A PHASE 1/2, MULTICENTER, OPEN-LABEL, DOSE FINDING STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF CC-122 IN COMBINATION WITH NIVOLUMAB IN SUBJECTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

PROTOCOL NUMBER:	**CC-122-HCC-002**
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SPONSOR NAME / ADDRESS:	[redacted]

CONFIDENTIAL

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

A phase 1/2, multicenter, open-label, dose finding study to assess the safety, tolerability, and preliminary efficacy of CC-122 in combination with nivolumab in subjects with unresectable hepatocellular carcinoma (HCC).

Indication

Adult subjects who have progressed after or were intolerant to no more than 2 previous systemic therapies for unresectable HCC, or are naïve to systemic therapy.

Objectives

The primary objective of the Phase 1 portion (dose finding) of the study is:

- To determine the safety and tolerability of CC-122 when administered orally in combination with nivolumab and to define the recommended Phase 2 dose (RP2D)

The primary objective of the Phase 2 portion (dose expansion) of the study is:

- To estimate the preliminary efficacy of CC-122 in combination with nivolumab based on overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

The secondary objectives of the study are:

- To evaluate the preliminary efficacy of CC-122 in combination with nivolumab based on various endpoints by RECIST 1.1
- To evaluate the pharmacokinetics (PK) of CC-122 in subjects coadministered multiple doses of CC-122 with nivolumab
- To determine nivolumab PK when coadministered with CC-122

Study Design

CC-122-HCC-002 is a Phase 1/2 dose escalation and expansion clinical study of CC-122 in combination with nivolumab in subjects who have progressed after or were intolerant to no more than 2 previous systemic therapies for unresectable HCC, or are naïve to systemic therapy. The dose escalation part of the study will explore 1 or more dose levels of CC-122 in combination with nivolumab using a modified dose escalation (3+3) design (Storer, 1989), followed by an expansion part once the RP2D is defined.

The study is designed to explore three dose levels, to identify the RP2D, and is not required to escalate to a nontolerated dose (NTD) or maximum tolerated dose (MTD). CC-122 will be administered orally 5 consecutive days out of 7 (5 days on/2 days off weekly) on Days 1 to 5, 8 to 12, 15 to 19 and 22 to 26 of each 28-day cycle. The starting daily dose of CC-122 will be 2.0 mg, and two subsequent dose levels (3.0 and 4.0 mg) are planned to be evaluated based on evaluation of pre-specified dose limiting toxicities (DLTs). The study intends to identify the RP2D at or below the 4.0 mg dose level, however intermediate dose levels, or a higher dose level, may be evaluated at the discretion of the Safety Review Committee (SRC). Nivolumab will be administered intravenously (IV) at the fixed dose of 3.0 mg/kg every 2 weeks.

Up to six subjects will be concurrently enrolled into a dose level. Decisions as to which dose level to enroll a new subject in will be based on the number of subjects enrolled and evaluable, the number of subjects experiencing DLTs and the number of subjects enrolled but who are not yet evaluable for toxicity in the current cohort at the time of new subject entry.

A dose is considered an NTD when 2 or more out of 6 evaluable subjects in a cohort experience a DLT in Cycle 1. During dose escalation, the decision to either evaluate a higher dose level, an intermediate dose level, declare an NTD, or define the RP2D will be determined by the SRC, based on their review of all available clinical data, PK, pharmacodynamic (PD) and laboratory safety data for a given dose cohort.

Non-evaluable subjects will be replaced at the discretion of the SRC.

Following completion of the dose escalation part, up to 30 additional subjects will be enrolled in an expansion cohort of mixed HCC etiology – hepatitis B virus (HBV), hepatitis C virus (HCV) and non-viral. A futility analysis will be conducted as follows: in the first 14 subjects treated, if no responder is observed out of 14 subjects then enrollment for the expansion cohort will stop for futility. Enrollment will continue during the evaluation of the 14 subjects. If ≥ 1 subject out of 14 responds (complete response [CR] or partial response [PR]), then approximately 30 total subjects will be enrolled in the expansion part. The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation and dose modification, as appropriate.

The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

Adult subjects with confirmed pathologic diagnosis of unresectable HCC, according to the American Association for the Study of Liver Diseases (AASLD) Guidelines (Bruix, 2005) who have progressed after or were intolerant to no more than 2 previous systemic therapies for unresectable HCC, or are naïve to systemic therapy.

Subjects at screening must have a Child-Pugh score less than 7 (class A) and have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

Up to approximately 20 subjects will be enrolled in the dose escalation portion of the study (Phase 1), depending upon the number of cohorts opened. Up to approximately 30 additional subjects will be evaluated for safety, PK, PD, and preliminary antitumor effects during the dose expansion portion (Phase 2). Therefore up to approximately 50 total subjects may be enrolled into the study.

Length of Study

The screening period will last approximately up to 28 days. Subjects may remain on treatment for up to 2 years or until disease progression, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death. If treatment is discontinued for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent, subjects will continue to be followed for tumor evaluation until progression. Subjects will be followed for survival status either until death, lost to follow-up, withdrawal of consent or until two years from enrollment, whichever event occurs first. The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last

data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

Study Treatments

All cohorts will receive different dose levels of CC-122 and a standard dose of nivolumab, 3.0 mg/kg IV every 2 weeks. The duration of treatment will not exceed 2 years. Study treatment may be discontinued if there is evidence of disease progression, unacceptable toxicity, or subject/physician decision to withdraw.

Subjects may continue to receive study drugs beyond disease progression at the discretion of the Investigator, especially if required to confirm after 4 to 6 weeks the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) for tumor progression.

Overview of Key Efficacy Assessments

Tumor assessments will be performed at screening (up to 28 days before the Cycle 1 Day 1 [C1D1] dose), every 8 weeks (±7 days) for the first 5 evaluations (10 months), and thereafter every 12 weeks (±7 days), regardless of treatment status. Tumor assessments should also be performed at any time, if clinically indicated. Tumor assessments should continue at the defined schedule until radiologic disease progression or new anticancer therapy, beyond the end of treatment if necessary.

All subjects will be evaluated for tumor response and progression by the Investigator according to RECIST 1.1 guidelines using the same scanning modalities used at screening.

Tumor response will also be determined by the Investigator based on irRECIST (Bohnsack, 2014) as an exploratory assessment. Other exploratory efficacy variables, such as ECOG PS, alpha-fetoprotein (AFP) reduction, etc, will be summarized as well. An independent review of the efficacy results may take place at any time during the study.

Following disease progression, survival status will be determined approximately every 3 months thereafter until 2 years from enrollment, lost to follow-up, death or withdrawal of consent, whichever occurs sooner.

New anticancer therapies will also be collected at the same schedule. New anticancer therapy includes (but is not limited to) any systemic or locoregional medication, surgery, radiation, or any other therapy intended to treat the subject's cancer.

Overview of Key Safety Assessments

All subjects will be monitored for adverse events (AEs), starting from the time the subject signs the informed consent form (ICF) until the end of treatment (EOT) visit, for 28 days after the last dose of CC-122 and for 90 days after the last dose of nivolumab, whichever occurs later. A thorough evaluation of medical conditions will be conducted during screening for eligibility. The safety variables for this study include AEs, safety clinical laboratory variables, 12-lead electrocardiograms (ECGs), left ventricular ejection fraction (LVEF) assessments, physical examinations, ophthalmologic exams, vital signs, ECOG PS, exposure to investigational product (IP), assessment of concomitant medications, and pregnancy testing for females of child bearing potential (FCBP).

Overview of Pharmacokinetic Assessments

Blood will be collected to estimate the PK of CC-122 when administered in combination with nivolumab and the PK of nivolumab when administered in combination with CC-122.

For CC-122, during the dose escalation part, intensive PK sampling will be performed in all subjects at multiple time points on Cycle 1 Day 15. For nivolumab, sparse PK (at predose and at the end of infusion) will be performed in all subjects on Cycle 1 Days 1 and 15. No PK will be collected during the dose expansion part.

[redacted]

Statistical Methods

Statistical analyses will be performed by study part, dose level/dosing regimen and/or HCC etiology as needed or applicable. All analyses will be descriptive in nature.

All summaries of safety data will be conducted using subjects receiving at least one dose of either IP (the Treated Population).

The efficacy variables of primary interest include overall response rate (ORR), overall survival (OS), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS) and time to progression (TTP). The primary assessment of tumor response will be according to RECIST 1.1 (Eisenhauer, 2009). Exploratory response assessment using irRECIST (Bohnsack, 2014) will also be performed. Other preliminary efficacy variables such as AFP response will be summarized using frequency tabulations for categorical variables or descriptive statistics for continuous variables, and further analyses will be performed as appropriate. Efficacy analysis will be repeated for the Treated Population and Efficacy Evaluable Population (receiving at least 50% of both assigned IP in the first 2 cycles, having a baseline tumor assessment and 1 on study tumor assessment), with the result using the Treated Population considered primary.

All biomarker-related data presentations will be based on treated subjects with at least one non-missing biomarker assessment (the Biomarker Evaluable [BE] Population), unless specified otherwise. Descriptive statistics will be presented for baseline and change from baseline of continuous biomarker endpoints.

Exploration of PK, PD, safety and efficacy relationships will be assessed.

During the dose escalation part, up to approximately 20 subjects will be enrolled. During the cohort expansion part, up to 30 subjects will be enrolled. At least 14 efficacy evaluable subjects will initially be accrued. If the response rate is 20% or more, there will be more than a 95% chance that 1 or more responders would be observed in the first 14 subjects (Gehan, 1961). If no responder is observed out of 14 subjects, the enrollment for the expansion cohort will stop for futility. Otherwise, the expansion cohort will be expanded to up to approximately 30 subjects if a responder is observed. Enrollment will continue during the evaluation of the initial 14 subjects. With 30 subjects enrolled and assuming the observed ORR is 35%, the two-sided 95% Wilson score confidence interval will exclude 20%, the estimated ORR for nivolumab monotherapy (El-Khoueiry, 2015).

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2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the Phase 1 portion of the study is: • To determine the safety and tolerability of CC-122 when administered orally in combination with nivolumab and to define the recommended Phase 2 dose (RP2D)
The primary objective of the Phase 2 portion of the study is: • To estimate the preliminary efficacy of CC-122 in combination with nivolumab based on overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
Secondary Objective(s)
The secondary objectives of the entire study are: • To evaluate the preliminary efficacy of CC-122 in combination with nivolumab based on various endpoints by RECIST 1.1 • To evaluate the pharmacokinetics (PK) of CC-122 in subjects coadministered multiple doses of CC-122 with nivolumab • To determine nivolumab PK when coadministered with CC-122
[redacted]
[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary Phase 1	The incidence of dose limiting toxicities (DLTs) and the incidence and severity of treatment-emergent adverse events (TEAEs)	See Section 7.6 for the definition of DLTs	End of Phase 1
Primary Phase 2	Preliminary efficacy as measured by overall response rate (ORR)	The combined incidence of complete response (CR) + partial response (PR), by investigator assessment of response by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1	End of Study
Secondary	Preliminary efficacy	Disease control rate (DCR), duration of response (DoR), progression free survival (PFS), overall survival (OS), and time to progression (TTP) based on investigator assessment of response using RECIST 1.1 guidelines	End of Study
Secondary	Plasma pharmacokinetic (PK) parameters	Including but not limited to maximum observed concentration (C_{max}), area under the concentration time curve (AUC), time to maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), apparent total body clearance (CL/F) and apparent volume of distribution (Vz/F) for CC-122 and nivolumab after multiple dose administration	End of Phase 1
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]

3. OVERALL STUDY DESIGN

3.1. Study Design

CC-122-HCC-002 is a Phase 1/2 dose escalation and expansion clinical study of CC-122 in combination with nivolumab in subjects with unresectable HCC who have progressed after or were intolerant to no more than 2 previous systemic therapies for unresectable HCC, or are naïve to systemic therapy.

Subjects will have received either none or no more than 2 previous systemic therapies. The dose escalation part of the study will explore 1 or more dose levels of CC-122 in combination with nivolumab using a modified dose escalation (3+3) design (Storer, 1989), followed by an expansion part once the recommended Phase 2 dose (RP2D) is defined.

The study is designed to explore three dose levels, as described in Section 7.2.1, to identify the RP2D, and is not required to escalate to a nontolerated dose (NTD) or MTD. CC-122 will initially be administered orally 5 consecutive days out of 7 (5 days on/2 days off weekly) on Days 1 to 5, 8 to 12, 15 to 19 and 22 to 26 of each 28-day cycle. The investigated starting daily dose of CC-122 will be 2.0 mg, and two subsequent dose levels (3.0 and 4.0 mg) are planned to be evaluated based on evaluation of pre-specified DLTs. The study intends to identify the RP2D at or below the 4.0 mg dose level, however intermediate dose levels, or a higher dose level, may be evaluated at the discretion of the Safety Review Committee (SRC). Dose escalation to the intermediate or higher dose levels of CC-122 will not exceed 50% of the previously established tolerable dose level. Smaller dose increments based on toxicity, PK profile and PD findings may be evaluated, if necessary. Nivolumab will be administered at the dose of 3.0 mg/kg intravenously (IV) every 2 weeks. Once the RP2D for dosing of CC-122 in combination with nivolumab is defined, expansion (Phase 2) will start.

A modified 3+3 dose escalation design will be used to identify the initial toxicity of the combination. Up to six subjects will be concurrently enrolled into a dose level. Decisions as to which dose level to enroll a new subject will be based on the number of subjects enrolled and evaluable, the number of subjects experiencing DLTs, and the number of subjects enrolled but who are not yet evaluable for toxicity in the current cohort at the time of new subject entry.

A dose is considered an NTD if 2 or more out of up to 6 evaluable subjects in a cohort experience a DLT in Cycle 1. During dose escalation, the decision to either evaluate a higher dose level, an intermediate dose level, or declare the RP2D dose (or if applicable, NTD) will be determined by the SRC, based on their review of all available clinical data, PK, PD and laboratory safety data for a given dose cohort.

The composition of the SRC will be defined in the SRC charter and will include at least all the Principal Investigators (PIs) of active sites and the Celgene medical monitors and safety physician.

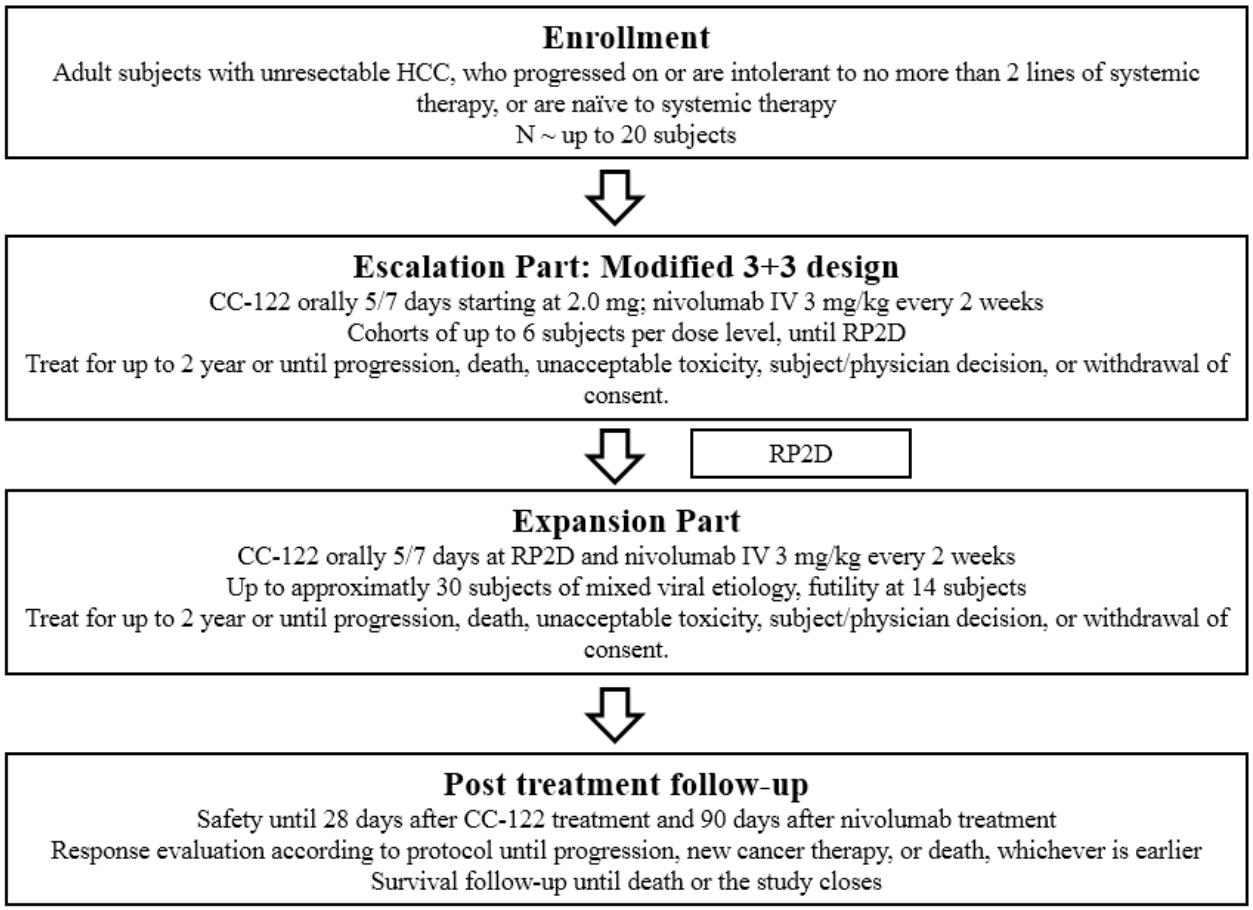
Non-evaluable subjects will be replaced at the discretion of the SRC.

Following completion of the dose escalation part (Phase 1), up to 30 additional subjects will be enrolled in an expansion part (Phase 2). A futility analysis will be conducted as follows. In the first 14 subjects treated, if no responder is observed out of 14 subjects then enrollment for the expansion cohort will stop for futility. Enrollment will continue during the evaluation of the 14

subjects. If ≥ 1 subject out of 14 responds (CR or PR), then approximately 30 total subjects will be enrolled in the Phase 2 portion. The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation and dose modification, as appropriate.

The study will be conducted in compliance with International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/ Good Clinical Practices (GCPs).

Figure 3: Overall Study Design



HCC = hepatocellular carcinoma; IV = intravenous; RP2D = recommended Phase 2 dose.

3.2. Study Duration for Subjects

The screening period will last approximately up to 28 days. Subjects may remain on treatment for up to 2 years or until disease progression, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death. If treatment is discontinued for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent, subjects will continue to be followed for tumor evaluation until progression and/or initiation of new anticancer therapies. Subjects will be followed for survival status either until death, lost to follow-up, or until two years from enrollment, whichever event occurs first.

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

The total number of subjects to be enrolled during dose escalation (Phase 1) is estimated to be up to approximately 20 depending on the number of cohorts and their sizes. Up to approximately 30 additional subjects will be evaluated for safety, PK, PD, and preliminary antitumor effects during the dose expansion part (Phase 2).

The study will be conducted in the US and European Union.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Subject has a confirmed pathologic diagnosis of HCC according to the American Association for the Study of Liver Diseases (AASLD) Guidelines (Bruix, 2005). Refer to Appendix D in Section 18.4. A biopsy performed at screening may serve as a diagnostic biopsy for subjects with radiographic diagnosis.
3. Subjects who have progressed after or were intolerant to no more than 2 previous systemic therapies for unresectable HCC, or are naïve to systemic therapy.
4. Subject has unresectable Stages B (intermediate), or C (advanced) HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging (Appendix E [Llovet, 2008]) in Section 18.5. Stage B subjects must have progressed after, or are not eligible for curative resection, transplantation, embolic, or ablative therapies.
5. Subject has at least one measurable lesion according to RECIST 1.1. Lesions previously treated with locoregional therapy may only be evaluated as target lesions if they are the only lesions available and have shown objective definite progression after prior treatment.
6. Subject agrees to provide a tumor biopsy prior to starting Cycle 1 and during Cycle 2.
7. Subject has a life expectancy of ≥ 12 weeks.
8. Subject has an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.
9. Subject has a Child-Pugh score less than 7 with neither encephalopathy nor clinically significant ascites (ascites requiring paracentesis within 3 months of signing the ICF is excluded). Child-Pugh status is calculated based on clinical findings and laboratory results during the screening period. Please refer to Appendix F in Section 18.6 for Child-Pugh classifications (Pugh, 1973).
10. Subject has the following laboratory parameters at screening:

    Adequate hematologic function including:

    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    b. Platelets ≥ 60,000 x 10^6/L

c. Hemoglobin (Hgb) ≥ 9 g/dL
d. International normalized ratio (INR) ≤ 1.7

Adequate hepatic function including:

e. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 x upper limit of normal (ULN)
f. Serum total bilirubin ≤ 2 x ULN
g. If serum total bilirubin is ≥ 1.5 and ≤ 2 x ULN then AST and ALT must be ≤ 3 x ULN
h. Serum albumin ≥ 2.8 g/dL

Note: The combined total of all laboratory values must still equal a Child-Pugh score < 7

Other laboratory parameters:

i. Serum creatinine ≤ 1.5 x ULN
j. Potassium within normal range or corrected with supplements

11. Subject is able to adhere to the study visit schedule and other protocol requirements.
12. Pregnancy Prevention Risk Management Plan (PPRMP) for CC-122 (Appendix G in Section 18.7):

a. Females of childbearing potential (FCBP) must undergo pregnancy testing based on the frequency outlined in the PPRMP and pregnancy results must be negative.
b. Unless practicing complete abstinence from heterosexual intercourse, sexually active FCBP must agree to use adequate contraceptive methods as specified in PPRMP.

   – Complete abstinence is only acceptable in cases where this is the preferred and usual lifestyle of the subject.

   – Periodic abstinence (calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable.

c. Males (including those who have had a vasectomy) must use barrier contraception (condoms) when engaging in sexual activity with FCBP as specified in PPRMP.
d. Males must agree not to donate semen or sperm for 3 months after last dose of CC-122 and/or nivolumab.
e. All subjects must:
   - Understand the information provided about pregnancy precautions and risks of fetal exposure after counseling and agree to follow the PPRMP (see PPRMP, Appendix G, Section 18.7)
   - Understand that CC-122 could have a potential teratogenic risk.
   - Agree not to share either IP with another person.
   - Agree that other than the subject, FCBP and males able to father a child should not handle CC-122 or touch the capsules, unless gloves are worn.
      - For nivolumab, agree to follow the pregnancy prevention plan described in the Summary of Product Characteristics (SmPC) or US Prescribing Information, specifically: females of childbearing potential must use effective contraception for at least 5 months following the last dose of nivolumab.

13. Subject must understand and voluntarily sign an informed consent document prior to conducting any study related assessments/procedures and be willing and able to adhere to the study visit schedule and other protocol requirements.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has received more than 2 previous systemic therapies for HCC. Prior treatment with regorafenib is also excluded.
2. Subject has received previous treatment with any anti-PD-1 or anti-PD-L1 antibody.
3. Subject has received any systemic or local anticancer therapy ≤ 4 weeks prior to starting IP. Subject has undergone major surgery ≤ 4 weeks or minor surgery ≤ 2 weeks prior to signing the ICF or who has not recovered from surgery.
4. Subject has received an investigational drug or therapy for disease other than HCC within ≤ 4 weeks or 5 half-lives, whichever is shorter, prior to starting study treatment on Cycle 1 Day 1.
5. Subject has completed any radiation treatment < 2 weeks prior to starting study treatment.
6. Subject has received the last dose of α-interferon, ribavirin, sofosbuvir and/or other antiviral therapies for HCV < 4 weeks prior to starting study treatment.
7. Subject has any clinically significant bleeding, including bleeding from esophageal/gastric varices within ≤ 3 months of signing the ICF, which required transfusion, surgical procedure or hospitalization. Esophageal varices should be treated according to local standard practice (eg, ligation or banding and procedure completed ≤ 3 months prior to signing the ICF).
8. Subject has histologic proof of fibrolamellar carcinoma, sarcomatoid HCC and combined hepatocellular-cholangiocarcinoma (cHCC-CC).
9. Subject has tumor invasion of stomach or duodenum or known symptomatic brain metastasis.
10. Subject has persistent diarrhea due to a malabsorptive syndrome (such as celiac sprue or inflammatory bowel disease) malabsorption ≥ National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 4.03) Grade 2, despite medical management, or any other significant gastrointestinal disorder that could affect the absorption of CC-122.
11. Subject has a concurrent second cancer requiring active, ongoing systemic treatment.
12. Subject has a known history of human immunodeficiency virus (HIV) seropositivity (HIV testing is not mandatory).
13. Subject has peripheral neuropathy ≥ NCI CTCAE Grade 2.
14. Subject has a history of persistent skin rash ≥ NCI CTCAE Grade 2.

15. Subject has impaired cardiac function or clinically significant cardiac disease including any of the following:
    a. Left ventricular ejection fraction (LVEF) < 45% as determined by multi-gated acquisition (MUGA) scan or echocardiogram (ECHO)
    b. Complete left bundle branch or bifascicular block
    c. Congenital long QT syndrome
    d. Persistent or clinically meaningful ventricular arrhythmias
    e. QTcF > 460 msec on screening electrocardiogram (ECG)
    f. Unstable angina pectoris or myocardial infarction ≤ 6 months prior to starting either IP
    g. Uncontrolled hypertension (blood pressure > 140/90 mmHg on at least 2 measurements on sequential visits, despite blood pressure medication)
    h. Troponin-T value > ULN or brain natriuretic peptide (BNP) > 300 pg/mL
        a. Subjects with baseline BNP > 100 pg/mL are eligible but must have a cardiologist evaluation prior to enrollment in the trial for baseline assessment and optimization of cardioprotective therapy.
16. Subject has acute or chronic active infectious disorders or uncontrolled nonmalignant illnesses whose control, in the opinion of the investigator, may be jeopardized by complications of this study therapy. Subjects with chronic HBV and HCV are excepted (ie, eligible for study).
17. Subject has undergone liver transplantation or other solid organ transplantation requiring ongoing immunosuppression.
18. Subject is receiving chronic treatment with systemic corticosteroids or other potentially immunosuppressive agent. Intermittent topical or local injection of corticosteroids and oral/IV aldosterone or other mineralocorticoids is allowed.
19. Subjects with history of non-healing wounds or ulcers, or bone fractures ≤ 3 months of a prior fracture.
20. Subject has active, known autoimmune disease.
21. Subject is a female who is pregnant or is breast feeding.
22. Subject is unwilling or unable to comply with the protocol, in the opinion of the investigator.
23. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
24. Subject has any condition that confounds the ability to interpret data from the study.
25. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.

5. TABLE OF EVENTS

Table 3: Table of Events

	Screening Period		Treatment Period											Follow-up Period	Follow-up Period	
	Screening[a]	Cycle 1				Cycle 2					Subsequent Cycles		EOT			
Day[b]	-28 to -1	1[c]	8	15	22	1	8	15	18	22	1	15		28 day follow-up	90 days follow-up	Disease Progression/ Survival/ Pregnancy
STUDY ENTRY																
Informed consent	X															
Pregnancy prevention counseling	Pregnancy risk counseling and education prior to dispensing of IP															
Demographics	X															
Prior cancer history	X															
Prior/post cancer therapies	X													At the same schedule as survival visits		
Complete medical history	X															
Prior/ concomitant medication evaluation	X	Continuous, until 28 days after treatment discontinuation														
Prior/ concomitant procedures evaluation	X	Continuous, until 28 days after treatment discontinuation														
Inclusion/exclusion criteria	X															
SAFETY ASSESSMENTS																
Adverse event collection	Continuous starting after informed consent signature, until 28 days after last dose of CC-122 and 90 days after the last dose of nivolumab or at any time afterwards if the PI feels the event is related to any IP															
Physical examination (source documented only)	X	X				X					X		X			
Ophthalmologic exam	X	As clinically indicated														

Table 3: Table of Events (Continued)

	Screening Period		Treatment Period											Follow-up Period	Follow-up Period	
	Screening[a]	Cycle 1				Cycle 2					Subsequent Cycles		EOT			
Day[b]	-28 to -1	1[c]	8	15	22	1	8	15	18	22	1	15		28 day follow-up	90 days follow-up	Disease Progression/ Survival/ Pregnancy
Weight	X	X				X					X		X			
Height	X															
Vital signs	X	X[b]	X	X	X	X					X		X			
ECOG PS	X	X[a]				X					X		X			
CBC with differential	X (-14 to -1)	X[a]	X	X	X	X	X	X	X	X	X	X Cycles 3-6 only	X			
Coagulation: PT, INR, PTT	X (-14 to -1)	X[a]				X					X					
Troponin-T and BNP	X	X[a]	X	X	X	X					X		X			
Chemistry laboratory (fasting, routine)	X (-14 to -1)	X[a]	X	X	X	X	X	X		X	X		X			
Amylase, lipase, T3, CK, TSH, fT4, immuno-globulins (IgG, IgM and IgA only) and T cell subsets (CD4+ and CD8+)	X	X[a]		X		X		X			X		X			
HBV and HCV serologies (HBsAg, HBeAg, HBsAb, HBeAb, HBcAb, HCVAb)	X															
HCV viral load	X															
HBV viral load	X	If HBsAg and/or HBcAb positive at screening, on day 1 of each cycle and at EOT														

Table 3: Table of Events (Continued)

	Screening Period		Treatment Period											Follow-up Period	Follow-up Period	
	Screening[a]	Cycle 1				Cycle 2					Subsequent Cycles		EOT			
Day[b]	-28 to -1	1[c]	8	15	22	1	8	15	18	22	1	15		28 day follow-up	90 days follow-up	Disease Progression/ Survival/ Pregnancy
Urinalysis	X (-14 to -1)					X					X					
Triplicate 12-lead electrocardiogram	X	X	X	X	X	X					X		X			
LVEF	X										X every 3 cycles		X			
Serum and/or urine β-hCG (in females of childbearing potential [FCBP] only)	X[d] (-14 to -1)	Prior to first dose of study drug and as PPRMP indicated.														
EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS																
[redacted]		[redacted]		[redacted]												
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]					
[redacted]	[redacted]															

Table 3: Table of Events (Continued)

	Screening Period		Treatment Period											Follow-up Period	Follow-up Period	
	Screening[a]	Cycle 1				Cycle 2					Subsequent Cycles		EOT			
Day[b]	**-28 to -1**	**1[c]**	**8**	**15**	**22**	**1**	**8**	**15**	**18**	**22**	**1**	**15**		**28 day follow-up**	**90 days follow-up**	**Disease Progression/ Survival/ Pregnancy**
Fresh paired tumor biopsy	X[f]								D18 (+/- 7 days, preferably after 3 continuous days of CC-122 adminis-tration)[g]							
Tumor evaluation (CT or MRI)	X (-28 to -1)	RECIST 1.1 Every 8 weeks (±7 days) for the first 10 months, then every 12 weeks (±7 days), until death, lost to follow up, withdrawal of consent, progression or start of new anticancer therapy. See Section 6.5.1 irRECIST: At time of RECIST 1.1 progression if subject continues on treatment beyond progression. Additional evaluations should be performed at the time of rescan 4-6 weeks after RECIST 1.1 progression, and then again per standard of care. See Sections 6.5.2 and 6.5.4														
Alpha-fetoprotein	X	X				X					X		X			
INVESTIGATIONAL PRODUCT																
Administer CC-122		5/7 days continuously														
Administer nivolumab		Q2W														
CC-122 accountability		X	X	X	X	X	X	X		X	X	X	X			
Nivolumab accountability		Q2W											X[h]			X[h]
FOLLOW-UP																
Survival follow-up																Every 3 months (+/- 7 days)

Abbreviations: β-hCG = beta human chorionic gonadotropin; BNP = brain natriuretic peptide; CBC = complete blood count; CK = creatine kinase; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = End of Treatment; FCBP = females of child bearing potential; FFPE = formalin-fixed, paraffin embedded; fT4 = free T4; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAb= hepatitis B surface antibody; HBeAb = hepatitis B e antibody; HBcAb = hepatitis B core antibody; HCVAb = HCV antibody; HCV = hepatitis C virus; IG = immunoglobulin; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PI = Principal Investigator; PK = pharmacokinetic; PPRMP = Pregnancy Prevention Risk Management Plan; PT = prothrombin time; PTT = partial thromboplastin time; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; TSH = thyroid stimulating hormone.

[a] All screening assessments must be performed prior to enrollment and subsequent treatment, however, these events may occur on the same calendar day as long as they are completed prior to enrollment.

[b] An administrative window of ± 3 days is permitted for all cycles except Cycle 1 Day 1 (C1D1).

[c] C1D1 assessment may be omitted if screening assessment performed within 72 hours of first dose with the exception of the pregnancy test, see footnote d.

[d] As per PPRMP, FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting CC-122. The first pregnancy test must be performed within 10-14 days prior to the start of CC-122 and the second pregnancy test must be performed within 24 hours prior to the start of CC-122. The subject may not receive CC-122 until the study doctor has verified that the results of these pregnancy tests are negative.

[e] Pharmacodynamics biomarker sample to be collected with on-treatment tumor biopsy on Day 18 (± 7 days) at approximately 3 ± 1 hour post dose.

[f] Archival tumor tissue will be required only if fresh tissue is not evaluable at screening. See Sections 6.8.1 and 6.8.2.

[g] Sample may be collected on Day 18 ± 7 days of Cycle 2. The sample must be collected at 3 to 6 (±1) hours postdose. Due to the intermittent schedule of CC-122 administration, the sample should preferably be collected after at least 3 continuous days of administration.

[h] After discontinuation of nivolumab, females of childbearing potential must use effective contraception for at least 5 months.

6. PROCEDURES

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days prior to first dosing except as noted below and in Table 3. All screening assessments must be performed prior to enrollment and subsequently treatment, however, these events may occur on the same calendar day as long as they are completed prior to enrollment.

Any questions regarding subject eligibility should be directed to the Celgene Medical Monitor or designee. Waivers to the protocol will not be granted during the conduct of this trial under any circumstances.

Unless otherwise specified, all assessments should be performed locally. Screening eligibility criteria laboratory values must demonstrate subject eligibility. Screening assessments may be repeated within the screening window if necessary, and the most recently obtained result should be used to demonstrate eligibility.

The following will be performed at screening as specified in the Table of Events (Table 3) after informed consent has been obtained:

- Review of inclusion/ exclusion criteria
- Commencement of pregnancy prevention counseling, per the PPRMP (Appendix G, Section 18.7)
- Demographics
- Prior cancer history (including specific information regarding diagnosis, staging, and histology)
- Prior cancer therapies: includes surgery, radiation, systemic, locoregional, or any other therapy (eg, hormonal) for the subject's cancer
- Medical history (all relevant medical conditions occurring < 28 days before screening should be included)
- Prior and concomitant medication evaluation (includes those taken ≤ 28 days before the screening visit, except those taken for cancer which are recorded as part of prior cancer therapy)
- Prior and concomitant procedures (includes all procedures occurring ≤ 28 days before the screening visit)
- Adverse event evaluation (begins when the subject signs the informed consent form [ICF])
- Physical examination (source documented only), height, weight
- Vital signs (including blood pressure, temperature and pulse)
- Eastern Cooperative Oncology Group Performance Status

- Ophthalmologic exam to include visual acuity, slit-lamp exam with fluorescein for the anterior chamber, iris, and with pupillary dilatation (if required and not contraindicated) to assess the vitreous
- Complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with absolute differentials (neutrophils, lymphocytes, monocytes, eosinophils and basophils), and platelet count (Days -14 to -1)
- Coagulation panel: prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT) (Days -14 to -1)
- Chemistry laboratory (fasting, routine): including sodium, potassium, chloride, bicarbonate or carbon dioxide (CO_2), glucose, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/ serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), lactate dehydrogenase (LDH) and uric acid (Days -14 to -1)
- Amylase, lipase, creatine kinase (CK), T3, thyroid stimulating hormone (TSH), fT4, immunoglobulins (IgG, IgM and IgA only) and T cell subsets (CD4+ and CD8+)
- Alpha-fetoprotein
- Hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies (hepatitis B surface antigen [HBsAg], hepatitis B e antigen [HBeAg], hepatitis B surface antibody [HBsAb], hepatitis B e antibody [HBeAb], hepatitis B core antibody [HBcAb], hepatitis C virus antibody [HCVAb])
- Measurement of HBV viral load (HBV DNA quantitative by polymerase chain reaction (PCR) and HCV viral load (HCV ribonucleic acid [RNA] quantitative by PCR)
  - Confirmation of antiviral therapy with an appropriate antiviral agent for HBV is required in subjects with positive hepatitis B surface antigen, HBcAb IgM, and/or viral load - appropriate first line agents include entecavir, tenofovir, and lamivudine (note that lamivudine has higher resistance rates). Subjects with a detectable HBV and/or HCV viral load, HBcAb IgM, and/or HBsAg should be under the care of an expert hepatologist.
- Urinalysis (Days -14 to -1)
- 12-lead ECG, central assessment; when an ECG time-point coincides with any other assessment, the ECG should always be collected first
- Echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan for LVEF
- Troponin-T and BNP, central assessment
- Serum and/or urine beta human chorionic gonadotropin (β-hCG) (females of childbearing potential [FCBP] only) as per PPRMP

- Mandatory paired tumor biopsies (formalin fixed paraffin embedded) collection. (See Section 6.8)
- Pharmacogenomic blood sampling (see Section 6.8)
- Blood samples for biomarker analyses (See Section 6.8)
- Radiologic response assessment/tumor evaluation

6.2. Treatment Period

The subject must start treatment within 28 days of signing the ICF. For all subsequent visits, an administrative window of ±3 days is permitted.

Treatment cycles are 28 days in duration.

The following evaluations will be performed at the frequency specified in the Table of Events, Table 3. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- Pregnancy prevention counseling (monthly), per the PPRMP (Appendix G, Section 18.7)
- Adverse event evaluation (continuously)
- Concomitant medications evaluation (including medications for best supportive care)
- Concomitant procedures evaluation
- Physical examination (source documented only) and weight
- Vital signs (including blood pressure, temperature and pulse)
- ECOG PS
- Ophthalmologic exam (as clinically indicated)
- Complete blood count (CBC) with differential and platelets
- Coagulation panel: PT, INR, PTT
- Troponin-T and BNP, central assessment
- Chemistry laboratory (fasting, routine)
- Amylase, lipase, CK, T3, TSH, fT4, immunoglobulins (IgG, IgM and IgA only) and T cell subsets (CD4+ and CD8+)
- Alpha-fetoprotein
- Hepatitis B virus viral load: Hepatitis B viral load performed only in subjects with positive hepatitis B viral load at baseline and/or positive HBsAg, HBcAb total, and/or HBcAb IgM. Laboratory test may be performed up to 48 hours before the visit.
- Urinalysis
- 12-lead ECG, central assessment; when an ECG time-point coincides with any other assessment, the ECG should always be collected first

- Echocardiogram or MUGA scan for LVEF
- Serum and/or urine β-hCG (weekly during Cycle 1, females of childbearing potential [FCBP] only) as per PPRMP
- Dispense and account for both IPs
- Pharmacokinetic sampling (see Section 6.6)
- Mandatory paired tumor biopsies (formalin fixed paraffin embedded) collection. (See Section 6.8)
- Blood samples for biomarker analyses. see (Section 6.8)
- Radiologic response assessment/tumor evaluation and assessment of disease progression (see Section 6.5)

6.3. End of Treatment

An end of treatment (EOT) evaluation should be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in the Table of Events, Table 3:

- Physical examination (source documented only) and weight
- Vital signs
- Concomitant medications evaluation
- Concomitant procedures evaluation
- ECOG PS
- Ophthalmologic exam (as clinically indicated)
- Complete blood count with differential and platelets
- Troponin-T and BNP, central assessment
- Chemistry laboratory (fasting, routine)
- Amylase, lipase, CK,T3, TSH, fT4, immunoglobulins (IgG, IgM and IgA only) and T cell subsets (CD4+ and CD8+)
- Alpha-fetoprotein
- Echocardiogram or MUGA scan for LVEF
- 12-lead ECG
- Adverse event evaluation
- Urine and/or serum β-hCG (for females of childbearing potential) as per PPRMP
- Radiologic response assessment/tumor evaluation and assessment of disease progression

- CC-122 and nivolumab accountability

6.4. Follow-up Period

6.4.1. Safety Follow-up

All subjects will be monitored for reporting of new or follow-up of existing concomitant medications, concomitant procedures and AEs for 28 days after the last dose of CC-122.

An additional safety follow-up is required after 90 days from the last dose of nivolumab.

Pregnancy will be reported according to Section 10.4.1, females of childbearing potential will be monitored for the mandatory use of effective contraception for at least 5 months after the last dose of nivolumab.

6.4.2. Efficacy Follow-up

All subjects who discontinue treatment for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study will be followed for response until confirmation of disease progression and/or initiation of new anticancer therapies.

6.4.3. Survival Follow-up

After the EOT visit, all subjects will be followed for survival status either until death, lost to follow-up, or until two years from enrollment, whichever event occurs first. This evaluation should be conducted every 3 months (±7 days) thereafter. New anticancer therapies will also be collected at the same schedule. New anticancer therapy includes (but is not limited to) any systemic or locoregional medication, surgery, radiation, or any other therapy intended to treat the subject's cancer.

Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

6.5. Efficacy Assessments

Tumor assessments will be performed at screening (up to 28 days before the start of study treatment), every 8 weeks (±7 days) for the first 5 evaluations (through Month 10), thereafter every 12 weeks (±7 days), regardless of treatment status. Tumor assessments should also be performed at any time, if clinically indicated. Tumor assessments should continue at the defined schedule until radiologic disease progression or the start of new anticancer therapy, beyond the end of treatment if necessary.

Response will be assessed using RECIST 1.1 (investigator assessment), and irRECIST as an exploratory assessment. An independent review of efficacy results may take place at any time at the discretion of the study Sponsor. Other exploratory efficacy variables, such as ECOG PS, AFP reduction, etc, will be summarized as well.

6.5.1. Assessment of Response According to RECIST 1.1

Response assessments include computed tomography (CT) scan or magnetic resonance imaging (MRI). The regions to be imaged are the chest and abdomen/pelvis, as well as any other sites

required for tumor imaging. The same mode of imaging for lesion evaluation at screening must be used consistently throughout the study.

The CT imaging should include contrast unless medically contraindicated. Conventional CT should be performed with contiguous cuts of 5 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm.

All subjects with evidence of objective tumor response (CR or PR) should have the response confirmed with repeat assessments at the next scheduled scan, but after no less than 4 weeks. Response assessments must have occurred ≥ 6 weeks from Cycle 1 Day 1 to be considered as stable disease (SD) for a best response.

Additional details and definitions of response are found in Appendix B in Section 18.2.

6.5.2. Treatment Beyond Progression

Subjects will be permitted to continue treatment beyond initial RECIST 1.1 defined progressive disease as long as they meet the following criteria:

- Continue to meet all other study protocol eligibility criteria
- Investigator assessed clinical benefit and do not have rapid disease progression or clinical deterioration
- Stable performance status
- Tolerance to IP
- Other treatment options, including no treatment and supportive care, have been discussed and subject has consented to continue IP

A follow-up scan should be performed within 4 to 6 weeks of the original PD to determine whether there has been a decrease in the tumor size, or continued PD. Thereafter, response assessment should occur per standard of care. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject may remain on study treatment. The decision to continue treatment should be discussed with the Celgene Medical Monitor and documented in the study source documents.

Study therapy should be discontinued if further progression is documented. For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This increase in tumor burden includes an increase in all target lesions and/or the development of new measurable lesions.

6.5.3. Other Assessments

Additional scans, including brain scans, or nuclear medicine bone scan may be performed if clinically indicated (eg, symptoms of brain metastasis) at the discretion of the Investigator.

6.5.4. Assessment of Response According to Immune-Related Response Criteria (irRECIST)

Evaluation of response will also be performed using irRECIST guidelines as an exploratory, but not treatment-determining, assessment. Evaluation via irRECIST will begin if treatment is continued beyond RECIST 1.1 documented progression. Additional details and definitions of irRECIST are found in Appendix C in Section 18.3.

6.6. Pharmacokinetics

Plasma/serum samples will be collected to assay plasma concentrations of CC-122 and nivolumab.

On PK sampling days, dosing and sample collection information including dosing date, dosing time (24 hour clock), and actual PK blood sampling time (24 hour clock) should be accurately documented on the appropriate electronic case report form (eCRF) pages.

6.6.1. Pharmacokinetics of CC-122

Pharmacokinetic samples will be collected during the dose escalation part. No PK will be collected during the dose expansion part.

Dose Escalation Part (all subjects): Cycle 1 Day 15: predose (-30 to -5 minutes prior to CC-122 dose), 0.5 hour (± 5 minutes), 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 10 minutes), and 8 hours (± 60 minutes) after administration of CC-122.

On C1D15, subjects will be asked NOT to take CC-122 at home. CC-122 will be administered to these subjects at the study center after the collection of the predose PK blood sample. For convenience, on PK collection days CC-122 should be administered first, followed by nivolumab.

6.6.2. Pharmacokinetics of Nivolumab

Pharmacokinetic samples will be collected during the dose escalation part. No PK will be collected during the dose expansion part.

Dose Escalation Part (all subjects): Predose (-30 to -5 minutes prior to nivolumab dose) and end of infusion on C1D1 and C1D15.

6.7. 12-lead Electrocardiograms

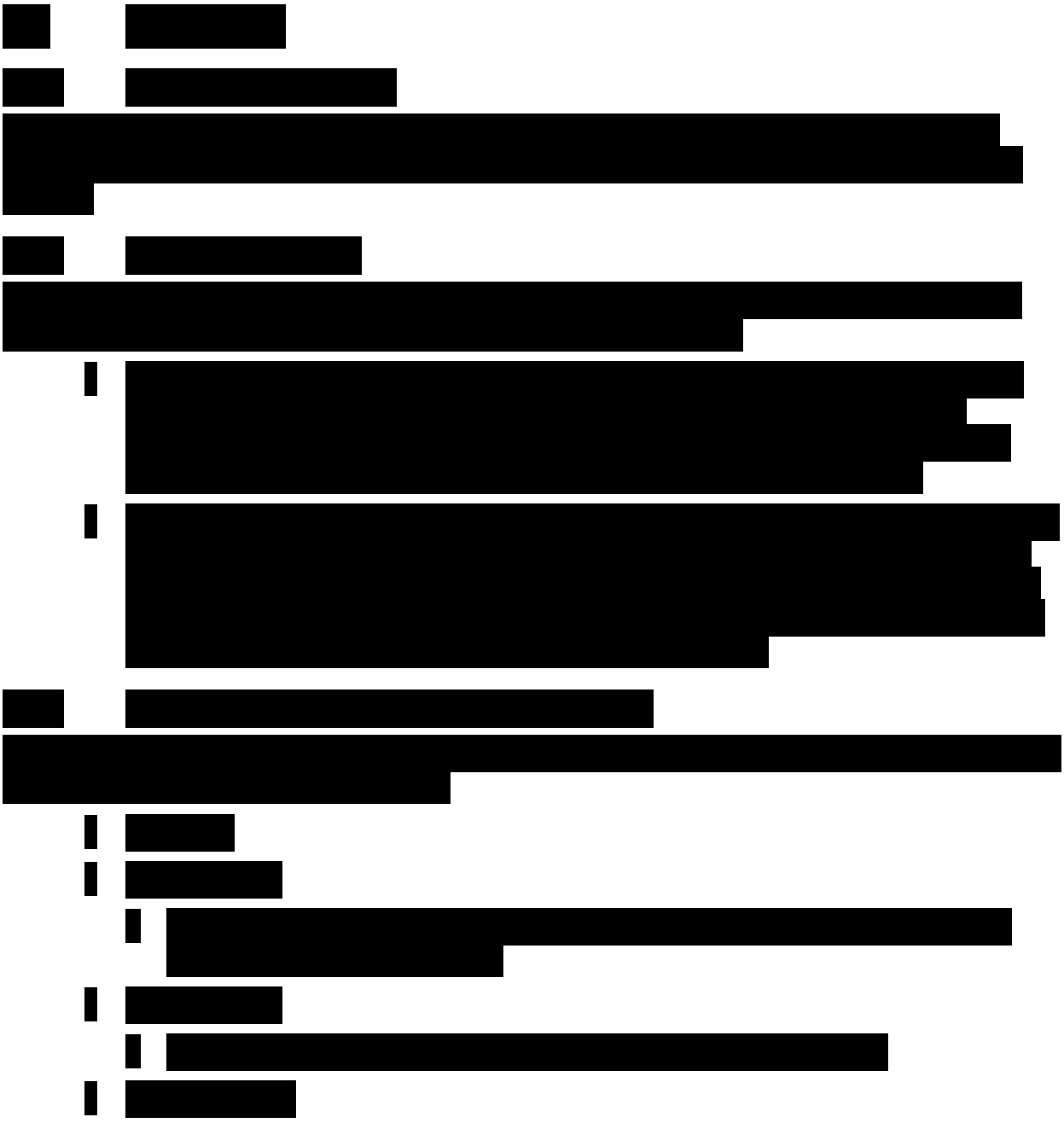
Triplicate 12-lead ECGs will be recorded at the visits listed in Table 3 and assessed centrally. The 12-lead ECGs (12-lead at 25 mm/second reporting rhythm, ventricular rate, PR-interval, QRS complex, QT interval, and QTcF interval) will be performed after the subject has been in the supine position for at least 5 minutes.

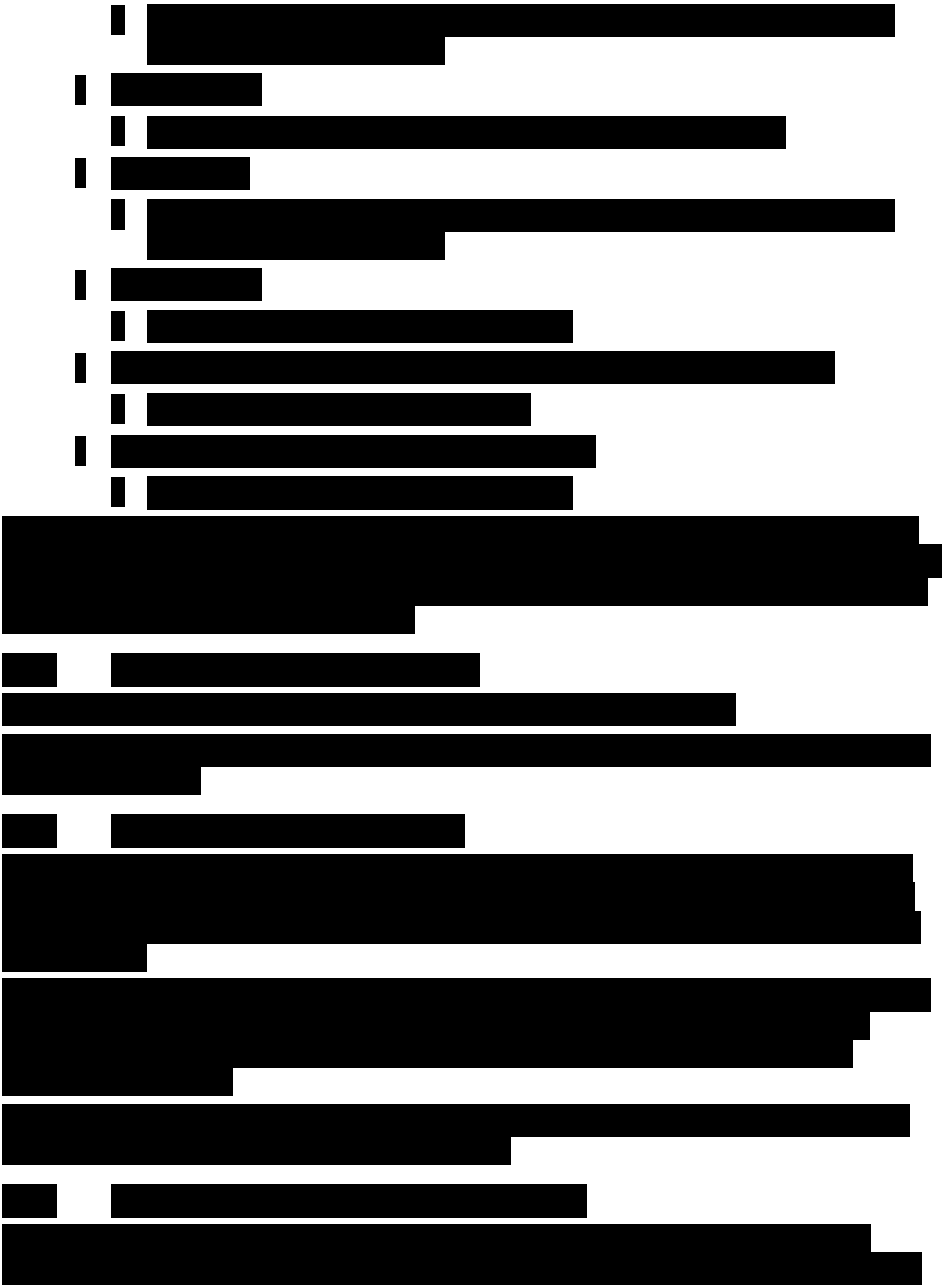
Triplicate ECGs (3 recordings within 2±1 minute intervals) will be performed at the following time points:

- Screening
- Cycle 1, Day 1 - Predose (0 hour; within 90 minutes prior to CC-122 dosing)

- Cycle 1, Day 8, 15, and 22 – Predose (0 hour; within 90 minutes prior to CC-122 dosing), 1.5 (±15 minutes) and 3 hours (±15 minutes) postdose
- Day 1 of Cycle 2 and subsequent cycles - Predose (0 hour; within 90 minutes prior to CC-122 dosing)

Subjects will be asked NOT to take CC-122 at home on ECG evaluation days. CC-122 will be administered to these subjects at the study center after the predose ECG is conducted. For convenience, on ECG evaluation days CC-122 should be administered first, followed by nivolumab.





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6.9. CC-122 Risk Counseling Prior to Dosing

CC-122 Pregnancy Risk Minimization Plan for Celgene Clinical Trials (Appendix G, Section 18.7) applies to all subjects receiving CC-122 therapy.

CC-122 will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene, or designee, in requirements specific to counseling of subjects. Once trained these healthcare staff will counsel subjects prior to the administration of CC-122 to ensure that the subject has complied with all requirements including use of birth control and that the subject understands the risks associated with CC-122. This step will be documented with a completed Education and Counseling Guidance Document, and CC-122 will not be administered until this step occurs.

A CC-122 Information Sheet will be provided to each subject before IP is dispensed.

Females of childbearing potential and fertile males, other than the subject, should not handle or administer CC-122 unless they are wearing gloves.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

7.1.1. CC-122

CC-122 will be supplied by Celgene Corporation. CC-122 is available as a 1.0 mg formulated capsule (equivalent to 1.13 HCl), 2.0 mg formulated capsule (equivalent to 2.254 HCl), 2.5 mg formulated capsule (equivalent to 2.818 HCl), 3.0 mg formulated capsule (equivalent to 3.38 HCl), 3.5 mg formulated capsule (equivalent to 3.95 HCl), and 4.0 mg formulated capsule (equivalent to 4.51 mg HCl). Each formulated capsule is provided in reddish brown gelatin capsules, containing the following excipients: Avicel PH 102, spray dried mannitol, crospovidone, aerosil and stearic acid.

7.1.2. Nivolumab

Nivolumab 100 mg vials (10 mg/mL) will be supplied by Celgene Corporation and labeled appropriately as investigational material for this study. Nivolumab vials must be stored in the refrigerator at 2°C to 8°C, protected from light and freezing.

7.2. Treatment Administration and Schedule

The study is designed to explore three dose levels of CC-122 to identify the RP2D, and is not required to escalate to a NTD or MTD. CC-122 will initially be administered orally 5 consecutive days out of 7 (5 days on/2 days off weekly) on Days 1 to 5, 8 to 12, 15 to 19 and 22 to 26 of each 28-day cycle. The investigated starting daily dose of CC-122 will be 2.0 mg, and two subsequent dose levels (3.0 and 4.0 mg) are planned to be evaluated as described in Table 4, based on pre-specified DLTs. Intermediate dose levels, or a higher dose level, may be evaluated at the discretion of the Safety Review Committee (SRC). Dose escalation to intermediate or higher dose levels of CC-122 will not exceed 50% of the previously established tolerable dose level. Smaller dose increments based on toxicity, PK profile and PD findings may be evaluated, if necessary. Nivolumab will be administered at the dose of 3.0 mg/kg IV every 2 weeks. Once the RP2D for dosing of CC-122 in combination with nivolumab is defined, expansion (Phase 2) will start. Investigational products will be administered for up to 2 years.

7.2.1. Dose Levels

Dose levels to be explored are shown in Table 4.

Table 4: Dose Levels

Dose Level	CC-122 Dose (mg)	CC-122 Schedule (days)	Nivolumab Dose (mg/kg)	Nivolumab Schedule
- 1	1.0	5/7	3.0	Every 2 weeks
1	2.0	5/7	3.0	Every 2 weeks
2	3.0	5/7	3.0	Every 2 weeks
3	4.0	5/7	3.0	Every 2 weeks

Dosing will start at dose level 1. Each dose level must be cleared by the SRC based on review of all available clinical, safety, PK, PD and laboratory data before initiating the next higher dose level. The study intends to identify the RP2D at or below the 4.0 mg dose level, however intermediate or higher dose levels may be explored at the discretion of the SRC.

During dose escalation, the decision to either evaluate a higher dose level, an intermittent dose schedule, or declare the RP2D (or if applicable NTD) will be determined by the SRC, based on their review of all available clinical data, PK, PD and laboratory safety data for a given dose cohort.

Intra-subject dose escalation of CC-122 is not permitted during Cycle 1, but may be permitted in later cycles if approved by the SRC.

Dose reduction of CC-122 and temporary interruption of one or both IPs due to toxicity during Cycle 1 is allowed but may constitute a DLT, as outlined in Section 7.6 and 7.9.

Study treatment may be discontinued if there is evidence of clinically significant disease progression, unacceptable toxicity or subject/physician decision to withdraw. Subjects may continue to receive CC-122 and nivolumab beyond disease progression at the discretion of the Investigator.

If any subject continues to experience unacceptable toxicity after permitted IP adjustments, one or both IPs will be discontinued permanently.

The estimated total number of subjects to be enrolled during dose escalation is approximately 20 to 30, depending on cohort size. Up to 30 additional subjects will be evaluated for safety, PK, PD, and preliminary anti-tumor effects in one or two expansion cohorts.

7.3. Definition of a DLT Evaluable Subject

All subjects who receive at least one dose of either CC-122 or nivolumab will be evaluable for DLT.

In the dose escalation part, a subject evaluable for DLT is defined as one who:

- Received at least 75% of the planned doses of CC-122 and of nivolumab during Cycle 1 without experiencing a DLT, having been followed for the entire DLT assessment period (see Section 7.6)

  or

- Experienced a DLT after receiving at least one dose of either IP.

Non-evaluable subjects will be replaced at the discretion of the SRC. Additional subjects within any dose cohort may be enrolled at the discretion of the SRC.

7.4. Definition of Non-tolerated Dose

An NTD is defined as a dose level at which 2 or more out of up to 6 evaluable subjects in any dose cohort experience a DLT in Cycle 1. Escalation to an NTD is not required in this study, as described in Section 7.2

7.5. Definition of Maximum Tolerated Dose (MTD)

If an NTD is identified, dose escalation will be stopped. The MTD is defined as the last dose level below the NTD with none or 1 out of 6 evaluable subjects experiencing DLT during Cycle 1. The RP2D may be a dose that meets the definition of MTD, however escalation to an MTD is not required in this study, as described in Section 7.2.1

7.6. Definition of Dose-Limiting Toxicity

During dose escalation, the DLT assessment period is defined as Days 1 to 28 of Cycle 1 including the predose assessments specified for Day 1 of Cycle 2.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 are used as a guide for the grading of severity of adverse events.

A DLT is defined as any of the following toxicities occurring within the DLT assessment window unless the event can clearly be determined to be unrelated to the drug. Dose-limiting toxicities are described below:

- Any toxicity that would lead to dose reduction or discontinuation of CC-122 or discontinuation of nivolumab during Cycle 1.
- Any Grade 4 non-hematologic toxicity of any duration.
- Any clinically relevant non-hematologic toxicity that is ≥ Grade 3 except for:
  - Grade 3 diarrhea or vomiting of not more than 5 days duration (with optimal medical management)
  - Grade 3 fatigue or asthenia of not more than 3 days duration with optimal medical management
- Grade 3 infusion-related reaction controlled by interruption of the infusion and medical management Any liver enzymes elevation according to the definitions below:
  - AST or ALT ≥8 x ULN of > 7 days duration
  - Total bilirubin ≥5 x ULN of > 7 days duration
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Hematological toxicities during Cycle 1 as follows:
  - Grade 4 neutropenia lasting > 7 days
  - Febrile neutropenia
  - Grade 4 thrombocytopenia lasting > 48 hours
  - Grade 3 or 4 thrombocytopenia with clinically significant bleeding
- Any ≥ Grade 2 uveitis or eye pain that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period (≤ 6 weeks and/or prior to next nivolumab dose), or requires systemic treatment.

- Any ≥ Grade 2 pneumonitis or interstitial lung disease that does not resolve with dose delay and systemic steroids. The management algorithm for pneumonitis or pulmonary toxicity can be found in the current nivolumab SmPC and in Appendix H.

Repeat laboratory assessments are required to confirm the duration of time-bound DLT criteria.

Isolated laboratory changes without associated clinical signs or symptoms (eg, hypomagnesemia, hypermagnesemia, hypoalbuminemia, hypophosphatemia, lymphocyte count increased or decreased) may not be included in this definition. These findings will be discussed and reviewed by the SRC.

Events meeting the DLT definition occurring beyond the first cycle will be taken into account when determining the RP2D. Any AE with the potential to become a DLT based on the duration should be followed appropriately to accurately determine the duration of the event.

Subjects should delay/interrupt or discontinue treatment if they experience any adverse event, laboratory abnormality or intercurrent illness (regardless of causality) which, in the opinion of the investigator, presents a substantial clinical risk to the subject with continued dosing of any IP. Such delay/interruption or discontinuation, however, will not be considered a DLT unless it meets at least one of the DLT criteria defined above or if deemed dose-limiting by the SRC.

7.7. Method of Treatment Assignment

An integrated response technology (IRT) will be used to track subject assignments to the dose levels.

7.8. Criteria for Dose Escalation

The SRC will make dose escalation decisions. The decision criteria for dose escalation are:

- If no DLT is observed in the first 3 evaluable subjects during the first cycle, dose escalation to the next higher dose level may occur.
- If 1 out of 6 evaluable subjects experiences DLT during the first cycle, dose escalation to the next higher dose level may occur. Additional subjects will be enrolled to expand the cohort to 6 evaluable subjects if less than 6 subjects are evaluable when the DLT is observed.
- If 2 or more out of up to 6 evaluable subjects experience a DLT during the DLT assessment period in a cohort, any further recruitment into that cohort will cease and this dose will be defined as an NTD.
- The SRC will determine if additional subjects will be enrolled in a parallel or at lower dose cohorts to have 6 evaluable subjects in order to define RP2D, or whether an intermediate dose level or an intermittent dosing schedule will be explored in up to 6 newly enrolled subjects. Additional subjects may be added at a given dose level to further assess the safety and/or PK.

Based on above criteria, if no DLT is observed in at least 3 evaluable subjects, the SRC may decide to escalate the dose to the next cohort.

If one DLT occurs prior to a decision by the SRC to dose escalate, the cohort will be expanded to enroll 6 evaluable subjects in total. Subjects 4 to 6 may be enrolled concurrently with the first 3 subjects if complete 28-day toxicity data are not yet available for the first 3 subjects.

If 1 subject out of 6 evaluable subjects experiences a DLT, the dose will be escalated in the next cohort, unless there are other safety considerations by the SRC. The dose may also be declared the RP2D.

The number of cohorts depends on incidence of DLT. A subject may experience more than 1 DLT. Dose escalation decisions are based on the number of subjects experiencing DLT events.

Intra-subject dose escalation beyond the dose initially assigned to a subject is not permitted in Cycle 1. Those continuing to take IP beyond Cycle 1, following approval by the SRC, may have the dose level increased providing the alternative dose level has been shown to be well tolerated by at least one cohort of other subjects in this study.

7.8.1. Definition of Stopping Criteria for Dose Escalation

Dose escalation stops when 2 or more out of up to 6 evaluable subjects at any dose level experience DLT, or when the RP2D is declared.

7.9. Permitted IP Adjustments

CC-122 dose reductions are permitted in any cycle, including Cycle 1; however in Cycle 1 this may constitute DLT. No dose reductions are allowed for nivolumab.

- Any toxicity, unless the event can clearly be determined to be unrelated to the IPs, should be managed according to the following tables.
- In the absence of clear alternative causes of liver enzyme abnormalities meeting DLT criteria, both IPs should be held and/or discontinued.
- Any treatment-related toxicity that leads to dose reduction or discontinuation of CC-122 or discontinuation of nivolumab that occurs in Cycle 1 during dose escalation will constitute DLT.
- Subjects will be allowed to continue with CC-122 at a reduced dose.

Allowed dose reductions for CC-122 are described in Table 5.

For CC-122, dose reductions below 1.0 mg are not allowed.

Table 5: Allowed Dose Reductions

CC-122 Starting Dose	First Reduction	Second Reduction
1.0 mg (5/7)	NA	NA
2.0 mg (5/7)	1.0 mg (5/7)	NA
3.0 mg (5/7)	2.0 mg (5/7)	1.0 mg (5/7)
4.0 mg (5/7)	3.0 mg (5/7)	2.0 mg (5/7)

5/7 = 5 out of 7 days; NA = not applicable.

- CC-122 may be dose reduced at the discretion of the investigator and based on guidelines in Section 7.10.
- If any subject continues to experience unacceptable toxicity after the dose reductions described above one or both IPs will be discontinued permanently.
- Once CC-122 dosage has been reduced, it can be escalated when toxicity reaches ≤ Grade 1. If toxicity recurs at the higher dose, the dose will be reduced a second time, but no re-escalation is then permitted.

7.10. Criteria for CC-122 Dose Reduction

Any IP-related toxicity meeting the definition of DLT will require dose reduction and/or interruption. The criteria for dose reduction listed in Table 6 and Table 7 should be used for dose modifications.

Chronic Grade 2 toxicity may warrant dose reduction of CC-122. It is recommended that such cases be discussed with the Sponsor before changes are made.

Table 6: Dose Adjustment Guidelines for CC-122 Related Non-hematologic Toxicities

Toxicity	Action
AST or ALT ≥8 x ULN, OR Total bilirubin ≥5 x ULN, OR Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN	• Hold CC-122 until laboratory values return to baseline and management with corticosteroids, if needed, is complete • Reintroduce CC-122 at the same or to the next lower dose level, if available, depending on whether toxicity meets DLT criteria (Section 7.6)
Grade 4 liver enzyme or bilirubin elevation or clinical liver failure	• Permanently discontinue CC-122
If recurrence of Grade 3 event after dose-reduction	• Reduce dose to the next lower dose level; if available.
If recurrence of Grade 4 event after dose reduction	• Discontinue CC-122
Any non-hematological toxicity requiring interruption for > 4 weeks	• Discontinue CC-122

Table 6: Dose Adjustment Guidelines for CC-122 Related Non-hematologic Toxicities (Continued)

Toxicity	Action
Troponin-T > ULN with associated 20% increase in BNP over baseline with an absolute value > 100 pg/mL (confirmed on repeated measurements) without associated cardiac symptoms or findings	• Hold CC-122 • Cardiology evaluation, notify Sponsor • Follow troponin-T, BNP, and ECG at least every 7 days • If troponin-T returns to normal levels in ≤ 7 days and there are no other significant cardiac findings, restart CC-122 at next lower dose level or same dose • If troponin-T elevation persists beyond 7 days or recurs upon rechallenge, permanently discontinue CC-122
Troponin-T > ULN with cardiac symptoms or significant changes in ECG or LVEF	• Discontinue CC-122, notify Sponsor
Rash Grade 1	• Management with topical corticosteroid creams and/or oral antipruritic as clinically indicated.
Rash Grade 2	• Continue therapy if involvement of < 30% of body surface area, are asymptomatic or toxicity can be managed with topical corticosteroid creams and antipruritics. • If rash does not meet the above criteria, hold CC-122 and initiate treatment with topical corticosteroids. o Consider systemic corticosteroids if rash does not improve to ≤ Grade 1 in ≤ 7 days.
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 CC-122 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, acneiform, or pustular rashes lasting ≤ 7 days medical management is warranted

Table 6: Dose Adjustment Guidelines for CC-122 Related Non-hematologic Toxicities (Continued)

Toxicity	Action
Peripheral neuropathy (neuropathies which begin or worsen while on study) ≥ Grade 3	• Hold CC-122 at Investigator's discretion • 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 ≥ Grade 3	• Hold CC-122 and start anticoagulation; restart CC-122 at Investigator's discretion (maintain dose level)
Pneumonitis Grade 2	• Hold CC-122 and nivolumab (see Table 8), consider corticosteroids • Restart CC-122 at next lower dose level once completely resolved
Pneumonitis ≥ Grade 3	• Discontinue CC-122 and nivolumab (see Table 8) • Corticosteroids recommended until symptoms resolve
Tumor flare reaction (TFR) Grades 1-2	• Continue CC-122, maintain dose level • NSAIDs and/or narcotics may also be used as per investigator's discretion • Initiate therapy with corticosteroids at the Investigator's discretion
Tumor flare reaction (TFR) Grades 3-4 (severe – disabling)	• Hold CC-122 • Initiate therapy with corticosteroids • NSAIDs and/or narcotics may also be used per Investigator's discretion • When symptoms resolve ≤ Grade 1, restart CC-122 at the same dose level
Other ≥ Grade 3	• Hold CC-122 at Investigator's discretion • When the toxicity resolves to ≤ Grade 2, restart CC-122 at the same dose level or the next lower dose level at Investigator´s discretion

AE = adverse event; BNP = brain natriuretic peptide; ECG = electrocardiogram: IP =investigational product; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal anti-inflammatory drug; ULN = upper limit of normal.

Table 7: Dose Adjustment Guidelines for CC-122 Related Hematologic Toxicities

Toxicity	Action
Grade 2 thrombocytopenia	• No action
Grade 3 thrombocytopenia	• Hold until resolution to Grade ≤ 1 or baseline • Follow complete blood count (CBC) at least every 7 days • If resolution to Grade ≤1 or baseline 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 or baseline • Repeat CBC within 24 to 48 hours • 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 5 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 CC-122 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

AE = adverse event; CBC = complete blood count; G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony stimulating factor.

7.10.1. Nivolumab Dose Delay/Interruption Criteria

Nivolumab treatment-related interruptions > 6 weeks requires treatment discontinuation (refer to 7.10.3).

Nivolumab administration should be delayed/interrupted according to Table 8:

Table 8: Recommended Treatment Modification for Nivolumab

Immune-related AE	Severity	Treatment Modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold nivolumab until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue nivolumab
Immune-related colitis	Grade 2 or 3 diarrhea or colitis	Withhold nivolumab until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhea or colitis	Permanently discontinue nivolumab
Immune-related hepatitis	AST or ALT ≥8 x ULN, OR Total bilirubin ≥5 x ULN, OR Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN	Withhold nivolumab until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 4 liver enzyme or bilirubin elevation or clinical liver failure	Permanently discontinue nivolumab
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold nivolumab until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue nivolumab
Immune-related endocrinopathies	Symptomatic endocrinopathies (including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency and diabetes)	Withhold nivolumab until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Nivolumab should be continued in the presence of hormone replacement therapy as long as no symptoms are present
Immune-related rash	Grade 1 rash	Management with topical corticosteroid creams and/or oral antipruritic as clinically indicated.

Table 8: Recommended Treatment Modification for Nivolumab (Continued)

Immune-related AE	Severity	Treatment Modification
	Grade 2 rash	Continue therapy if involvement of < 30% of body surface area, are asymptomatic or toxicity can be managed with topical corticosteroid creams and antipruritics. If rash does not meet the above criteria, hold nivolumab and initiate treatment with topical corticosteroids. Consider systemic corticosteroids if rash does not improve to ≤ Grade 1 in ≤ 7 days.
	Grade 3 rash	Withhold dose until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue nivolumab

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Nivolumab should also be permanently discontinued for Grade 2 or 3 immune-related AEs that persist despite treatment modification or for inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day.

Consider resuming nivolumab only in subjects whose adverse reactions recover to ≤ Grade 1 or baseline.

Please refer to the nivolumab SmPC for updated details.

7.10.2. Nivolumab Dose Reductions

There will be no intra-subject dose reductions of nivolumab during the study.

7.10.3. Nivolumab Dose Interruption / Discontinuation

- Any Grade 2 drug-related uveitis or 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 (≤ 6 weeks and/or prior to next nivolumab dose) OR requires systemic treatment.
- Any dosing delay/interruption lasting > 6 weeks with the following exceptions: Dosing delays/interruptions to manage drug-related AEs such as prolonged steroid tapers are allowed. Prior to re-initiating treatment in the subjects with dosing delays/interruptions lasting > 6 weeks, the Celgene Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed/interrupted.
- Dosing delays/interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Celgene Medical Monitor. Prior to re-initiating treatment for the subjects with a dosing delay/interruption lasting > 6 weeks, the Celgene

Medical Monitor must be consulted. Tumor assessment should continue as per protocol even if dosing is delayed/interrupted.

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

7.10.4. Management of Expected AEs While Receiving CC-122

7.10.4.1. Neutropenia, Thrombocytopenia, Anemia

Approximately 50% of subjects treated in Part B of CC-122-ST-001 experienced neutropenia (preliminary data). Neutropenia and febrile neutropenia should be managed with CC-122 dose interruption and G-CSF administration. Hematopoietic growth factors or other hematologic support, such as erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF), GM-CSF, RBC- or platelet- transfusions are allowed in the study with therapeutic intent. Therapeutic use of G-CSF is allowed at any time for subjects experiencing Grade 4 neutropenia or any grade febrile neutropenia. Prophylactic use of granulocyte (or granulocyte-macrophage) growth factors is not allowed during Cycle 1.

7.10.4.2. Infection

In prior studies with CC-122 pyrexia and infections were observed in > 20% of subjects. Vigilance for the signs and symptoms of infection should be practiced and managed according to institutional standard medical practice. Routine infectious disease prophylaxis is not recommended; however, antibiotic, antiviral, antipneumocystis, antifungal, or other prophylaxis may be implemented during the study at the discretion of the investigator and/or SRC.

7.10.4.3. Pain

Tumor pain or treatment-induced pain can be controlled with opioid and opioid-related analgesics, such as codeine, meperidine, propoxyphene or morphine, administered at the clinician's discretion, and as dictated by medical need.

7.10.4.4. Dose Modification and Management of Cardiac Laboratory Abnormalities

Elevations of troponin-T or BNP warrant further investigation including assessment of the subject for signs and symptoms of cardiac injury, consideration of a cardiology consultation, and other cardiac evaluations (such as an exercise stress test, additional evaluation of LVEF, or other cardiac tests or cardioprotective medications recommended by a cardiologist), and the addition of cardioprotective therapy (eg, beta blockers or calcium channel blockers) as appropriate. Laboratory evaluation to assess for assay interference may also be warranted. For any confirmed elevation of troponin-T > ULN associated with significant elevation of BNP (20% increase from baseline and an absolute value > 100 pg/mL), CC-122 dosing should be held and the Sponsor should be notified. Additional cardiac monitoring should be performed as described in Table 6 and as medically indicated. CC-122 may be restarted at a reduced dose or the same dose, in consultation with the Sponsor, based on troponin-T/BNP guidelines in Table 6. For troponin-T elevations > ULN that either persist for > 7 days, recur with CC-122 rechallenge or are

associated with cardiac symptoms or significant changes in ECG or LVEF, CC-122 should be permanently discontinued.

In addition to routine ECG monitoring, please refer to the nivolumab SmPC for additional information regarding potential cardiac toxicity with nivolumab.

7.10.4.5. Dose Modification and Management of Pneumonitis

Pneumonitis has been observed in subjects taking CC-122. The diagnosis should be considered in subjects presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, dyspnea, or interstitial pulmonary infiltrates, and in whom infectious, neoplastic and other causes are excluded by appropriate investigations. Subjects should be specifically advised to report promptly any new or worsening respiratory symptoms they experience.

Those with radiological features suggestive of non-infectious pneumonitis but with minimal (Grade 1) symptoms may continue CC-122 without dose alteration. For drug-related Grade 2 pneumonitis, CC-122 and nivolumab treatment should be interrupted and corticosteroids may be indicated. Once symptoms have resolved to Grade 0 or 1, CC-122 may be reintroduced at the next lower dose level. For drug-related Grades 3 or 4 pneumonitis, CC-122 and nivolumab must be permanently discontinued and corticosteroids are recommended until clinical symptoms have resolved.

Pneumonitis has been also observed in subjects taking nivolumab. Pneumonitis may be considered related to both IPs. Please refer to nivolumab SmPC (or Appendix H in Section 18.8) for pneumonitis management guidelines in subjects receiving nivolumab.

7.10.4.6. Dose Modification and Management of Tumor Flare Reaction

Subjects in this study should be monitored for tumor flare. Tumor flare reaction (TFR) is defined as a sudden and tender increase in the size of the disease-bearing sites, including the lymph nodes, spleen and/or the liver, often accompanied by low-grade fever, and non-pruritic diffuse rash. Tumor flare usually occurs within the first cycle of treatment. Tumor flare reaction may mimic progression of disease; however, the TFR will generally subside over time. Therefore, careful monitoring and evaluation is important prior to discontinuing a study subject for PD in the initial cycles of CC-122 therapy.

There are currently no laboratory or radiological tests that distinguish TFR from PD. The distinction should be made on clinical grounds, incorporating observations such as associated physical findings, laboratory findings, and pace of disease before and after institution of treatment. Tumor flare will be recorded as an AE (graded using the NCI CTCAE version 3.0 criteria) and not as PD.

Treatment of the TFR is up to the discretion of the investigator depending on the severity and clinical situation. In mild to moderate cases (Grades 1 to 2), it is suggested that CC-122 be continued along with symptomatic treatment such as nonsteroidal anti-inflammatory drugs (NSAIDs) and/or narcotics. Corticosteroids can be administered at the investigator's discretion. In more severe cases (Grade 3 to 4), CC-122 and/or nivolumab should be interrupted and therapy with corticosteroids should be initiated. NSAIDs and/or narcotics may also be used at the investigator's discretion. When symptoms resolve to ≤ Grade 1, CC-122 and/or nivolumab can be restarted at the same dose level.

7.10.4.7. Management and Follow-up of Liver Function Test Abnormalities Grade 3

Subjects experiencing a Grade 3 liver function test (LFT) elevation should undergo the additional testing below until LFT abnormalities improve to Grade 1 or better:

- Hepatitis A, B, and C acute infection serology testing
- Once weekly HBV viral load (for subjects with known HBV infection)
- Twice weekly check of AST, ALT, bilirubin, alkaline phosphatase, PT, PTT, INR

7.10.4.8. Management of Dermatological Toxicity

Rash is a toxicity which has been previously observed with CC-122 therapy. Additionally, dermatological toxicity (rash and pruritis) is a documented immune related adverse event associated with checkpoint inhibitors. Initial treatment options may include topical corticosteroid creams and oral antipruritics. For Grade 3 rash, drug should be interrupted and treatment with oral corticosteroids may be warranted (Postow, 2015).

For Grade 2 toxicity, both drugs may be withheld and treatment with topical corticosteroids initiated with consideration for systemic corticosteroids if there is no improvement in symptoms within 1 week. Therapy may be continued if involvement of < 30% of body surface area, are asymptomatic, or toxicity can be managed with topical corticosteroid creams and antipruritics (Villadolid, 2015).

7.10.5. Management of Expected AEs While Receiving Nivolumab

Please refer to nivolumab SmPC (or Appendix H in Section 18.8) for additional guidelines on nivolumab toxicity management, or refer to the current local label.

7.11. Definition of an Overdose

Overdose, as defined for this protocol, refers to CC-122 and nivolumab dosing.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified doses of CC-122 and/or nivolumab assigned to a given subject, regardless of any associated adverse events or sequelae.

- Orally (PO) any amount over the protocol-specified dose
- Intravenously (IV) 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the rate specified in the local label.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 10.1 for the reporting of AEs associated with overdose.

7.12. Treatment Delay

Treatment may be interrupted until treatment-related toxicity reaches either ≤ Grade 1 or baseline levels. Treatment may restart either at the same, or a reduced, dose level, at the Investigator's discretion as described in Section 7.10.

7.13. Packaging and Labeling

The label(s) for CC-122 and nivolumab will include sponsor name, address and telephone number, the protocol number, drug name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.14. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.15. Investigational Product Compliance

Only the pharmacist or the Investigator's designee will dispense CC-122. A record of the number of capsules dispensed to and taken by each subject must be maintained. The pharmacist or the investigator's designee will document the dose dispensed in the appropriate study records.

Subjects will use weekly diary cards to record their daily self-administration of CC-122 at home. These will be reviewed by study staff each time the subject visits the clinic. Entries will be clarified, as necessary, so that appropriate information can be captured on the eCRFs. Study site personnel will perform a CC-122 administration compliance check and record this information on the subject's source documentation and on the appropriate eCRF.

Accurate recording of nivolumab IV administration will be made in the appropriate section of the subject's eCRF and source documents. The investigator or designee is responsible for accounting for all study-specific IPs both administered or in their custody during the course of the study.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

The primary objectives of this Phase 1/2, multicenter, open-label, dose finding study are to determine the safety and tolerability of CC-122 when administered orally in combination with nivolumab, to define the recommended Phase 2 dose (RP2D) and to determine the preliminary efficacy of CC-122 in combination with nivolumab based on RECIST 1.1 (Eisenhauer, 2009).

Data summaries/statistical analyses will be performed by study part, dose level/dosing regimen and/or HCC etiology as needed or applicable.

9.2. Study Population Definitions

The study population definitions are as follows:

- Enrolled Population – All subjects who meet all the inclusion/exclusion criteria and are eligible for the study.
- Treated Population – All subjects who enroll and take at least one dose of either IP (CC-122 or nivolumab).
- Dose limiting toxicity evaluable population: defined in Section 7.3
- Efficacy Evaluable (EE) Population – All subjects who enroll and meet eligibility criteria and receive at least 50% of both assigned IP in the first 2 cycles, have a baseline efficacy (tumor) assessment, and at least one post-baseline efficacy (tumor) assessment.
- Pharmacokinetic (PK) Evaluable Population –All subjects who enroll and receive at least one dose of either IP and have at least one measurable concentration of CC-122 or nivolumab.
- Biomarker Evaluable (BE) Population – all subjects who enroll and take at least one dose of either IP, and have at least 1 non-missing biomarker assessment, excluding the disqualified assessments.

9.3. Sample Size and Power Considerations

During the dose escalation part (Phase 1) of the study, a modified 3+3 dose escalation design (Storer, 1989) will be used to identify initial toxicity of the combinations as described in Section 7.2 and up to approximately 20 subjects will be enrolled depending on the number and size of dose cohorts evaluated.

During the dose expansion part (Phase 2), 30 additional subjects will be enrolled to an expansion cohorts of mixed HCC etiology (HBV, HCV and non-viral). The sample size is not determined based on power calculation but rather on clinical, empirical and practical considerations traditionally used for exploratory studies of this kind. If the response rate is 20% or more, there will be more than a 95% chance that one or more responders would be observed in the first 14 subjects (Gehan, 1961). If no responder is observed out of 14 subjects, the enrollment for the expansion cohort will stop for futility. Otherwise, the cohort will be expanded to up to approximately 30 subjects. Enrollment will continue during the evaluation of the initial 14

subjects. The 2-sided 95% CI for 20% and 35% response rate is tabulated in Table 9 for different sample size scenarios.

With 30 subjects enrolled and assuming the observed overall response rate is 35%, the two-sided 95% Wilson score CI will exclude 20%, the estimated overall response rate for nivolumab monotherapy (El-Khoueiry, 2015).

Table 9: Confidence Interval for 20% and 35% Response Rate for Different Scenarios of Sample Size (Wilson Score Interval)

CI	Response Rate	Sample Size			
		14	20	30	40
0.95	0.2	(0.068 ,0.461)	(0.081 ,0.416)	(0.095 ,0.373)	(0.105 ,0.348)
0.95	0.35	(0.159 ,0.606)	(0.181 ,0.567)	(0.205 ,0.529)	(0.221 ,0.505)

CI = confidence interval.

9.4. Background and Demographic Characteristics

Subjects' age, weight, height and other continuous demographic and baseline variables will be summarized using descriptive statistics, while gender, race and other categorical variables will be summarized with frequency tabulations. Medical history data will be summarized using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Prior therapies will be summarized by frequency tabulation, if available. Supportive corresponding subject listings will also be provided.

9.5. Subject Disposition

Subject disposition (analysis population allocation, ongoing, discontinued from treatment and/or study, along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Protocol violations will be summarized using frequency tabulations. Supportive corresponding subject listings will also be provided.

9.6. Efficacy Analysis

Efficacy analyses will be based on the Treated Population and certain efficacy analyses will also be performed on the EE Population.

The efficacy variables include ORR, DCR, duration of response (DoR), PFS, TTP and OS. Tumor response and progression will be determined by the Investigator based on RECIST 1.1 (Eisenhauer, 2009) as a primary guideline, and irRECIST (Bohnsack, 2014) as an exploratory assessment.

Tumor response will be summarized using frequency tabulation. Two-sided 95% Clopper-Pearson exact CIs of the response rate will be provided (Clopper, 1934). A case-by-case description of all subjects who exhibited a complete or partial response will be provided.

The Kaplan-Meier estimate of the median of PFS, OS, DoR and TTP along with their 95% CI will be provided as appropriate (Brookmeyer, 1982). Progression free survival and OS rates at

selected time point(s) will be computed using the Kaplan-Meier estimates, along with standard errors of rate ([redacted]).

Other exploratory efficacy variables, such as AFP reduction, etc, will be summarized using frequency tabulations for categorical variables and/or descriptive statistics for continuous variables, as appropriate. Alpha-fetoprotein response rate will be provided with its 95% CI. Alpha-fetoprotein response is defined as normalization or > 50% decline from baseline. The AFP response rate is the percentage of subjects with baseline elevation in AFP who meet AFP response criteria. A descriptive analysis for other evidence of antitumor activity will be provided based on clinical, radiographic, and biologic assessments of efficacy.

Listings and graphical displays will be provided where useful for the interpretation of results.

Full details on the efficacy analysis are described in the SAP.

9.7. Safety Analysis

All summaries of safety data will be conducted using subjects receiving at least one dose of either IP (the Treated Population).

Adverse events observed will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of the toxicities will be graded according to the NCI CTCAE (Version 4.03) whenever possible. The frequencies of adverse events will be tabulated by MedDRA (Version 17.1 or higher) SOC and PT. In the by-subject analysis, a subject having the same AE more than once will be counted only once. Adverse events will also be summarized by NCI CTCAE grade. Investigational product-related AEs, AEs leading to dose reduction/interruption, or permanent discontinuation of study treatment, events classified as CTCAE Grade 3 or 4, deaths, and SAEs will be tabulated. By-subject listings of all AEs, deaths, serious AEs (SAEs) and their attribution will be provided.

Clinical laboratory results will be summarized descriptively, which will include a display of change from baseline. Bidirectional shift tables (low and high) demonstrating the change of CTCAE grades from baseline to the worst post-baseline severity grade during the treatment period will also be presented for applicable tests. Listings of abnormal clinical laboratory data according to NCI CTCAE severity grades (if applicable), abnormal flags (low or high) will be provided. Graphical displays (eg, “spaghetti” plots or box plots) will be provided for key laboratory tests.

Descriptive statistics for ECG, vital sign and LVEF measurement, both observed values and changes from baseline, will be summarized. Shift tables demonstrating the changes from baseline to the worst post-baseline qualitative assessment of abnormality will be displayed in cross-tabulations. Post-baseline abnormal ECG and LVEF values will be summarized using frequency tabulations. Electrocardiogram, vital sign and LVEF measurements will be listed by subject. Graphical displays will be provided where useful to assist the interpretation of results.

9.8. Interim Analysis

Not applicable.

9.9. Other Topics

9.9.1. Assessment of Pharmacokinetics

Blood will be collected according to intensive and sparse sampling strategies to estimate the population PK of CC-122 when administered in combination with nivolumab.

Noncompartmental analyses will be performed using Phoenix WinNonlin Version 6.3 (Pharsight Corp., Mountain View, CA). The following PK measurements will be determined for CC-122 in subjects with intensive PK sampling:

- Area under the plasma concentration time-curve (AUC).
- Peak (maximum) plasma concentration (C_{max}).
- Terminal half-life ($t_{1/2}$).
- Time to maximum plasma concentration (T_{max}).
- Apparent total body clearance (CL/F).
- Apparent volume of distribution (Vz/F).

Sparse serum concentrations of nivolumab will be evaluated after the first dose administration with nivolumab and at steady state. Sparse concentrations of nivolumab will be summarized by descriptive statistics by cohort, visit and nominal time. If warranted, the impact of CC-122 on target mediated disposition of nivolumab will be assessed by non-mixed effect modeling (NMEM) compartment approach.

Descriptive statistics (N, mean, standard deviation, coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum) for plasma concentration and PK parameters will be provided. Correlations of drug exposure with safety, PD and clinical endpoints may also be analyzed as exploratory endpoints. Results will be presented in tabular and graphic forms as appropriate.

[redacted]

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF. (See Section 7.11 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an IP should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-122 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of CC-122 and until 90 days after the last dose of nivolumab and those SAEs made known to the investigator at any time thereafter that are suspected of being related to CC-122 or nivolumab. Adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication that has no worsened from baseline.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to CC-122 and nivolumab, action taken regarding both IPs, and outcome.

10.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the NCI CTCAE (Version 4.03), whenever possible:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the NCI CTCAE, Version 4.03, (eg tumor flare reaction) should be evaluated for severity/intensity according to Version 3.0):

Otherwise, the following scale should be used:

Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of CC-122 and nivolumab and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IPs and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with CC-122 and nivolumab as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or reduction of either IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of either IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or female partner of a male subject are immediately reportable events.

In the event, of a pregnancy occurring in a female subject of childbearing potential or female partner of the male subject, Celgene Drug Safety will follow up with the clinical investigator each trimester of the pregnancy and for 1 year following the birth of the infant (if applicable).

Please reference the informed consent (permission) forms for data collection regarding the pregnancy of a female subject participating in a Celgene sponsored study, the pregnancy of a female partner of a male subject participating in a Celgene sponsored study and the pregnancy of a non-subject pregnant female. In all scenarios, data collection will occur each trimester of the pregnancy and for 1 year after birth of infant (if applicable).

The exposure of any non-subject pregnant female (eg, caregiver, pharmacist, study coordinator or monitor) to CC-122 is also an immediately reportable event.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated -βhCG and/or a positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on CC-122, or within 28 days of the subject's last dose of CC-122, or within 5 months of the last dose of nivolumab are considered immediately reportable events. CC-122 and nivolumab are to be discontinued immediately. The subject will be instructed to return any unused CC-122 to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject should be referred to her obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

In the event, of a pregnancy occurring in a female subject of childbearing potential, Celgene will follow up with the clinical investigator each trimester of the pregnancy and for 1 year following the birth of the infant (if applicable). Any follow-up information or outcome information must be reported to Celgene Drug Safety immediately.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure CC-122 or nivolumab should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant while the male subject is still receiving treatment or within 90 days of the male subject's last dose of CC-122, the male subject taking CC-122 and nivolumab should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

In the event, of a pregnancy occurring in a female partner of the male subject, Celgene will follow up with the clinical investigator each trimester of the pregnancy and for 1 year following the birth of the infant (if applicable). Any follow-up information or outcome information must be reported to Celgene Drug Safety immediately.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to CC-122 or nivolumab) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of CC-122 or until 90 days after the last dose of nivolumab) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to either IP. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board (IRB) /Ethics Committee (EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-122 based on the Investigator Brochure. Celgene Drug Safety will determine the expectedness of events suspected of being related to nivolumab based on the SmPC.

In the US, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and

presentation of adverse reaction reports arising from clinical studies on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Events of disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of CC-122 in this study or in other studies that is both serious and unexpected (ie, SUSAR).
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information.)

[redacted]

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the IP:

- Adverse event
- Progressive disease
- Symptomatic deterioration (global deterioration of health status)
- Physician decision
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Other (to be specified on the eCRF)

The reason for discontinuation should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

12. EMERGENCY PROCEDURES

[redacted]

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Investigational product can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has

been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc.).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- Good clinical practice noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of case report forms (CRFs) or CD-ROM.

14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer.

Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institutions should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigator's Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a GCP Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with GCP guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication, must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

18. APPENDICES

18.1. Appendix A: Table of Abbreviations

Table 10: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AASLD	American Association for the Study of Liver Diseases
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse events
AFP	Alpha-fetoprotein
AIC	Active ingredient in capsule
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
ANC	Absolute neutrophil count
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	Area under the concentration time curve
β-hCG	Beta human chorionic gonadotropin
BCLC	Barcelona Clinic Liver Cancer
BE	Biomarker Evaluable
bFGF	Basic fibroblast growth factor
B-hCG	Beta human chorionic gonadotropin
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
cHCC-CC	Combined hepatocellular cholangiocarcinoma
CI	Confidence interval
CK	Creatine kinase
CL/F	Apparent total body clearance
C_{max}	Maximum observed concentration
CO_2	Carbon dioxide
CP	Child-Pugh
CR	Complete response
CRBN	Cereblon

Table 10: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
CRF	Case report form
CT	Computed tomography
CV%	Coefficient of variation
CYP	Cytochrome P450
D	Day
DCR	Disease control rate
DLBCL	Diffuse large B cell lymphoma
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EOT	End of treatment
EE	Efficacy Evaluable
EEA	European Economic Area
EMA	European Medicines Agency
FCBP	Females of child bearing potential
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
GBM	Glioblastoma multiforme
GCP	Good Clinical Practices
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte-macrophage colony stimulating factor
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen

Table 10: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCVAb	Hepatitis C virus antibody
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HUVEC	Human umbilical vein endothelial cells
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IGF	Insulin like growth factor
IHC	Immunohistochemistry
IL	Interleukin
IMiD	A proprietary series of drugs with immunomodulatory and other properties
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRT	Integrated response technology
IV	Intravenously
LDH	Lactate dehydrogenase
LFT	Liver function test
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MMPA	mouse Matrigel plug assay
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose

Table 10: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
MUGA	Multi-gated acquisition
NASH	Non-alcoholic steatohepatitis (ie, non-alcoholic fatty liver disease)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's lymphoma
NK	Natural killer (cells)
NMEM	Non-mixed effect modeling
NSAIDS	Nonsteroidal anti-inflammatory drugs
NTD	Nontolerated dose
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PD-1	Programmed death 1
PD-L1	PD-1 ligand receptor
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetics
PO	Orally
PPRMP	Pregnancy Prevention Risk Management Plans
PR	Partial response
PBMC	Peripheral blood mononuclear cells
PT	Prothrombin time
PT	Preferred term
PTT	Partial thromboplastin time
QD	Once a day
QTcF	QT interval corrected Fridericia
RANTES	Regulated upon activation, normal T cell expressed and secreted
RBC	Red blood cell

Table 10: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RRMM	Relapsed or refractory multiple myeloma
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SEB	Staphylococcal enterotoxin B
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard operating procedure
SRC	Safety review committee
SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal half-life
TAA	Tumor-associated antigens
TCR	T cell diversity
TEAE	Treatment-emergent adverse events
TESAE	Treatment-emergent serious adverse event
TFR	Tumor flare reaction
TSH	Thyroid stimulating hormone
T_{max}	Time to maximum concentration
TTP	Time to progression
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
VEGFR 1-3	Vascular endothelial growth factor receptor 1-3
Vz/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. Per Food and Drug Administration (FDA) request on Investigator Brochure (IB) Edition 9, protocol was updated to include standard Cytochrome P450 (CYP) interaction language in alignment with all CC-122 studies.

   Revised Sections: 8.2.

2. Updates to exclusion criteria.

   Exclusion criteria #1 was updated to exclude all subjects who have had prior treatment with regorafenib. This change is based on the recent FDA approval of regorafenib for hepatocellular carcinoma (HCC) in the second line setting in order to maintain the homogeneity of the patient population.

   Exclusion criteria #3 was updated to exclude any subjects with systemic therapy in the 4 weeks prior to starting investigational product in order to allow for an appropriate wash out period for any prior therapies.

   Exclusion criteria #15h was changed from >100 pg/mL to >300 pg/mL to allow for inclusion of subjects with brain natriuretic peptide (BNP) between 100-300 pg/mL with cardiologist evaluation (specified under section 15.h.a). This change was made to allow subjects at low cardiac risk to be enrolled in the trial despite slightly elevated BNP. This language was updated in alignment with existing wording in other CC-122 protocols (eg, CC-122-ST-001).

   Revised Sections: 4.3.

3. Due to the incidence of rash (and subsequent dose limiting toxicities) observed during the dose escalation portion of the study, language was added to the protocol to provide guidelines on the management of Grade 1 and Grade 2 rash. Rash is known to be a potential overlapping toxicity between CC-122 and nivolumab and these guidelines are being implemented to help mitigate the risk of these rashes reaching Grade 3 or higher.

   Revised Sections: Table 6, Table 8, 7.10.4.8 (added).

4. Per Celgene protocol template and Informed Consent Form (ICF) template, updates to pregnancy language as defined by Drug Safety for teratogenic compounds (including CC-122).

   Revised Sections: 10.4, 10.4.1, 10.4.2.

Minor changes included in this amendment are summarized below:

Minor editorial changes throughout.

Revised Sections: Global

Addition of Celgene Therapeutic Area Head name and Title.

Revised Section: Celgene Therapeutic Area Head Signature Page

Protocol Summary was updated to include withdrawal of consent as a reason why subjects would not be followed for tumor evaluation until progression. This update was made for consistency with section 3.2.

Revised Section: Protocol Summary (Length of Study)

Clarification of language surrounding when archival tumor biopsies may be accepted in lieu of fresh tumor biopsies.

[redacted]

Revised Sections: 4.3.

Clarification of wording surrounding pregnancy testing requirements to include serum and/or urine testing according to the Pregnancy Prevention Risk Management Plan (PPRMP).

Revised Sections: Table 3, 6.1, 6.2, 6.3.

Clarification of wording surrounding the timing of Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).

Revised Sections: Table 3, 6.5.4.

Updated screening procedures to require hepatitis B virus (HBV) and hepatitis C virus (HCV) viral load at screening for all subjects to ensure consistency with table of events.

Revised Sections: 6.1.

Updated text of protocol for consistency with Protocol Summary to include that an independent review of efficacy results may take place at any time.

Revised Sections: 6.5.

Added text to clarify that CC-122 should not be taken at home on days when predose assessments are scheduled for consistency with Section 6.6.1 Pharmacokinetics of CC-122.

Revised Sections: 6.7, 6.8.3.

Updated text to reference the Summary of Product Characteristics (SmPC) for additional information regarding potential adverse events with nivolumab.

Revised Sections: 7.10.4.4.

Additional references were added with revisions and/or new information: Flockhart, Postow and Villadolid.

Revised Sections: 7.10.4.8, 8.2, 17

Changed text to clarify that a nivolumab overdose (on an infusion rate basis) is now defined as “any rate faster than the rate specified in the local label”. This was changed from “any rate faster than the protocol specified rate”.

Revised Sections: 7.11.