6] In CheckMate-067, previously untreated advanced melanoma patients were randomized to receive combination nivolumab plus ipilimumab (followed by maintenance nivolumab), nivolumab alone, or ipilimumab alone.[1] The response rates to treatment were 58%, 44% and 19% respectively. Both nivolumab-containing arms improved OS compared to ipilimumab. At 3 years, the OS rate was 58%, 52%, and 34% respectively in these cohorts. The toxicity of combination nivolumab plus ipilimumab can be severe and prohibitive. In CheckMate-067, the rate of grade 3 and 4 adverse events to combination therapy was 59% and the rate of treatment discontinuation secondary to toxicity was 30% compared to 8% on nivolumab alone. Similarly, in KEYNOTE-029, low-dose ipilimumab was combined with standard-dose pembrolizumab in a phase 1b trial that enrolled 153 patients.[7] The ORR to the combination was 61% with one year PFS and OS of 69% and 89% respectively. Overall, 45% patients experienced grade 3 and 4 adverse events and 14% had to discontinue pembrolizumab and ipilumumab due to toxicity. In the absence of proven survival benefit for combination anti-PD1 plus anti-CTLA-4 immunotherapy compared to anti-PD1 therapy alone, single agent anti-PD1 therapy using pembrolizumab or nivolumab remain an appropriate standard of care for metastatic or unresectable melanoma as first-line therapy. This is endorsed as a category 1

recommendation in the NCCN guidelines (Version 2.2018). In addition, this is an appropriate option after progression (or plateau of response) on combination mitogen activating protein kinase (MAPK)-directed treatment for those patients whose tumors harbor a mutation in *BRAF* V600.

In ongoing research efforts in melanoma, important questions being addressed include optimizing the response to first-line anti-PD1 therapy as well as identifying mechanisms to abrogate the development of resistance to anti-PD1 therapy.[8] Similarly the optimal duration of anti-PD1 therapy stratified by response has yet to be refined, as studies of anti-PD1 therapy in melanoma have generally continued treatment until the development of disease progression, unacceptable toxicity, up to 24 months, or even without a pre-specified end-date to treatment in cases of perceived therapeutic benefit. Several agents targeting the tumor or the microenvironment are currently under investigation aiming to add to the known efficacy of pembrolizumab or nivolumab in melanoma. Some of these include targeting other checkpoint pathways (TIM3, LAG3, CD137, GITR, etc.) or molecular targets (BRAF, MEK, IDO, HDAC, VEGF).

Approximately 40-45% of cutaneous melanomas harbor an oncogenic mutation in *BRAF* resulting in constitutive activation of the MAPK pathway. In independent phase III trials, combination therapy with a BRAF inhibitor and MEK inhibitor has been shown to improve survival compared to a BRAF inhibitor alone.[9,10-12] The combinations of dabrafenib and trametinib, or vemurafenib and cobimetinib are now approved in the management of advanced *BRAF*-mutated melanoma. While these combinations have a high response rate, resistance is invariable and the median time to progression is typically between 10 and 12 months. Current therapeutic strategies are examining the combination of MAPK-targeted therapy with checkpoint inhibition, though these are in the early stages of conduct.

The demonstrable efficacy of cellular immunotherapies, including checkpoint blockade, Tumor Infiltrating Lymphocyte (TIL) therapy, Chimeric Antigen Receptor (CAR)-T cells [13-15] and other immune modulators have drastically altered the landscape of cancer therapeutics. There is, however, an urgent need to further delineate mechanisms associated with immune suppression, and to identify targetable pathways that control the intratumoral activity of antigen-specific T-cells. Virtually all of these therapeutic T-cell modalities face potential inactivation after entering the hostile environment of solid tumors, where nutrient and oxygen depletion decreases their migration to the cancer site and reduces their cytotoxic potential in the tumor bed. Overcoming the functional limitations caused by microenvironment-induced restrictions may potentially improve all types of T-cell-related immunotherapies including responses to checkpoint blockade.

2.2 RATIONALE

Immunomodulatory drugs (IMiDs) like thalidomide and lenalidomide, which have proven efficacy in hematological malignancies including multiple myeloma, non-Hodgkin's lymphoma and myelodysplastic syndrome have had limited success in solid tumors including melanoma. In a phase II trial in melanoma, thalidomide demonstrated no objective response and one stable disease in 14 treated patients.[16] In a separate phase II trial, 7/20 (35%) melanoma patients experienced stable disease for a median of 16 weeks.[17] Reported toxicity was as anticipated including constipation, somnolence, fatigue and xerosis. This initial enthusiasm for thalidomide as an effective drug in melanoma due to its biologic modulatory and anti-angiogenic effects rapidly led to its incorporation into combination therapy trials with chemotherapy or other biologic agents. In a small dose-finding trial, the combination of thalidomide and temozolamide was shown to be tolerable and active.[18] In a follow-up study of 38 patients with advanced melanoma, twelve experienced an objective response (32%), including one with a complete response.[19] The median overall survival was 9.5 months. However a larger phase 2 multi-center trial (Southwest Oncology Group 0508) in 64 patients failed to confirm this efficacy yielding a response rate of 13%, 6-month PFS of 15%,

and 1-year overall survival of 35%.[20]

Based on pre-clinical and phase 1 clinical study data, lenalidomide has also been examined as a single agent in metastatic melanoma. In a large randomized, double-blind phase 2/3 study, 294 patients were randomized to receive oral lenalidomide at 5mg or 25mg daily.[21] There was no significant difference between the response rates (3.4% versus 5.5% respectively), PFS or OS between the two groups. Myelosuppression was observed in 37% of patients. Similarly a parallel study comparing lenalidomide (25mg/d, days 1-21 in a 28-day cycle) to placebo in 306 previously treated melanoma patients demonstrated no difference in the response rate, time to progression or OS between the two arms.[22] The authors concluded limited efficacy of this single agent, but suggested further investigation as a part of combination therapy in melanoma. Separate studies of combination of lenalidomide with sorafenib, valproic acid and bevacizumab have been shown to be safe with evidence of clinical benefit in melanoma among other solid tumors.[23-25]

Pre-clinical data suggests synergy between immune checkpoint inhibitors and iMiDs. In a phase 1 trial, ipilimumab at escalating doses (1.5-3mg/kg iv every 3 weeks X 4 doses) was combined with lenalidomide (10-25mg daily for 21 of 28 days) in 36 patients.[26] The maximum tolerated dose was not reached and ipilimumab at 3mg/kg (every 3 weeks X 4) plus lenalidomide at 25mg daily (21/28 days) was identified as the recommended phase 2 dose. Grade 3 rash and grade 3 pancreatitis were identified as dose-limiting toxicities and 8 patients experienced tumor shrinkage ranging from -79% to -2% based on immune-related response criteria (iRECIST).

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[redacted]

[redacted]

As of the data cutoff date, no cycle 1 DLTs were reported in Dose Level 1 (2 mg QD CC-122 formulated

[redacted]

[redacted]

Hypothesis:
Summary Statement: The synergy of the combination will enhance reversal of T-cell exhaustion and improve anti-tumor immunity.

We hypothesize that Avadomide (CC-122; Celgene Corporation) will increase immunosurveillance and clinical efficacy in combination with anti-PD1 immunotherapy. Enhanced polyamines suppress aging in vertebrate species and increase the survival of long-lived memory T-cells. Thus, the ultimate test of this hypothesis is to administer CC-122, a potent IMiD, in combination with anti-PD1 in vivo.

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to determine the efficacy and toxicity of the combination of CC-122 and nivolumab in advanced melanoma. Extensive biomarker analyses are planned to obtain a better understanding of the metabolic and immune changes that occur with this combination.

Primary Objective:

1. To determine the response rate of the combination of CC-122 plus nivolumab in advanced melanoma as measured by RECIST v1.1.

Secondary Objectives:

1. To assess the toxicity of this combination.
2. To determine the iRECIST response, progression-free survival and overall survival with this combination.
3. Examine blood and tissue-based biomarkers that will further our understanding of the complex interplay between the metabolic needs/changes in the tumor and the immune microenvironment.
   a. To determine if clinical improvement is associated with c-Myc induction, glucose uptake, polyamine production, and T-cell persistence.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a single-center, open label phase II clinical trial examining the combination of CC-122 plus nivolumab in anti-PD1 therapy naïve or refractory advanced melanoma.

4.2 STUDY ENDPOINTS

The primary end-point is to determine the objective response rate of the combination of CC-122 plus nivolumab in both anti-PD1 therapy naïve advanced melanoma as well as in anti-PD1 therapy refractory melanoma (primary refractory or progressing after an initial response or stable disease). Survival analyses will be conducted. A strong component of this clinical trial is collection of biological specimens to assess pharmacodynamics markers of response to CC-122 and nivolumab and to explore immunometabolic changes that occur in the tumor, microenvironment and blood with this therapy. This may help inform further immune checkpoint pathways/molecules in cancer as well as enable understanding of mechanisms of resistance to anti-PD1 therapy.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

The participating subject must meet all of the following inclusion criteria to be eligible to enroll in this study.

1. Unresectable or metastatic melanoma of cutaneous, mucosal, conjunctival, or unknown origin. *Uveal melanoma is not permitted.*
   A. **Cohort 1**: Naïve to anti-PD1 therapy
   B. **Cohort 2**: Progressed on previous anti-PD1 therapy. Subjects who have received anti-PD1 therapy in the adjuvant setting for previously resected melanoma are eligible for this cohort provided the disease relapse has occurred within 6 months of the last dose of anti-PD1 therapy. If this interval is equal to or greater than 6 months from the last dose of anti-PD1 therapy, they will be eligible to participate in **Cohort 1**. Patients with BRAF V600 mutant melanoma who have PD-1 refractory disease must have received treatment with BRAF and/or MEK inhibitors.
2. Be willing and able to provide written informed consent for the trial.
3. Be >/=18 years of age on day of signing informed consent.
4. Have measurable disease based on RECIST 1.1.[43]
5. Have a performance status of 0 or 1 on the ECOG Performance Scale.
6. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
7. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 28 days after last dose of avadomide or 5 months after the last dose of nivolumab; whichever is longer. Females of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
8. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through3 months after the last dose of avadomide or 7 months after last dose of nivolumab; whichever is longer.
9. Demonstrate adequate organ function as defined below:
   - *Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L*
   - *Platelets ≥ 100,000 x 10^6/L*
   - *Hemoglobin (Hgb) ≥ 9 g/dL, without the need for transfusion*
   - *Serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN) OR measured creatinine clearance ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN*
   - *Serum AST and ALT ≤ 2.5 x ULN (or ≤ 5 x ULN in case of liver metastases)*
   - *Serum bilirubin ≤ 1.5 x ULN (or ≤ 3 X ULN if known Gilbert's syndrome)*

5.2 PARTICIPANT EXCLUSION CRITERIA

The subject must be excluded from participating in the trial if the subject:

1. Has received an investigational drug or other anti-cancer therapy within 3 weeks of the first dose of treatment or ≤ 5 half-lives of that agent, whichever is shorter. Any toxicity from prior therapy must have recovered to ≤ grade 1.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (equivalent to > 10mg/d of prednisone) or any other form of immunosuppressive therapy within 7 days prior to

the first dose of trial treatment (only exception to this is the need for steroids for CNS metastases; see #6 below). Inhaled, intra-articular, or topical steroids are permissible.

3. Has a history of hypersensitivity to nivolumab.
4. Has a known additional malignancy that is progressing or requires active treatment, the lack of which would pose a risk to the health of the subject, in the opinion of the investigator.
5. Has known symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable without evidence of progression by imaging for at least four weeks after definitive intervention and using no more than the equivalent of dexamethasone 2mg/d for the management of vasogenic edema, if necessary. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
6. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy [</= 10 mg/d equivalent of prednisone] for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
7. Had previous toxicity from anti-PD1/PD-L1 immunotherapy that led to treatment discontinuation.
8. Has active pneumonitis or a history of non-infectious pneumonitis that required steroids.
9. Has grade $\geq$ 2 peripheral neuropathy.
10. Has clinically significant cardiac disease including any of the following: Left ventricular ejection fraction (LVEF) < 45% as determined by a by multi-gated acquisition (MUGA) scan or echocardiogram (ECHO), complete left bundle branch or bifascicular block, congenital long QT syndrome, persistent or clinically meaningful ventricular arrhythmias, QTcF > 460 msec on screening electrocardiogram (ECG), unstable angina pectoris or myocardial infarction ≤ 6 months prior to starting study treatment, uncontrolled hypertension (blood pressure > 140/90 mmHg on at least 2 measurements on sequential visits, despite blood pressure medication), or troponin-T/I value > ULN or brain natriuretic peptide (BNP) > 300 pg/mL
11. Has a history of persistent skin rash
12. Has an active infection requiring systemic therapy.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial, in the opinion of the investigator.
14. Is pregnant or breastfeeding.
15. Has a known history of Human Immunodeficiency Virus (HIV), active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA is detected).
16. Has received a live vaccine within 30 days of planned start of study therapy.
    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

    It should be noted that screening of a potential subject may proceed after appropriate informed consent has been obtained even if all inclusion/exclusion criteria are not met at the time of signing the ICF.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

This trial will be open to all potential subjects who meet eligibility criteria, including women and minorities. Participants considered vulnerable (children, pregnant women, incarcerated, mentally ill, incapable of informed consent) will not be enrolled in this study. Subjects will be identified through the multi-disciplinary Cutaneous Oncology clinic at the Moffitt Cancer Center.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

Participants may withdraw voluntarily from the study or the PI may terminate a participant from the study.

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study in the following circumstances:

- If any clinically adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interests of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Any subject who becomes pregnant during the study, must be promptly withdrawn from the study and discontinue further study treatment. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. This is discussed in additional detail in section 8.4.5 along with the required reporting guidelines.

If the subject is agreeable, all efforts will be made to continue follow-up of withdrawn or terminated participants, especially for safety and efficacy end-points. All protocol specific safety follow-up procedures to capture adverse events, serious adverse events and unanticipated problems will be made.

The above does not apply to those subjects who come off protocol specific treatment for unequivocal progression of disease. For this group, appropriate follow-up will continue for safety and survival as specified in the protocol.

All subjects who have received at least one dose of CC-122 and/or nivolumab will be included in the safety analysis. Subjects who withdraw during screening after being deemed eligible but have not started protocol specific therapy will be replaced. For patients to be included in the efficacy analysis, they should have received at least 75% of the cumulative dose of CC-122 during cycle 1. If this parameter is not met, they will be replaced after discussion with the study statistician.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <investigator, funding agency, the IND/IDE sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and

satisfy the sponsor, IRB and/or FDA.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

The following are the study drugs being used in this trial:

1. CC-122:
Celgene will supply CC-122 as capsules for oral administration in 0.5, 1, (both of these dose formulations are are encapsulated in size 3 capsule shells) and 2 mg (encapsulated in size 1 capsule shell) strengths. Each pinkish brown capsule shell contains microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide, and stearic acid.

Drug Safety Contact Information:

2. Nivolumab:
Commercial supply of nivolumab will be used in this study. This will be obtained through the Moffitt Cancer Center pharmacy.

6.1.1 DOSING AND ADMINISTRATION

CC-122 will initially be administered orally once daily (QD) on 5 consecutive days each week (5 days on, 2 days off). The starting dose will be 2 mg with dose adjustments for toxicity per the following table. Each cycle of treatment will be 28 days. The daily dose of CC-122 should be taken in the morning at least 1 hour before or 2 hours after a meal (breakfast) with a glass of water. CC-122 may be taken up to 12 hours late if dosing has been delayed on a single day; otherwise that day's dose should be omitted. A study diary will be maintained to assess compliance with drug therapy.

The following table outlines the dose reduction levels permitted on this study for CC-122. If a patient is unable to tolerate CC-122 at the 1mg dose, this drug will be permanently discontinued. The patient will be permitted to continue nivolumab as clinically appropriate.

	CC-122 Dose; 5 days on, 2 days off
Starting Dose	2 mg
1st Dose Reduction	1.5 mg
2nd Dose Reduction	1 mg

Nivolumab is given by intravenous infusion at a flat dose of 240mg on days 1 and 15 in a 28-day treatment

cycle. While regulatory approval for dosing at 480mg IV every 28 days was also recently obtained, we will maintain the approved biweekly dosing schedule in this trial based on the safety data from Study CC-122-HC-002 in hepatocellular carcinoma. Dose administration of +/- 2 days is permissible and will not constitute a deviation. There will be no dose adjustments for nivolumab. Please refer to the OPDIVO Package Insert (November-2018) for full prescribing information.

6.1.2 DURATION OF THERAPY

In the absence of progression or intolerable toxicity, therapy will continue up to a maximum of 52 weeks (13 cycles). For those patients who demonstrate continued improvement in radiographic response at scheduled restaging (anticipated around week 48) performed prior to reaching this landmark will be given the option of continuation of therapy. This provision is based on the recently reported analysis of advanced melanoma patients who achieved a complete response to pembrolizumab on KEYNOTE-001 where the median time to achieve CR was 12 months (range, 3-36).[44] For these subjects, therapy will continue for 1 cycle beyond CR (should they achieve this) or until 2 consecutive staging studies demonstrate a plateau in response. For those patients achieving CR as best response prior to 52 weeks, therapy can be discontinued provided they have completed at least 26 weeks of treatment.

If either CC-122 or nivolumab require discontinuation due to toxicity attributed exclusively to that agent (e.g., neutropenia secondary to CC-122), the second drug can continue for the duration as outlined above.

6.1.3 DOSE MODIFICATIONS

Dose delay criteria apply for all drug-related adverse events regardless of whether or not the event is attributed to nivolumab, CC-122, or both unless it is explicitly clear that the toxicity is exclusive to one drug alone. All study drugs must be delayed until treatment can resume, unless in the judgement of the clinical investigator (with discussion with the PI), there is compelling evidence to continue one of the agents without the other.

Causality should be assessed and provided individually for each study drug (CC-122 and nivolumab) for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

6.1.3.1 CC-122 Dose Delay and/or Modifications:

The criteria for dose reduction and/or interruption for **non-hematological toxicities attributed to CC-122** are listed in the following table. Chronic Grade 2 toxicity attributed to CC-122 may warrant dose reduction of CC-122. If necessary, the PI may reach out to the appropriate medical personnel at Celgene to discuss this further.

Toxicity	Action
Any Grade 4 including LFT elevation (exceptions include lymphopenia, asymptomatic amylase and lipase)	• Discontinue CC-122
Grade 3 or 4 clinical liver failure	• Discontinue CC-122

If recurrence of Grade 3 event after dose-reduction	• Reduce dose to the next lower dose level; if available – If none available, CC-122 should be discontinued.
If recurrence of Grade 4 event after dose reduction	• Discontinue CC-122
Any non-hematological toxicity requiring interruption for > 4 weeks	• Discontinue CC-122
Troponin-T/I > ULN with associated significant elevation in BNP or with cardiac symptoms or significant changes in ECG or LVEF[1]	• Hold CC-122 • Consider cardiology evaluation • Follow troponin-T/I, BNP, and ECG at least every 7 days • If troponin-T/I returns to normal levels in ≤ 7 days and there are no other significant cardiac findings, resume CC-122 at the next lower dose level • If troponin T/I level elevation persists > 7 days, or recurs upon re-challenge, discontinue CC-122
Rash ≥ Grade 3	• If Grade 3 hold CC-122 until recovery to grade ≤ 1; if AE resolution to Grade ≤ 1 occurs ≤ 8 days, reintroduce CC-122 at the same dose level • If AE resolution to Grade ≤ 2 or > 7 days, reintroduce CC122 on lower level, if available • Discontinue CC-122 for 2nd occurrence of ≥ Grade 3 rash • For desquamating (blistering) Grade 3 or any Grade 4 rash, discontinue CC-122 • For maculopapular, aceiform, or pustular rashes lasting ≤ 7 days medical management is warranted including topical corticosteroids, anti-pruritic agents (if indicated). If this does not improve, oral steroids may be used. It is likely that this intervention will be utilized given the overlap of this toxicity with nivolumab (see appendix D)
Peripheral Neuropathy (neuropathies which begin or worsen while on study) ≥ Grade 3	• Hold CC-122 • When the toxicity resolves to ≤ Grade 2 or to baseline, restart CC-122 at the next lower dose level
Allergic Reaction or Hypersensitivity ≥ Grade 3	• Discontinue CC-122

Venous Thrombosis / Embolism (VTE) ≥ Grade 2; anticoagulation indicated	• Hold CC-122 and start anticoagulation; restart CC-122 (maintain dose level) once therapeutic anticoagulation achieved AND it is clinically appropriate to resume.[2]
Pneumonitis / Interstitial Lung Disease[3]	• Grade 1: continue CC-122 • Grade 2: interrupt CC-122; can resume at one dose level lower once ≤ grade 1 AND steroid taper completed. If recurrent Grade 2 toxicity on re-challenge, permanently discontinue CC-122 • ≥ Grade 3: permanently discontinue CC-122
Other Grade 3[4]	• Hold one or both study drugs (based on attribution) • When the toxicity resolves to < Grade 2, restart CC-122 at the next lower dose level

1. For BNP, greater than 20% increase from baseline value is considered significant. Any new ST segment or T wave changes, new bundle branch block, or new atrial or ventricular arrhythmia while on treatment with CC-122 is considered clinically significant. An absolute decrease in LVEF of > 10% from baseline (even if asymptomatic), or a decrease of estimated LVEF to ≤ 45% would mandate holding further CC-122 for up to 4 weeks. If improved LVEF (repeated 2-4 weeks after holding drug) to baseline value, resume CC-122 at next lower dose level, if available. If the decrease in LVEF is ≥ 20% (absolute decrease) from baseline or there is any evidence of symptomatic congestive heart failure, CC-122 will be permanently discontinued.
2. There are no prospective data available on the need to interrupt immunomodulatory agents like thalidomide, lenalidomide, CC-122 at the time of diagnosis of the VTE event. However as these drugs are prothrombotic, it is reasonable to hold CC-122 till therapeutic anticoagulation is achieved. For anticoagulants that do not require monitoring (such as low molecular weight heparin), CC-122 will be restarted 7 days after the initial hold. For drugs requiring monitoring (unfractionated heparin, warfarin), CC-122 will be resumed once the aPTT or INR are in the recommended therapeutic range for that individual agent, but no sooner than 7 days from the hold. Prior to resuming CC-122, clinically significant symptoms or signs related to VTE (e.g., chest pain, dyspnea, etc.) should have resolved. Persistence of leg/arm swelling (in case of DVT) would not be a contra-indication to resume therapy.
3. As pneumonitis is an expected toxicity with nivolumab, it may be difficult to ascertain the causality to one specific drug in this combination. The management algorithm to be followed based on the grade of toxicity is outlined in Appendix D.
4. Exceptions to this include lymphopenia, asymptomatic elevation in amylase or lipase, and isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae. Isolated electrolyte aberrations (e.g., sodium, potassium, magnesium, etc.) may require appropriate exogenous supplementation, but repeat levels must meet criteria outlined in the table to resume therapy.

Guidelines for hematological toxicity attributed to CC-122:

Toxicity	Action
Grade 2 thrombocytopenia	• No action
Grade 3 thrombocytopenia	• Hold until resolution to Grade ≤1 • Follow CBC at least every 7 days • If resolution to Grade ≤1 occurs ≤ 8 days, reintroduce CC-122 at the same dose level • If AE resolution occurs > 8 days, or event occurs within the same cycle, reintroduce CC-122 at the lower dose level, if available
Grade 4 thrombocytopenia	• Hold CC-122 until recovery to Grade ≤1 • Follow CBC at least every 7 days • Reintroduce CC-122 at the lower dose level, if available
Grade 3 neutropenia	• Hold until resolution to Grade ≤ 1 • Follow CBC at least every 7 days • If AE resolution to Grade ≤ 1 occurs ≤ 8 days, reintroduce CC-122 at the same dose level • If AE resolution occurs > 8 days, or event occurs within the same cycle, reintroduce CC-122 at one dose level lower, if available
Grade 4 neutropenia	• Grade 4: Hold CC-122 until recovery to Grade ≤1. • Follow CBC at least every 7 days • Reintroduce CC-122 at the lower dose level, if available • Use of growth factors (G-CSF, GM-CSF) is permitted at the discretion of the Investigator*
Febrile neutropenia	• Hold further dosing until recovery to Grade ≤ 1 then resume dosing at one dose level lower, if available • Use of growth factors (G-CSF, GM-CSF) is permitted at the discretion of the Investigator*

Any hematological toxicity requiring interruption for > 3 weeks	• Discontinue CC-122

*The use of myeloid growth factors (filgastrim, sargramostin, peg-filgastrim, or biosimilars), if considered should be in accordance with the 2015 American Society of Clinical Oncology guidelines for the use of WBC growth factors.[45] This includes use in subjects with neutropenia and fever who are at high risk for infection-related complications. These high-risk features are sepsis, age > 65 years, pneumonia, invasive fungal infection, other clinically documented infections, profound neutropenia (< 0.1 X 10^9/L) and hospitalization at the time of neutropenia. The growth factor should be continued until the absolute neutrophil count (ANC) has improved to ≤ grade 1 (equal to or greater than 1.5 X 10^9/L). If resumption of CC-122 in planned at a lower dose (if available), growth factors should have been discontinued at least 48 hours prior with reconfirmation of acceptable ANC on the day of planned resumption of treatment.

Additional toxicity-related precautions with CC-122:

CC-122 absorbs ultraviolet (UV) light between the frequencies of 290 and 700 nm and has been shown to distribute to the skin and eyes in nonclinical animal studies. As a precautionary measure, it is recommended that subjects avoid prolonged exposure to UV light, wear protective clothing and sunglasses, and use UV-blocking topical preparations while taking CC-122. This is outlined in the informed consent document.

6.1.3.2 Nivolumab Dose Delays and/or Modifications:

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any adverse event, laboratory abnormality, or inter-current illness, which in the judgment of the investigator warrants delaying the dose of study medication.

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

Criteria to Resume Treatment with Nivolumab:

Participants may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if they are asymptomatic and with normal pulse oximetry

readings in the absence of oxygen supplementation.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment provided any symptoms attributed to this event have improved to baseline. If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled time point per protocol. However, if the treatment is withheld past the window period of the next scheduled time point per protocol to ensure adequate recovery from the adverse event or tapering of immunosuppression, the next scheduled time point will be delayed until dosing resumes. If treatment is withheld > 6 weeks from the last dose, the participant must be permanently discontinued from study therapy.

Treatment with Nivolumab should be **permanently discontinued** for the following:

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

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug- related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade 3 drug-related AST, ALT or Total Bilirubin requires discontinuation
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia $\leq$ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation of nivolumab.

- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.

The algorithms for management of immune toxicity attributed to nivolumab will follow recommendations outlined in the OPDIVO package insert and labeling information (November-2018) plus generally accepted guidelines for clinical care of IO toxicity management. These guidelines are summarized in Appendix D.

Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Treatment of Nivolumab Related Infusion Reactions:

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE [version 5.0]) guidelines.

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

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for <24 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor participant until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the

participant as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

CC-122 will be shipped to, stored, and dispensed by the Investigation Drug Services (IDS) at Moffitt Cancer Center. Dispensation will occur on day 1 of each cycle after confirmation of appropriate parameters to start or continue therapy. Handling of this agent will be commensurate with guidelines from the Investigators Brochure and Pharmacy Manual. Any expired or unused product will be disposed using standard operating procedure or returned to the sponsor as per contract.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

The Investigator or authorized designee must obtain documented consent from each potential subject prior to participating in a clinical trial and prior to any study specific screening procedures.

General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on an IRB-approved consent form.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB approval in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements as well as applicable laws and regulations.

Screening Visit (Day -28 to -1)

- Confirm informed consent of potential participant has been obtained.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Collect/schedule study specific laboratory/biomarker tests and other studies that are outlined in the Schedule of Events.
- Schedule biopsy of appropriate metastatic (or appropriately accessible) tumor site for biomarker analysis.

Baseline Visit (Cycle 1, Day 1)

- Verify inclusion/exclusion criteria based on screening studies. The specific eligibility is typically completed ahead of this visit through the Moffitt Internal Monitoring Core.
- Obtain serum or urine pregnancy test for women of child-bearing age; this could have been completed and verified negative up to 72 hours prior to this visit.
- Obtain demographic information, medical history, and medication history.
- Record vital signs (including weight), results of examinations. Recording of height is necessary only at screening or baseline visit
- Collect study specific laboratory/biomarker tests and other studies that are outlined in the Schedule of Events. This also includes standard of care assessments.
- Administer the study treatment (nivolumab plus CC-122; first dose of CC-122 to be administered in the Clinical Research Unit).
- Collect blood for biomarker analysis at 5 hours post CC-122 administration.

Follow-up Visit (Visit 2; C1 Day 15; +/- 2 days)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, confirm medical history and perform physical examination
- Collect blood for routine testing and biomarker analysis as specified.
- Administer nivolumab per institutional standard.
- Record participant's adherence to treatment program.
- Schedule/remind subject of follow-up tumor biopsy (same site as done at screening) to be done between days 22 and 29 of cycle 1.

Follow-up Visit (Visit 3; Cycle 2, day 1, +/- 2 days)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, confirm medical history and perform physical examination
- Administer nivolumab and provide CC-122 for home use
- Record participant's adherence to treatment program.

Subsequent Visits to follow the 'Schedule of Events' calendar: All scheduled visits have the same window of +/- 2 days. If there is a need to schedule outside of this window, this may be done at the discretion of the principal investigator as long as there is no perceived jeopardy to the health of the participant. Tumor measurements by cross-sectional imaging will be performed every 12 weeks (+/- 7days) unless documented progression or subject taken off the clinical trial. Adverse events as reported by the subject or observed by the investigator will be recorded at each visit.

Final/End of Treatment (EOT) Study Visit

- This should occur after the participant has completed all planned therapy or been discontinued from protocol therapy due to progression or toxicity. This visit should occur within 30 days of the last administered study drug or at the time of start of new anti-neoplastic therapy for melanoma, whichever is sooner. If study therapy related toxicity has not resolved by the date of this evaluation, follow up should continue till resolution of toxicity. Note that this is not necessary for toxicities that require long-term replacement therapy (e.g., thyroid replacement therapy, steroid replacement therapy, management of immune-mediated hyperglycemia).
- Record adverse events as reported by participant or observed by investigator.
- Record vital signs and physical examination
- Collect blood for EOT. Obtain biopsy of metastatic site if feasible, especially in case of progression to help inform mechanisms of resistance to anti-PD1 therapy.
- Record participant's adherence to treatment regimen.
- Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (± 7 days) by radiologic imaging to monitor disease status up to 24 months after the final patients is enrolled or until receiving treatment outside of this protocol. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.2 SCHEDULE OF EVENTS TABLE

	Pre-study/Screening	C1D1	C1D15	C2D1	C2D15	C3 and beyond[6]	End of Treatment
Informed consent	X						
Medical history	X	X	X	X	X	X	X
Demographics	X						
Weight	X	X	X	X	X	X	X
Performance status	X	X		X		X	X
Concomitant medications	X	X		X		X	
Vital signs	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Tumor measurement[4]	X					X	X
CBC/diff, platelets	X	X[1]	X	X	X	X	X
CMP + LDH	X	X[1]	X	X	X	X	X
Pregnancy Test	X	X		X		X	
TSH, Free T4	X			X		X	
ACTH, cortisol	X						
Testosterone (males only)	X						
Trop I or T; BNP[10]	X			X		X	
Echo / MUGA[9]	X						
Blood for Biomarker Analysis[7]	X[2]	X[2]	X[2]	X	X	X	X

Nivolumab[5] (240mgIV)		X	X	X			
CC-122[5]		X		X		X	
Tissue Biopsy[8]	X			X			X

1. Does not need to be repeated if done within 7 days of study drug administration – serum or urine HCG must be done on day of administration of CC-122 or within 72 hours prior. CBC/Diff, CMP, LDH are SOC. Hormonal panel at screening is SOC for checkpoint inhibitor therapy.
2. Details provided below in Biomarker Collection Schedule table.
3. Thyroid panel outlined to be done on day 1 of every cycle (SOC)
4. Tumor measurements every 12 weeks (+/- 7 days) as above unless documented progression or subject taken off clinical trial. If a patient has reached 52 weeks without evidence of progression, the interval between imaging studies should remain 12 weeks (+/- 7 days) in year 2; 16 weeks (+/- 14 days) in year 3, and 24 weeks (+/- 14 days) in years 4 and 5. Typical modality is CT TAP (with contrast); CT neck with contrast only if clinically indicated. This is SOC. At baseline, patients will also get MRI brain (with contrast) and every 6 months thereafter (this is SOC). For those patients who are allergic to CT IV contrast dye, an option would be to consider whole body FDG-PET imaging at the same time-points or non-contrast CT chest with contrast MRI abdomen/pelvis. This is likely to be less than 10% of the study population. In the event of PD, imaging of the same modality will be repeated in 4-6 weeks to confirm PD and meet criteria set forth as iRECIST. Any CR should preferably be confirmed by repeat imaging 4-6 weeks after attaining CR.
5. See schedule outlined in synopsis above
6. Starting with C3D1, history and physical examination will be required on day 1 of each study cycle (standard of care; level 4 EP visit)
7. Starting with baseline and then at follow up visits indicated, peripheral blood (5x 10ml heparin sodium tubes) will be collected on odd number cycles only (day 1) and at end of treatment or progression, whichever occurs first
8. US-guided core biopsy for secondary correlates; in selected cases, this will be CT-guided. Second biopsy to be done between day 22 and 29 of C1. Both biopsies are research-related. Details of biomarkers to be analyzed detailed below. End of treatment biopsy will be pursued only if easily access ble.
9. 2D-echocardiography (or MUGA) will be performed at baseline and every 12 weeks thereafter; this will be done sooner if clinically indicated
10. Troponin I (or T; based on institutional standard) and BNP should be performed at screening and on day 1 of every cycle. In the absence of clinical symptoms or signs or cardiac dysfunction, treatment with CC-122 can proceed pending these results.

Biomarker Collection Schedule:

Biomarker Plan	Pre-study	C1D1[1]	C1D15	C2D1	C2D15	C3 and beyond[3]	End of Treatment
Blood for Biomarker Analysis using peripheral blood mononuclear cells (cells to Celgene for Aiolos, IL-2, IFNg, bead array		X		X		X	X
Multiparameter flow panel for T cell activation markers, memory, myeloid populations, Tregs (no activation)		X	X	X	X	X	X
Multiparameter flow panel for T cell activation markers, memory, glucose uptake, glycolysis, OxPhos, Myc, IL-2, IFNg, Bcl2, PD1, CTLA4, Lag3, Tim3, Ox40 (requires activation)		X	X	X	X	X	X
Activation of T cells for global metabolomic profiling by mass spec (maximum 30 patients)	X						X
Tissue Biopsy[2]	X			X			X
CLIA Analytic Microscopy Immuno- profiling Multiplex IF Vectra Panel 1: • CD3 • CD8 • FoxP3 • PD1 • PDL1 • DAPI • AE1/AE3 tokeratin) Panel 2: (requires development) • CD3 • CD8 • PD1 • Ki67 • Myc • DAPI • AE1/AE3	X			X			X
NanoString CLIA Analytical Microscopy for gene expression in FFPE samples • PanCancer Profilling panel 770 genes (include analysis of 12-	X			X			X

Biomarker Plan	Pre-study	C1D1[1]	C1D15	C2D1	C2D15	C3 and beyond[3]	End of Treatment
chemokine gene signature							
RNASeq[4]	X			X			X

1. C1D1 collection is pre-dosing of study therapy; a second collection will occur approximately 5 hours following CC-122 dosing on day 1 for pharmacodynamic assessments including effects on levels of Aiolos
2. Tissue biopsy to be done prior to C1D1 dosing; (can be within -7 days); tissue sent to Moffitt Tissue Core for accession and distribution.
3. Starting with C3, blood for biomarker analysis will be collected with odd number cycles only and at EOT.
4. Samples to be stored till methodology finalized – for single cell RNASeq and TCR immune repertoire analysis

7.3 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRFs are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable

7.5 PECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Study drug therapy may be interrupted for elective or emergency surgery, as deemed appropriate by the PI.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

The use of systemic steroids in doses exceeding the equivalent of prednisone 10mg daily, except for the use of immune mediated toxicity, as replacement for adrenal insufficiency, or for control of vasogenic edema in treated brain metastases is prohibited.

CYP3A4/5 and CYP1A2 appear to be the major isozymes involved in oxidative metabolism of CC-122, with very minor contributions by other CYP enzymes, including CYP2C8 and CYP2C19. Hence, caution should be used when coadministering CC-122 with drugs that are known strong inducers or inhibitors of CYP3A4/5 or CYP1A2, as these may affect the exposure to CC-122. The effects of these compounds on the exposure to CC-122 have not been evaluated in a clinical setting. Concomitant medications will be reviewed with the clinical pharmacist at the start of the subject' participation in the trial to determine if an alternative exists and if any changes may be necessary to the regimen.

Examples of these drugs are (not inclusive):

- CYP3A4/5 inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin.
- CYP3A4/5 inducers: rifampin and carbamazepine.
- CYP1A2 inhibitors: ciprofloxacin, enoxacin and fluvoxamine.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

For patients anticipated to need high-dose steroids for a period of one month or longer as treatment for immune mediated toxicity, consideration to prophylaxis against Pneumocystis carinii infection should be considered. In addition, prophylaxis for osteoporosis is also recommended.

The topical use of Emla cream or equivalent as an anesthetic is permitted.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a))

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

AEs and suspected adverse reactions are considered "serious" if, in the view of either the investigator or sponsor, they result in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS

OHRP considers unanticipated problems (UPs) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

All AEs will be graded using the CTCAE 5.0 criteria.
[For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.]

8.2.2 RELATIONSHIP TO STUDY AGENT

The clinician's assessment of an AE's relationship to the study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug

(dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (eg, the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (eg, the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews with study participants presenting for medical care, or upon review by a study monitor. All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of event. All AEs occurring during the study must be documented appropriately, regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened (after signing the informed consent) will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of AEs will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization is achieved.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

8.4.2 SERIOUS ADVERSE EVENT REPORTING

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated to the study agent/device, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness..
- Other SAEs, regardless of relationship to study agent/device, will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying 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.

Serious Adverse Events: Serious Adverse Events (SAEs) from this protocol will be reported concurrently to the IRB and the study sponsor. All SAEs will be documented in Oncore within 24 hours of the study team becoming aware of the occurrence. The Protocol Monitoring Committee (PMC) at Moffitt Cancer Center will review these SAEs in accordance with the protocol specific DSMP. The data and safety plan will define dose-limiting toxicities, rules for escalation of dose, and criteria for stopping the trial. This trial will be continuously monitored by the PI and the research team and reviewed at weekly Cutaneous Research Group meetings. Safety and monitoring reports will be submitted to the PMC per existing SOP or more frequently if requested by the PMC. This protocol will be subject to periodic internal audits based on risk or as recommended by the PMC.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable.

8.4.5 REPORTING OF PREGNANCY

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial or 30 days following cessation of treatment. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Any subject who becomes pregnant during the study, must be promptly withdrawn from the study and discontinue further study treatment. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, congenital anomaly, ectopic pregnancy, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.
Such events must be reported within 24 hours of their knowledge of the event to Celgene using the Serious Adverse Event Form. Because the effect of the Celgene medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Celgene medicinal product will be reported by the Investigator within 24 hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation, this may require prior consent of the partner. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

9 CLINICAL MONITORING

Data will be captured in OnCore, Moffitt's electronic Clinical Trials Database. For each subject enrolled, the electronic CRF must be completed by the assigned data manager or other authorized study staff. Any paper forms should be typed or filled out indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those subjects who fail to complete the study. If a subject stops dosing or terminates from the study, the dates and reasons must be noted on the CRF. If a subject terminates from the study because of toxicity, thorough efforts should be made to clearly document the outcome. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center monitoring policies. The monitoring will include source data verification, utilizing research subjects' medical records. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the protocol monitoring committee.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

This is a phase II study with interim analysis for futility using Simon's two-stage design[46,47] for the anti-PD1 therapy naïve and refractory subjects as follows:

Cohort 1: Anti-PD1 therapy naïve subjects:
Patients will be treated with CC-122 plus Nivolumab. The primary end point is response rate. The null hypothesis that the true response rate is 40% will be tested against a one-sided alternative of 60%. Targeting 90% power and 10% type I error, 28 evaluable subjects will be enrolled in stage 1 (n=28); if $\leq$ 11 responders by RECIST – further enrollment will be stopped to this arm for futility. Otherwise enrollment will continue for an additional 13 patients in stage 2 for a total cohort sample size of 41 evaluable subjects. The null hypothesis will be rejected if 21 or more responses are observed in 41 patients.

Cohort 2: Anti-PD1 refractory subjects:
This cohort includes subjects who have demonstrated progression on previous anti-PD1 therapy and for whom continuation/resumption of an anti-PD1 agent would not be likely to elicit a radiographic response. Retrospective data using ipilimumab suggest a response of 10% following prior anti-PD1 therapy.[48] For this cohort, we have set the null hypothesis rate to 10% with an alternative hypothesis of 30%. This sample size will be 25 if full accrual (16 patients in stage 1; If 2 or more responses - proceed to full accrual). The null hypothesis will be rejected is 5 or more subjects experience an objective response to therapy. This design yields a type I error rate of 9.5% with a power of 90%.

The maximum number of patients to be enrolled assuming complete enrollment will be 66 (41 + 25); minimum would be 44.

10.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

1. All toxicity analyses will be collated according to grade and frequency. This will include all events considered possibly, probably, or definitely related to study therapy.
2. Progression free survival will be calculated from the start of study therapy till the first documentation of disease progression, death, or change of treatment. Subjects receiving ongoing therapy at the time of data analysis will be censored.
3. Overall survival will be calculated from the start of therapy till death from any cause. Subjects alive at

the time of data analysis will be censored.

10.3 EFFICACY ANALYSIS

Objective response rate is the primary end point in this combination trial involving an immune checkpoint inhibitor in combination with an immunomodulatory agent. Response rates per RECIST 1.1 will be evaluated.

RECIST as assessed by the investigator will be used as the primary response rate efficacy end-point and make treatment decisions.

Immunotherapeutic agents such as nivolumab and pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may not provide a complete response assessment of immunotherapeutic agents such as nivolumab, therefore the irRECIST have been developed to encompass this. This will also be assessed as a secondary end-point of efficacy.

Broadly, irRECIST includes the concept of treatment beyond progression, if radiologic imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment, while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, subjects will be discontinued from trial therapy. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions.

In subjects who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a subject on study treatment, until repeat imaging is obtained a minimum of 4 weeks later. This decision should be based on the clinical judgment of the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- *No decline in ECOG performance status*
- *Absence of rapid progression of disease*
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

Subjects who continue treatment beyond initial radiographic progression while awaiting confirmation imaging will need to be re-consented for their ongoing treatment with nivolumab and avadomide on the clinical trial. All other elements of the main consent including description of reasonable foreseeable risks or discomfort, and other alternative therapy will still apply.

Stopping Rules for Excessive Toxicity:

To evaluate the safety, we will monitor the toxicity continuously using a Pocock-type boundary.[49] Sequential boundaries will be used to monitor dose-limiting toxicity (DLT) rate. As this is a phase II trial, DLT is defined as discontinuation of one or both drugs secondary to toxicity. The accrual will be halted if excessive numbers of DLTs are seen, that is, if the number of DLTs is equal to or exceeds b_n out of n patients with full follow-up (per table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 25% when the rate of DLT is equal to the acceptable DLT rate of 25%.

Table: Stopping rules for toxicity

The trial will be stopped for review if the number of dose limiting toxicities (DLTs) is equal to or exceeds b_n out of n patients with completed follow-up. This is targeting 25% DLT with 25% probability of early stopping for each cohort. For cohort 1, the maximum accrued number of patients will be 41 while the maximum accrued number of patients will be 25.

For cohort 1, the maximum accrued number of patients will be 41. The trial will be stopped if the number of dose limiting toxicities is equal to or exceeds b_n out of n patients with completed follow-up.

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	2	3	3	4	4	4	5	5	5	6	6	6	7	7	7	8	8	8	9

Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	9	9	10	10	10	11	11	11	11	12	12	12	13	13	13	14	14	14	15	15

Number of Patients, n	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Boundary, b_n	15																			

This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.25, using a one-sided level 0.09 test.

For cohort 2, the maximum accrued number of patients will be 25. The trial will be stopped if the number of dose limiting toxicities is equal to or exceeds b_n out of n patients with completed follow-up.

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	2	3	3	3	4	4	5	5	5	6	6	6	6	7	7	7	8	8	8

Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	9	9	9	10	10															

This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.25, using a one-sided level 0.11 test.

10.4 PLANNED INTERIM ANALYSES

Each cohort will be analyzed after stage 1 has completed enrollment to conduct the futility analysis. During this time, additional enrollment to that cohort will be halted. The PI will communicate the results of the

analysis to the assigned biostatistician and the Moffitt Protocol Monitoring Committee and make the appropriate determination on resumption of enrollment.

10.4.1 EXPLORATORY ANALYSES

[redacted]

10.5 SAMPLE SIZE

Details provided above.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The PI and other appropriate study staff are responsible for maintaining appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Representatives of Celgene and federal regulatory agencies may examine records for the purpose of quality assurance reviews, evaluation of the study safety, progress of the trial, and data validity.

Source documentation in both electronic and paper form shall be retained for at least two years after the final closure of the trial. These include hospital records, clinical research subject charts (with paper AE logs), research laboratory notes, electronic CRFs, and pharmacy dispensing records.

12 QUALITY ASSURANCE AND QUALITY CONTROL

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the Moffitt Internal Monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (eg, good laboratory practices (GLP), good manufacturing practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol:

1. Oral Study Drug Compliance Diary
2. CC-122 Investigators Brochure, Edition 11, May 2018

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.
The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

[redacted]

[redacted]

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

[redacted]

14.2 STUDY RECORDS RETENTION

[redacted]

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
4.6 5.1 Quality Assurance and Quality Control, section 5.1.1
4.7 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within established guidelines of the Moffitt Clinical Trials office. All deviations must be addressed in study source documents. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (ie, the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

Not Applicable

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry or any other party of interest is critical. Therefore any actual conflict of interest of persons who have a role in the design conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the study sponsor has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. This will conform to guidelines set forth by the Conflict of Interest Policy of the Moffitt Cancer Center.

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APPENDIX

Appendix A

Version	Date	Significant Revisions

Appendix B: ECOG Performance Status

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

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix C: iRECIST (immune Response Evaluation Criteria in Solid Tumors)

Tumor response will be assessed by the RECIST 1.1 (primary) and iRECIST (secondary).[43,50] The latter is a reconciliation of RECIST guidelines v1.1 with the original immune-related Response Criteria (irRC). The latter standard incorporated principles important for assessment of immune-checkpoint blocking immunotherapy for cancer, but fundamentally differed from RECIST in using 2-dimensional tumor assessment. In contrast, iRECIST is based on 1-dimensional tumor measurement, but it differs from RECIST guidelines v1.1 in the following key ways:

- Under RECIST guidelines v1.1, the appearance of new lesions indicates PD. Under iRECIST, new measurable lesions are incorporated in the tumor burden, which is used to determine immune-related progressive disease (iPD), immune-related partial response (iPR), and immune-related complete response (iCR). New non-measurable lesions preclude iCR.

- Under RECIST guidelines v1.1, there is no confirmation for PD. In addition, responses and iPDs must be confirmed by consecutive scans at least 4 weeks apart, assuming no clinical deterioration.

The following sub-section describes iRECIST in detail.

Tumor Burden:
At baseline, the tumor burden is the sum of single diameters (short axis for nodal lesions, longest diameter for other lesions) for the target lesions. In subsequent scans, the diameters of new measurable lesions are added to the tumor burden. If a subject is retreated, then up to 5 target lesions (perhaps different from the original lesions) will be selected and a new baseline tumor burden will be established.

Overall Response at a Single Time Point

The table below outlines determination of disease response at a single assessment based on iRECIST.

iRECIST: Overall Response

Tumor Burden (Baseline and New)	Non-Target Lesions (Baseline and New)	Response
Disappearance of non-nodal lesions. All pathologic lymph nodes < 10 mm (short axis)	Disappearance of non-nodal lesions. All pathologic lymph nodes < 10 mm (short axis)	irCR[a]
≥ 30% decrease from baseline	Any	irPR[a]
≥ 20% increase from nadir and at least 5 mm	Any	irPD[a]
Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD	Any	irSD
Disappearance of all non-nodal lesions. All pathologic lymph nodes < 10 mm	Any other than disappearance of all non-nodal lesions and reduction of pathologic lymph nodes < 10 mm	irPR[a]
Not all evaluated[b]	Any	irNE

a. Selection as best response requires confirmation by 2 consecutive measurements at least 4 weeks apart.
b. If some lesions are measured, response may be inferred from available measurements. For example, growth in evaluated target lesions may be sufficient for irPD regardless of status of non-evaluated lesions.

Appendix D: Immune Adverse Events Management Algorithm

The following section outlines general principles for the management of immune-related adverse events. A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated. The updated package insert for OPDIVO (nivolumab) will be concurrently followed to assist with clinical decision making.