Official Title of Study:

A Phase 2, Multicenter, Open-label, Multi-cohort Study to Assess Safety and Efficacy of CC-90011 in Combination with Nivolumab in Subjects with Advanced Cancers

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A PHASE 2, MULTICENTER, OPEN-LABEL, MULTI-COHORT STUDY TO ASSESS SAFETY AND EFFICACY OF CC-90011 IN COMBINATION WITH NIVOLUMAB IN SUBJECTS WITH ADVANCED CANCERS

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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 Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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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.	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 3.0:

This Protocol Amendment is to reduce the duration of survival follow-up period. As of this amendment, 92 patients have been enrolled across the 3 cohorts, with 41 patients in Cohort A (4 confirmed responses), 15 patients in Cohort B (0 confirmed responses), and 36 patients in Cohort C (2 confirmed responses). With the limited number of enrolled patients, overall survival (OS) may not provide meaningful interpretative data. As a result, OS is being moved to an exploratory objective and endpoint. The survival follow-up period is being modified by removing the up to 2-year duration and adding in that survival follow-up will stop after the 100-day safety follow-up visit of the last subject on study treatment.

The Protocol Summary has also been updated in accordance with changes made in the body of the protocol.

The revisions in this Protocol Amendment apply to all participants who are on the study.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page; Protocol Summary; Section 1.1.2.1: Current Treatment for First Line Extensive-stage Small Cell Lung Cancer	Added the Bristol-Myers Squibb Company (BMS) compound number.	For clarification purposes.
Protocol Summary (Objectives, Statistical Methods); Section 2: Study Objectives and Endpoints, Table 4 (Study Objectives), Table 5 (Study Endpoints); Section 9.6.2: Secondary Endpoint	Removed overall survival from secondary objective and endpoint and added to exploratory objective and endpoint.	Moved to exploratory given limited data availability due to shortened duration of survival follow-up.
Section 1.4: Risk/Benefit Assessment	New section added referring to the newly added appendix.	As the stand-alone risk benefit assessment document is now incorporated into the protocol.
Section 2: Study Objectives and	Added “in combination with nivolumab” to the	For clarification purpose.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Endpoints, Table 5 (Study Endpoints)	phamacokinetic endpoint description.	
Figure 3: Overall Study Design; Section 3.2: Study Duration for Subjects; Section 6.3.3: Survival Follow-up	Removed the up to 2-year duration and added in that survival follow-up will stop after the 100-day safety follow-up visit of the last subject on study treatment.	To reduce the duration of survival follow-up collection due to the limited number of enrolled patients.
Section 5: Table of Events, Table 6 (Table of Events)	Added the "X" at the 100-day safety follow-up timepoint.	To align with the updated survival follow-up period.
Appendix G: Risk Benefit Assessment	New appendix was added.	To incorporate the stand-alone risk benefit assessment document into the protocol.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

PROTOCOL SUMMARY

Study Title

A Phase 2, multicenter, open-label, multi-cohort study to assess safety and efficacy of CC-90011 in combination with nivolumab in subjects with advanced cancers.

Indication

This trial will enroll subjects with small cell lung cancer (SCLC) and squamous non-small cell lung cancer (sqNSCLC) who have progressed after 1 or 2 lines of therapy.

Based on safety/tolerability and preliminary efficacy data, the combination of CC-90011 (also known as BMS-986363) and nivolumab could be expanded to add cohorts of subjects with other tumor types and the Sponsor may consider amending the study design to investigate the efficacy of the combination versus the current standard of care in one or more tumor types.

Objectives

Primary Objective

The primary objective is to evaluate in each individual cohort the:

- Overall response rate (ORR) in subjects with SCLC or sqNSCLC treated with CC-90011 in combination with nivolumab

Secondary Objective(s)

The secondary objectives are to evaluate in each individual cohort the following endpoints/outcomes in subjects with SCLC or sqNSCLC receiving CC-90011 in combination with nivolumab:

- Safety and tolerability
- Duration of response (DOR)
- Time to response (TTR)
- Progression-free survival (PFS) assessed by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Time to first subsequent therapy (TFST)

Exploratory Objectives(s)

The exploratory objectives in each individual cohort are to:

- Evaluate overall survival (OS)
- [redacted]
- [redacted]
- [redacted]

[redacted]

- Explore the relationship between pharmacokinetics (PK), pharmacodynamic (PD) biomarkers and/or clinical outcomes of CC-90011 in combination with nivolumab
- Evaluate the disease control rate
- Assess the pharmacokinetics and immunogenicity of nivolumab in small cell lung cancer and squamous non-small cell lung cancer cohort subjects
- Assess the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serologic status on subjects and to support health authority requests

Study Design

This is a Phase 2, multicenter, open-label, multi-cohort study designed to assess the safety and efficacy of CC-90011 in combination with nivolumab in subjects with small cell lung cancer or squamous non-small cell lung cancer who have progressed after 1 or 2 lines of therapy.

For the purpose of this protocol, immune checkpoint inhibitor (ICI) means anti-PD-1 or anti-PD-L1 treatments.

Approximately 135 subjects total globally will be enrolled into one of the following cohorts in 2 stages:

- Cohort A: SCLC in ICI naïve subjects
- Cohort B: SCLC in ICI progressor subjects
- Cohort C: sqNSCLC in ICI progressor subjects

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

Study Population

Adult subjects 18 years and older with SCLC or sqNSCLC who have progressed after 1 or 2 lines of therapy.

Length of Study

The Screening Period will last up to 28 days. Treatment must begin within 3 days of enrollment. Subjects will be treated until death, progressive disease, unacceptable toxicity, withdrawal of consent from treatment, physician decision, or for up to 2 years. In the event of discontinuation of the study treatments, subjects will be followed in survival follow-up until death, withdrawal of consent from the entire study, lost to follow-up, the 100-day safety follow-up visit of the last subject on study treatment, or end of study.

Enrollment is expected to take approximately 18 months. The total study duration is estimated to be approximately 36 months from the enrollment of the first subject to last subject last visit.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment survival 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 prespecified in the protocol, whichever is the later date.

Study Treatments

Celgene Corporation (Celgene) will supply the investigational product, CC-90011, and nivolumab for administration, labeled appropriately for investigational use as per the regulations of the relevant country's health authority.

All cohorts will receive CC-90011 at a dose of 40 mg unless otherwise determined during the ongoing safety evaluation (Section 7.3.1.1) given orally (PO) once weekly in a continuous 28-day cycle, and nivolumab at a dose of 480 mg intravenously (IV) every four weeks. Subjects will be treated until death, progressive disease, unacceptable toxicity, withdrawal of consent from treatment, physician decision, or for up to 2 years. For subjects who progress with only brain metastasis, treatment with investigational product (IP) will be stopped, but may be continued after completion of, and recovery from local radiation treatment per the Investigator's judgement.

Subjects may continue to receive investigational product beyond disease progression at the discretion of the Investigator.

Overview of Key Efficacy Assessments

All subjects will be evaluated for tumor response and progression by Investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines, at screening, every 6 weeks (± 7 days) post Cycle 1 Day 1 (C1D1) for the first 24 weeks and then every 8 weeks (± 7 days) until documented disease progression, start of new anticancer therapy, withdrawal of consent from the entire study, or death. Tumor assessments should also be performed at any time, if clinically indicated.

Response assessments will include computed tomography (CT) scan or magnetic resonance imaging (MRI).

After the end of treatment visit, survival status will be followed every 2 months (± 14 days) until death, withdrawal by subject from the entire study, lost-to-follow-up, or the 100-day safety follow-up visit of the last subject on study treatment, whichever occurs first, or the End of Trial.

New anticancer therapies should 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

A thorough evaluation of medical conditions will be conducted during screening. Documented physical examination, vital signs, laboratory assessments (eg, serum chemistry, hematology), 12-lead electrocardiogram (ECG), and Eastern Cooperative Oncology Group (ECOG) performance

status will be monitored regularly. Preventative measures will be taken to avoid pregnancy in study subjects or their partners, and females of childbearing potential will have pregnancy testing performed at screening and then throughout the study. The full schedule of assessments is described in Table 6.

All subjects will be monitored for adverse events starting from the time the subject signs the informed consent form (ICF) until 28 days after the last dose of CC-90011 or 100 days after the last dose of nivolumab, whichever is later, as well as those serious adverse events (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to study treatment. Toxicity severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Concomitant medications and procedures are collected from 28 days prior to enrollment and until 28 days after the last dose of CC-90011 and until 100 days after the last dose of nivolumab.

Statistical Methods

The primary objective of the statistical analysis is to evaluate the overall response rate of subjects treated with CC-90011 in combination with nivolumab in 3 cohorts:

- Cohort A: SCLC in ICI naïve subjects
- Cohort B: SCLC in ICI progressor subjects
- Cohort C: sqNSCLC in ICI progressor subjects

The overall response rate is defined as the proportion of subjects in the treated population who had confirmed complete response (CR) or confirmed partial response (PR) as assessed by Investigator review per RECIST v1.1. The point estimate of ORR will be summarized along with a 95% confidence interval (CI) using exact binomial method proposed by Clopper and Pearson (Clopper, 1934).

In Cohort A, expected ORR for nivolumab monotherapy is 14% while target ORR is 30%. To achieve at least 80% power with one-sided type 1 error 0.1, 39 subjects will be enrolled according to a 2-stage group sequential design based on a binomial test. In Stage 1, 12 subjects will be enrolled and treated with CC-90011 in combination with nivolumab. If there are 2 or more subjects responding, Cohort A will continue to enroll an additional 27 subjects. If 1 or less subjects respond in Stage 1, Cohort A will stop for futility.

In Cohort B and C, the expected ORR for nivolumab monotherapy is 5% while the target ORR for the combination is 15%. To achieve at least 80% power with one-sided type 1 error 0.1, 48 subjects will be enrolled according to a 2-stage group sequential design based on a binomial test. In Stage 1, 14 subjects will be enrolled and treated with CC-90011 in combination with nivolumab. If there are 1 or more subjects responding, Cohort B and C will continue to enroll an additional 34 subjects each. If 0 subjects respond in Stage 1, Cohort B and C will stop for futility.

The secondary efficacy endpoint includes safety and tolerability, duration of response, time to response, progression-free survival, and time to first subsequent therapy. The DOR is defined as

the time from the first occurrence of a confirmed documented response to the time of first documented tumor progression, as determined by Investigator review per RECIST v1.1, or death from any cause, whichever comes first. The DOR will be summarized based on the Kaplan-Meier method. The time to response is defined as the time from the first dose of study drug to the date of the first confirmed documented response (CR or PR), as assessed by Investigator per RECIST v1.1. Time to response will be summarized for responders (confirmed CR or PR) using descriptive statistics.

Progression-free survival is defined as the time from the first dose of the study drug to the date of the first objectively documented tumor progression or death from any cause, whichever occurs first. Progression-free survival will be summarized based on the Kaplan-Meier method. The time to first subsequent therapy will be defined as the time in days from the date of first dose of study drug to the date of the next cancer therapy or death. Time to first subsequent therapy will be analyzed similarly to PFS. All efficacy analyses will be primarily performed in the treated population, which is defined as subjects receiving at least 1 dose of CC-90011 or nivolumab.

All safety analyses will be performed on the treated population. Adverse events (AE) will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Treatment-emergent AEs (TEAE) leading to death, TEAEs leading to discontinuation from treatment, NCI CTCAE Grade 3 or Grade 4 TEAEs, TEAEs any NCI CTCAE grade, TEAEs related to study treatment and serious TEAEs will be summarized separately. Clinical laboratory results will be summarized descriptively, which will also include a display of change from baseline.

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1 INTRODUCTION

1.1 Disease Background

1.1.1 Lung Cancers

Lung cancer is the most common cancer worldwide with approximately 1.8 million new diagnoses and 1.59 million deaths in 2012, which corresponds to the third highest incidence among cancers and the most common cancer-related mortality (Ferlay, 2015). The World Health Organization (WHO) divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

Small cell lung cancer accounts for up to 13% to 15% of all lung cancer diagnoses, with 250,000 cases diagnosed annually worldwide. It is the sixth most-common cause of cancer-related mortality (Govindan, 2006; Jemal, 2007; Lozano, 2012). Non-small cell lung cancer accounts for 80% to 90% of lung cancers and includes 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types); and (2) squamous cell (epidermoid) carcinoma. Squamous histology account for approximately 20% to 30% and is associated with shorter survival than non-squamous histology (Cheng, 2016; Lortet-Tieulent, 2014; Soldera, 2017).

As lung cancer can be asymptomatic at early stages, most patients are diagnosed at an advanced stage which is not curable by surgery (Yang, 2017), and thus have poor prognoses. Screening programs for lung cancer have allowed for earlier diagnoses but the majority of patients are still diagnosed with advanced disease. Most solid tumors, including those with recent advances in targeted and immune mediated therapy such as anti-programmed cell death 1 (PD1)/programmed death-ligand 1 (PD-L1), still have patients who do not achieve long term disease control.

In SCLC, cytotoxic chemotherapy remains an important disease control modality in both first- and second-line treatment, though long-term disease control is limited, and there is modest improvement with anti-PD1/PD-L1 therapies. Although chemotherapy, targeted therapy, and/or anti-PD-1/PD-L1 therapies provide long term benefit to NSCLC patients, the majority of NSCLC patients will ultimately progress due to resistance mechanisms and succumb due to the disease.

1.1.2 Small-Cell Lung Cancer

Small cell lung cancer is an aggressive high-grade neuroendocrine tumor associated with a short doubling time, a high growth fraction, and early development of widespread metastases, which contribute to the extremely poor disease prognosis (Sabari, 2017). These aspects of SCLC, as well as the limited success of current treatments, perhaps due to cancer stem cells (CSCs) (discussed below), highlight the unmet medical need for the development of new therapeutics for SCLC, particularly in relapsed disease.

Historically, SCLC is staged by the Veterans' Affairs Administration Lung Cancer Study Group classification (Kalemkerian, 2012) (0). At time of diagnosis, approximately 70% of patients have extensive stage (ES) SCLC, meaning that the tumor has spread outside of the hemithorax, with presence of metastases (Alvarado-Luna, 2016; Gaspar, 2012).

1.1.2.1 Current Treatment for First Line Extensive-stage Small Cell Lung Cancer

Standard first-line treatment for ES SCLC consists of platinum-based chemotherapy, mainly 4 to 6 cycles of cisplatin or carboplatin plus etoposide (Fruh, 2013; Kalemkerian, 2018). Treatment beyond 6 cycles is not recommended based on several trials suggesting the increased risk of cumulative toxicity with no benefits in overall survival (OS) (Fruh, 2013). In patients with ES SCLC, response rates of 60% to 70% can be achieved with combination chemotherapy alone. Despite the initial chemosensitivity, almost all patients relapse and have limited or no response to subsequent therapy. The median progression-free survival (mPFS) is from 4 to 7 months (Alvarado-Luna, 2016; Foster, 2011; Nicholson, 2016) and the median overall survival (mOS) is approximately 10 months (Farago, 2018), with a 5-year overall survival of 1% to 5% (Nicholson, 2016) in front line treatment.

Many strategies have been evaluated to improve the treatment regimen for ES SCLC, including the addition of a third agent. The addition of ifosfamide to carboplatin and etoposide yielded a modest survival benefit, however the addition of an alkylating agent significantly increased the hematologic toxicity (Miyamoto, 1992). More recent trials have further confirmed the lack of survival improvement with 3-drug chemotherapy regimens (Berghmans, 2017; Jalal, 2017). Similarly, paclitaxel added to platinum-based chemotherapy did not improve survival and was associated with unacceptable toxicity in a Phase 3 study (Niell, 2005).

While the exploratory use of other chemotherapy regimens has not yielded significant survival improvement in patients with extensive disease, the introduction of immune checkpoint inhibitors (ICI) has provided an important advancement in the treatment of ES SCLC. On 18-Mar-2019, the United States Food and Drug Administration (FDA), and on 06-Sep-2019, the European Medicines Agency (EMA), approved atezolizumab, an anti-PD-L1, in combination with carboplatin plus etoposide, followed by maintenance atezolizumab as first-line treatment for ES SCLC. The addition of an anti-PD-L1 to chemotherapy resulted in 0.9 months improvement in mPFS, from 4.3 to 5.2 months (hazard ratio [HR] for disease progression or death, 0.77; 95% confidence interval [CI], 0.62 to 0.96; p = 0.02), and a 2-month benefit in mOS, from 10.3 to 12.3 months (HR for death, 0.70; 95% CI, 0.54 to 0.91; p = 0.007). However, the confirmed overall response rate (ORR) was similar in both groups, 60.2% versus 64.4%, with 5 patients (2.5%) having a completed response (CR) in the atezolizumab group and 2 patients (1%) with a CR in the chemotherapy alone group (Horn, 2018).

Similar results from a clinical trial of durvalumab (anti-PD-L1) in addition to the standard chemotherapy, cisplatin, or carboplatin plus etoposide in first line ES SCLC were recently presented. Overall survival increased from 10.3 months with chemotherapy, to 13 months with the addition of durvalumab (HR for death, 0.73; 95% CI, 0.591 to 0.909; p = 0.0047; mPFS was similar in both arms with 5.4 months for chemotherapy and 5.1 months for the durvalumab arm (HR for disease progression or death, 0.78; 95% CI, 0.645 to 0.936) (Paz-Ares, 2019).

The safety profile of atezolizumab or durvalumab added to platinum-based chemotherapy was consistent with the previously reported safety profile of the individual agents. The increase of

toxicities related to the addition of an ICI to platinum-based chemotherapy are minimal compared to platinum-based chemotherapy alone (Horn, 2018; Paz-Ares, 2019). The addition of durvalumab to platinum-based chemotherapy had similar profiles between both arms: the incidences of Grade 3/4 adverse events (AEs) was 61.5% versus 62.4% and AEs leading to discontinuation was 9.4% for each arm; the incidence of hematological toxicities was numerically higher in the platinum-based chemotherapy arm (Paz-Ares, 2019).

Despite the recent approval of atezolizumab as first-line treatment for ES SCLC, and the positive but still modest results with the addition of durvalumab, overall attempts to improve long-term survival rates have failed to yield significant advantages. The progression-free survival (PFS) at one year is still low at 17.5% with the addition of durvalumab (Paz-Ares, 2019) and below 20% with the addition of atezolizumab (Horn, 2018). Given the efficacy of immunotherapy in SCLC is observed in a minority of subjects, a predictive biomarker study is warranted for finding patients most likely to benefit (Ahn, 2019). Biomarker such as PD-L1 expression was not predictive of response to nivolumab or nivolumab and ipilimumab (Antonia, 2016) and tumor mutation burden did not differentiate benefit of atezolizumab (Horn, 2018).

Despite the rationale to combine chemotherapy with ICI, based on immunogenic cell death induction and immunogenicity of tumor cells modulation by chemotherapy, the benefits observed are modest (Ahn, 2019). Explanation of this resistance could be found in the nature the SCLC tumor with characteristics of a "cold tumor": limited PD-L1 expression, decreased major histocompatibility complex 1 (MHC1) expression, activation or accumulation of suppressors cells, myeloid derived suppressor cells, regulatory lymphocytes, ineffective priming or activation of dendritic cells and lymphocytes T-cells, and finally low rate of immune cell infiltration (Hamilton, 2019). Modifying one of these characteristics by using CC-90011 (also known as BMS-986363) would have the potential to enhance ICI activity (see Section 1.3).

Most patients relapse despite the initial chemosensitivity indicating the inability to eradicate residual tumor cells and suggesting the existence of CSC that are resistant to radiation and cytotoxic therapy. The CSC theory is a key component of cancer cell biology and is hypothesized to be associated with aggressive cancer spread and metastatic progression, as well as resistance to therapy (Codony-Servat, 2016). After relapse, these patients have a median survival of only 4 to 5 months when treated with further systemic therapy (Owonikoko, 2012). Therefore, exploring treatment strategies that target CSC and address this mechanism of resistance appears to be essential (Nunes, 2018).

1.1.2.2 Current Treatment for Second and Third Line Extensive-stage Small Cell Lung Cancer

Subsequent systemic therapy provides significant palliation in many patients; however, the likelihood of response is highly dependent on the time from initial therapy to relapse. This interval of time is also referred to as platinum sensitivity (Owonikoko, 2012). If the interval to relapse is less than 3 months (platinum refractory disease), response to most agents or regimens is poor ($\leq$ 10%). If more than 3 months have elapsed (sensitive disease), expected response rates are approximately 25% (Fruh, 2013; Kalemkerian, 2018). If subjects relapse more than 6 months after

first-line treatment, then treatment with their original platinum-based regimen is recommended (Owonikoko, 2012; Postmus, 1987). For refractory subjects or subjects with early relapse (< 6 weeks), participation in a clinical trial or best supportive care is recommended (Fruh, 2013).

While there are numerous systemic therapy options for patients who have relapsed 6 months or less after initial therapy, the likelihood of response is low, and duration of response is very limited. Recommended subsequent systemic therapies for these patients include topotecan, irinotecan, paclitaxel, docetaxel, temozolomide, vinorelbine, oral etoposide, gemcitabine, cyclophosphamide, doxorubicin and vincristine (CAV), and bendamustine (Cheng, 2007; Kalemkerian, 2018). Single-agent topotecan is approved by the FDA as second-line therapy, after it was shown to have better symptom control including slower time to quality-of-life deterioration and improved survival compared with best supportive care in a study in which half of the subjects had resistant disease. The median overall survival increased from 13.9 weeks to 25.9 weeks with topotecan (O'Brien, 2006).

In CheckMate-331, the overall survival in subjects with SCLC who relapsed after a first-line platinum-based chemotherapy was not statistically improved significantly with nivolumab versus chemotherapy (7.5 months versus 8.4 months). There was an initial OS advantage with chemotherapy; however, OS curves showed late but sustained separation favoring nivolumab beyond 10 to 11 months. Although ORR was numerically higher and PFS longer with chemotherapy, 16.5% and 3.8 months, compared to 13.7% and 1.4 months with nivolumab, a trend towards longer duration of response (DOR) with nivolumab (8.3 months) versus chemotherapy (4.5 months) was observed. Subgroup analyses suggest a trend towards OS benefit for nivolumab in some select groups of subjects, including platinum-resistant subjects (7.0 months with nivolumab versus 5.7 months with chemotherapy) (Reck, 2018).

In third-line treatment, both nivolumab and pembrolizumab were approved by FDA for subjects with ES SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. Pembrolizumab has shown an ORR of 18.7%, a DoR ≥ 9 months for 77% of the responders, mPFS of 2 months and mOS of 9 months (Chung, 2018). In another study in which only enrolled patients expressing PD-L1 either in the tumor or in the immune cells, pembrolizumab has shown ORR of 33.3%, DoR of 19.4 months, mPFS of 1.9 months and OS of 9.7 months (Ott, 2017). Nivolumab has demonstrated an ORR of 12%. Responses were durable for 6 months or longer in 77%, 12 months or longer in 62%, and 18 months or longer in 39% of the 13 responding patients (Antonia, 2016).

Activity of ICIs after progression on platinum-based chemotherapy is modest with low response rates and low progression-free and overall survival rates, thus prompting the testing of combination therapy as a potential modality to enhance ICI efficacy and improve outcomes in SCLC patients. However, the durable DoR observed is supporting the use of ICIs in second-line but understanding how to enhance efficacy and enrich subject selection are key.

A summary of studies with anti-PD-1 and anti-PD-L1 inhibitors for the treatment of SCLC can be found in Table 1.

Table 1: Studies with Anti-PD-1 or Anti-PD-L1 Inhibitors for the Treatment of SCLC

	First-line Treatment				Second-line Treatment	
Study	**IMpower 133 (Horn, 2018)**		**CASPIAN (Paz-Ares, 2019)**		**CHECKMATE-331 (Reck, 2018)**	
Subjects	**N = 403**		**N = 805[a]**		**N = 569**	
Treatment	Atezolizumab + carboplatin + etoposide (n=201)	Carboplatin + etoposide (n=202)	Durvalumab + platinum + etoposide (n=268)	Platinum + etoposide (n=269)	Nivolumab (n=284)	Chemotherapy (n=285)
mOS (months)	12.3 (10.8 – 15.9)	10.3 (9.3 – 11.3)	13.0 (11.5 – 14.8)	10.3 (9.3 – 11.2)	7.5 (5.7 – 9.2)	8.4 (7.0 – 10.0)
HR (95% CI)	0.70 (0.54 – 0.91; p = 0.007)		0.73 (0.59 – 0.91; p = 0.0047)		0.86 (0.72 – 1.04; p = 0.11)	
mPFS (months)	5.2 (4.4 – 5.6)	4.3 (4.2 – 4.5)	5.1 (4.7 – 6.2)	5.4 (4.8 – 6.2)	1.4 (1.4 – 1.5)	3.8 (3.0 – 4.2)
HR (95% CI)	0.77 (0.62 – 0.96; p = 0.02)		0.78 (0.65 to 0.94)		1.41 (1.18 – 1.69)	
ORR (%)	60.2 (53.1 – 67.0)	64.4 (57.3 – 71.0)	68	58	14	16
p-value	NA	NA	NA	NA	NA	NA
TEAE > Grade 3/4 (%)	57	56	62	62	14	73

Abbreviations: CI = confidence interval; HR = hazard ratio; mPFS = median progression-free survival; NA = not available; ORR = overall response rate; mOS = median overall survival; TEAE = treatment emergent adverse event.

[a] Study includes another treatment arm of durvalumab + tremelimumab + platinum + etoposide, which has not met predefined statistical significance threshold at time of interim analysis.

1.1.3 Squamous Non-Small Cell Lung Cancer

Advanced squamous non-small cell lung cancer (sqNSCLC) remains a recalcitrant disease. While non-squamous NSCLC has benefited from advances in chemotherapy doublets (pemetrexed and platinum), VEGF targeted therapy (bevacizumab) and tumor profiling with actionable mutations for therapeutic interventions (ie, EGFRmut, ALK, BRAF, ROS1), the same has not occurred in the setting of sqNSCLC. Together, these factors make sqNSCLC an especially challenging disease to manage (Socinski, 2016) such that new therapies, especially ICI and combinations, could have a large impact.

1.1.3.1 Current Treatment for First-Line Squamous Non-Small Cell Lung Cancer

Platinum-based doublet chemotherapy (cisplatin or carboplatin) has been the standard first-line treatment for sqNSCLC for decades. Taxanes (including paclitaxel, albumin-bound paclitaxel [*nab*®]-paclitaxel or docetaxel) or gemcitabine commonly complete the standard chemotherapy

backbone as the initial systemic therapy for patients with advanced sqNSCLC without major comorbidities and with a performance status of 0 to 2 (Scarpace, 2015).

More recently, the introduction of ICIs in combination with first-line platinum doublets has resulted in improvements in ORR, PFS and OS. This has resulted in the FDA approval of pembrolizumab and atezolizumab.

Pembrolizumab, an anti-PD-1, in combination with platinum-based chemotherapy and paclitaxel or *nab*-paclitaxel, is approved and recommended for patients with any PD-1 expression and without any contraindication to ICIs (Ettinger, 2018; Paz-Ares, 2018; Planchard, 2019). In KEYNOTE-407, the combination of pembrolizumab plus chemotherapy was associated with improved ORR (57.9% versus 38.4%) and improved mOS of 15.9 versus 11.3 months (HR for death, 0.56; 95% CI; 0.49 to 0.85, P < 0.001) (Paz-Ares, 2018). In the IMpower131 study, atezolizumab plus carboplatin and *nab*-paclitaxel improved PFS compared with carboplatin plus *nab*-paclitaxel (mPFS 6.5 versus 5.6 months, HR 0.75; 95% CI; 0.64 to 0.88), but no improvement in OS (mOS 14.2 versus 13.5 months, HR 0.88; 95% CI, 0.73 to 1.05, P = 0.16) was observed at the first interim analysis (Cappuzzo, 2019). However, atezolizumab with carboplatin and *nab*-paclitaxel is also an option in first-line therapy (Planchard, 2019).

Despite several limitations, expression of PD-L1 has been recognized as a predictive marker of ICI agents' sensitivity in NSCLC. For patients with tumor PD-L1 expression ≥ 50%, ESMO and National Comprehensive Cancer Network (NCCN) guidelines recommend pembrolizumab alone as first-line therapy (Langer, 2016; Planchard, 2019; Reck, 2016). For subjects with a high tumor mutation burden (≥ 10 mutations), a combination of nivolumab and ipilimumab is an option regardless of PD-L1 status (European Society of Medical Oncology [ESMO]). For patients with tumor PD-L1 expression < 50%, ICI combinations with platinum-based chemotherapy is recommended for good performance status patients (Planchard, 2019).

1.1.3.2 Current Treatment for Second-Line Squamous Non-Small Cell Lung Cancer

Three anti-PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, and atezolizumab) have been approved by the FDA and the EMA as second-line treatment based on Phase 3 studies demonstrating improved survival rates, longer duration of response, and fewer adverse events in comparison to docetaxel. However, these therapies were evaluated in immunotherapy-naïve patients, prior to approval of ICIs in the first line setting.

There is a general trend in the Phase 3 studies in second-line (nivolumab, pembrolizumab and atezolizumab versus docetaxel) for enriched efficacy of anti-PD-1/PD-L1 agents in subjects with higher PD-L1 expression compared with those with no/less PD-L1 expression. However, unselected subjects may still have improved survival and tolerability with anti-PD-1/PD-L1 agents compared with docetaxel. Nivolumab, pembrolizumab and atezolizumab are the treatment of choice for most subjects with advanced, previously treated, anti-PD1/anti-PD-L1-naive NSCLC, irrespective of PD-L1 expression. Compared to docetaxel, nivolumab showed an mOS of 9.2 months (95%, CI, 7.3 to 13.3) versus 6 months (95% CI, 5.1 to 7.3), an ORR of 20% versus 9%

(P = 0.008), and a mPFS of 3.5 months versus 2.8 months (HR for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; P < 0.001) (Brahmer, 2015).

Treatment options are limited for sqNSCLC patients who are intolerant to immunotherapy or for patients whose disease has progressed on anti-PD-1/PD-L1 therapy. In this case, retreatment with platinum-based doublet chemotherapy, docetaxel (with or without ramucirumab), or gemcitabine is recommended (Planchard, 2019).

As switching to another PD-l/PD-L1 inhibitor is not routinely recommended after a patient progresses on PD-1/PD-L1 inhibitor (Ettinger, 2018), there are several combinations involving ICIs that are being investigated in patients who progressed during or after an ICI therapy.

A summary of studies with anti-PD-1 and anti-PD-L1 inhibitors for the treatment of advanced or metastatic NSCLC can be found in Table 2.

Table 2: Studies with Anti-PD-1 or Anti-PD-L1 Inhibitors for the Treatment of NSCLC

	First-line Treatment		Second-line Treatment						
Study	**KEYNOTE 407 (Paz-Ares, 2018)[a]**		**KEYNOTE 10 (Herbst, 2016)[a,b]**			**CHECKMATE 017 (Brahmer, 2015)**		**OAK (Rittmeyer, 2017)[a]**	
Subjects	**N = 559**		**N = 1034**			**N = 272**		**N = 1225**	
Treatment	Pembrolizumab 200 mg + ChT (n=278)	Carboplatin + (*nab*) paclitaxel [ChT] (n=281)	Pembrolizumab 2 mg/kg (n=344)	Pembrolizumab 10 mg/kg (n=346)	Docetaxel (n=343)	Nivolumab (n=131)	Docetaxel (n=129)	Atezolizumab (n=425)	Docetaxel (n=425)
OS (months)	15.9 (13.2 - NR)	11.3 (9.5 - 14.8)	10.4 (9.4 – 11.9)	12.7 (10.0 – 17.3)	8.5 (7.5 – 9.8)	9.2	6	13.8 (11.8 - 15.7)	9.6 (8.6 - 11.2)
HR (95% CI)	0.64 (0.49 - 0.85; p<0.001)		0.71 (0.58 – 0.88; p = 0.0008)	0.61 (0.49 – 0.75; p = 0.0001)	NA	0.59, (0.44 - 0.79; p<0.001)		0.73 (0.62 - 0.87; p=0003)	
mPFS (months)	6.4 (6.2 - 8.3)	4.8 (4.3 - 5.7)	3.9 (3.1 – 4.1)	4.0 (2.7 – 4.3)	4.0 (3.1 – 4.2)	3.5	2.8	2.8 (2.6 - 3.0)	4.0 (3.3 - 4.2)
HR (95% CI)	0.56 (0.45 to 0.70; p<0.001)		0.88, (0.74 – 1.05; p=0.068)	0.79, (0.66 – 0.94; p=0.004)	NA	0.62, (0.47 – 0.81; p<0.001)		0.95 (0.82 - 1.10)	
ORR (%)	57.9 (51.9 - 63.8)	38.4 (32.7 - 44.4)	18 (14 – 23)	18 (15 – 23)	9 (7-13)	20	9	14	13
p-value	NA	NA	P<0.001	P<0.001	NA	P=0.008	NA	NA	NA
TEAE > Grade 3 (%)	69.8	68.2	13	16	35	7	55	15	43

Abbreviations: CI = confidence interval; FDA =Food and Drug Administration; HR = hazard ratio; mPFS = median progression-free survival; NA = not available; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; TEAE = treatment emergent adverse event.

[a] Included squamous and non-squamous NSCLC.

[b] FDA accelerated approval was granted for pembrolizumab in the metastatic NSCLC population with PD-L1 ≥ 1%.

1.2 Compound Background

Please refer to the Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational product (IP).

1.2.1 Lysine-specific Histone Demethylase 1A

The epigenetic code influences when, and where specific genes are expressed. It is a dynamic and reversible process, during which histone modifications are written, erased, and read by families of enzymes. Initiation and progression of cancer has increasingly been linked to misreading, miswriting or miserasing of histone modifications (Chi, 2010).

Lysine-specific histone demethylase 1A (LSD1) is an eraser of the epigenetic code, thereby regulating the expression of many genes important in cancer progression and cell proliferation (Hoffmann, 2012; Lynch, 2012; Scoumanne, 2007). LSD1 over-expression promotes proliferation, migration, and tumor invasion (Lv, 2012) and has been documented in many human solid tumors including bladder, breast, colorectal, prostate and SCLC (Hayami, 2011; Kahl, 2006; Kauffman, 2011; Serce, 2012). Moreover, LSD1 over-expression has been correlated with poor prognosis in hepatocellular carcinoma, neuroblastoma, prostate cancer, non-small cell lung cancer, and estrogen receptor negative breast cancer (Chen, 2015; Kahl, 2006; Lim, 2010; Lv, 2012; Schulte, 2009; Zhao, 2012).

LSD1 is required for normal differentiation in adult as well as embryonic cells (Wang, 2007). It controls the balance between histone H3 lysine 4 (H3K4) and histone H3 lysine 27 (H3K27) methylation, thereby regulating differentiation-associated genes (Adamo, 2011). It is required for normal hematopoiesis through interaction and modulation of growth factor independence 1b (GFI1b) transcriptional programs, and loss of LSD1 impairs hematopoiesis through a block in differentiation (Saleque, 2007; Sprussel, 2012).

The importance of LSD1 in normal differentiation suggests that aberrant gene expression resulting from dysregulation of LSD1 may result in alterations in pathways associated with a stem-cell like phenotype. Moreover, LSD1 plays a part in stem cell maintenance, regulation of epithelial-to-mesenchymal transition (Adamo, 2011; McDonald, 2011), and has been shown to be an essential regulator of leukemia stem cell potential (Harris, 2012). LSD1 is a master regulator of normal stem cell phenotype, which is required for regulation of pluripotency genes, such as the transcription factor SRY (sex determining region Y)-box 2 (SOX2) and NANOG (Whyte, 2012), and which represses expression of lineage commitment genes (Adamo, 2011). In mouse embryonic stem cell lines, 2 experiments, ribonucleic acid (RNA) interference–mediated knockdown of LSD1 expression and treatment by small molecule LSD1 inhibitor, have demonstrated inhibition of the proliferation of pluripotent cancer cells including teratocarcinoma, embryonic carcinoma, and seminoma or embryonic stem cells that express the stem cell markers OCT4 and SOX2, while displaying minimum growth-inhibitory effects on non- pluripotent cancer or normal somatic cells (Wang, 2011). Short hairpin RNA (shRNA) knockdown experiments in human embryonic stem cell lines show that decreased LSD1 activity lessens the proliferation and self-renewal ability of embryonic stem cells while promoting differentiation.

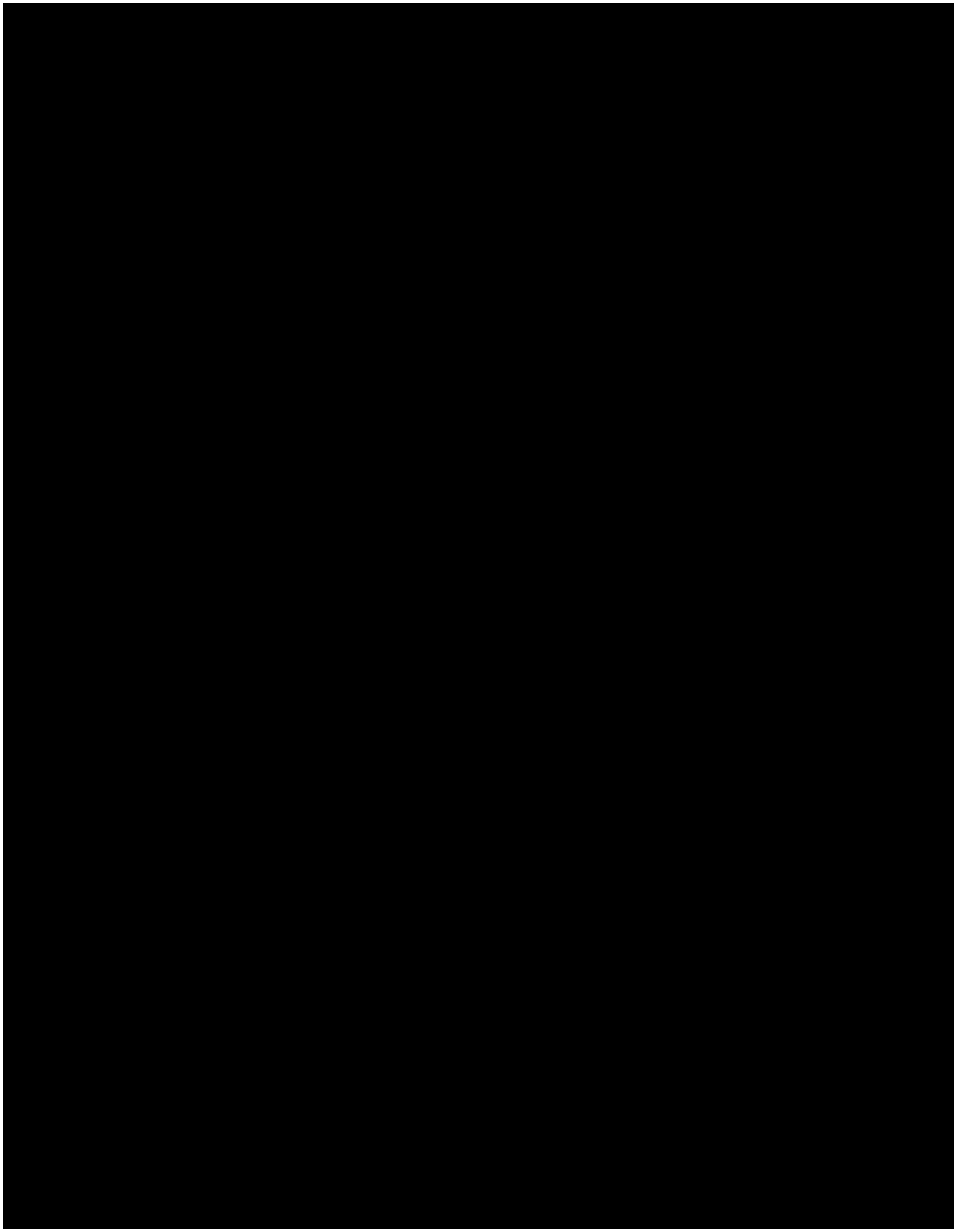
1.2.2 Overview of CC-90011 Mechanism of Action and In Vitro and In Vivo Nonclinical Pharmacology

Lysine-specific histone demethylase 1A was the first lysine demethylase to be discovered and, unlike the Jumonji class of demethylases, belongs to the broad family of monoamine oxidases that uses flavin adenine dinucleotide (FAD) as a cofactor in its enzymatic demethylase activity (unpublished data, current version of the IB).

The importance of LSD1 in development is exemplified by the embryonic lethality seen in knockout mice (Wang, 2007). The shRNA knockdown experiments in human embryonic stem cell lines show that suppression of LSD1 activity decreases the proliferation and self-renewal ability of ES cells while promoting differentiation towards endoderm and mesoderm lineages (unpublished data, current version of the IB). In the adult setting, LSD1 is necessary for normal hematopoiesis through interaction and modulation of GFI1b transcriptional programs and loss of LSD1 results in impaired hematopoiesis through a block in differentiation (Mohammad, 2015). The importance of LSD1 in normal differentiation suggests that aberrant gene expression resulting from dysregulation of LSD1 may result in alterations in pathways associated with a stem-cell like phenotype.

In prior studies, proliferation screens of cell lines representing a number of tumor types indicated that SCLC is sensitive to LSD1 inhibition (Mohammad, 2015). In SCLC, LSD1 and H3K4 methylation are associated with regions of chromatin that are implicated in the regulation of cell state. Inhibition of LSD1 increases methylation and LSD1 enrichment at these sites. While differentiation of SCLC is not well understood, LSD1 positioning at genes associated with neuronal differentiation and transcriptional regulation may suggest that inhibition of LSD1 will promote alterations in expression programs associated with differentiation of this tumor type (Mohammad, 2015).

[redacted]



1.2.4 Overview of Nonclinical Toxicology

Exploratory and Good Laboratory Practice (GLP)-compliant repeated-dose toxicity studies of oral CC-90011 for up to 3 months in mice and dogs following several weekly dosing schedules (mouse = once daily [QD], QDx5/week, and every other day [QOD]x3/week; dog = once weekly [QW], twice a week [BIW], and once every 2 weeks [Q2W]) were conducted to 1) assess the systemic exposure and toxicities over a range of dose levels and dose schedules, 2) to aid in dose and dose schedule selection for clinical trials, and 3) to further characterize CC-90011-related toxicity.

In 4-week studies, treatment-related mortality was observed at 45 mg base/kg/dose in mice following a QDx5/week dose schedule; and at ≥ 0.375 mg base/kg/dose in dogs following a QW dose schedule. The cause of mortality in mice was not determined; the moribund condition of dogs was due to CC-90011-related gastrointestinal (GI) toxicity and ensuing septicemia.

In mice dosed at up to 45 mg base/kg/dose for 4 weeks, there was dose-proportional marrow toxicity, evidenced by a myeloid shift and/or marrow hypocellularity. The marrow space was replaced by fibrosis in the sternum and/or femur, with hyperostosis of endosteal, periosteal, and trabecular bone surfaces of affected sternebrae. Collectively, these changes persisted through a

recovery period at the highest dose only. Some increase in marrow megakaryocytes (without peripheral correlate) was noted at all doses, also persisting at the highest dose. Marrow toxicity occurred in concert with declines in peripheral red cell mass (red blood cell [RBC] count, hemoglobin, and hematocrit), and declines in platelet, reticulocyte and/or leukocyte counts along with significant increases in splenic extramedullary hematopoiesis at all doses (a reactive change to which mice are particularly sensitive). Depletion of splenic marginal zone lymphocytes was observed in all but the lowest dose groups but did not persist through a recovery period.

In dogs dosed for 4 weeks, findings were more clearly inflammatory in nature. The predominant finding centered on GI inflammation which in some instances was ulcerative and associated with secondary septicemia and mortality at higher doses. Changes in the bone marrow reflected peripheral demand, with myeloid hypercellularity and variable evidence of marrow toxicity reflected in the peripheral blood as either a decrease or increase in peripheral leukocyte numbers; unlike mice, no reactive bone alterations were noted.

In one 4-week dog study, there was mortality at ≥ 0.375 mg base/kg/dose, with morbidity generally attributed to gastric inflammation and/or ulceration. Slight to marked, acute to subacute inflammation was observed variably in the esophagus, stomach, small and/or large intestines, and/or rectum of dogs dying early. Findings that correlated with these microscopic changes included dehydration, abnormal feces (liquid, red), red vomitus, decreased food consumption and body weight, hypoactivity, fever, and/or GI tract discomfort. Related clinical pathology findings included decreased albumin, albumin:globulin ratio, calcium, and inorganic phosphorous; increased monocytes, large unstained cells, and neutrophils; and decreased red cell mass, platelets, reticulocytes, and eosinophils. Other findings in these animals were attributed to generalized inflammation and/or septicemia secondary to mucosal ulceration in the GI tract (inflammation in multiple lymph nodes, subcutaneous edema, acute inflammation in the heart or liver), and/or physiologic stress, including extramedullary hematopoiesis in the spleen and an increased myeloid:erythroid ratio in the sternal marrow. In surviving animals, only minimal to moderate acute inflammation of the intestines and/or rectum was observed at ≤ 0.75 mg/kg/dose, with complete recoverability following a 4-week non-dosing interval.

In a 4-week study at lower doses (0.125 or 0.25 mg base/kg/dose QW or 0.5 mg/kg/dose Q2W), there was no mortality, and findings were of lower severity, with acute inflammation in the cecum, ileum, and/or gut-associated lymphoid tissue of dogs from the highest dose-groups from each dosing-interval. Changes were minimal when dosed Q2W, becoming marked when dosed QW. Other findings included minimal extramedullary hematopoiesis in animals from the highest dose groups of either dosing regimen.

All CC-90011-related findings in mice and dogs treated for 4 weeks demonstrated evidence of partial to complete reversibility following a 4-week treatment-free period.

In mice dosed daily for up to 3 months at up to 10 mg/kg/dose, further evidence of CC-90011-related systemic inflammation was observed. Inflammation affected multiple tissues, with instances of mortality (10 mg/kg/dose level) being associated with more severe inflammatory foci. Specifically, scattered neutrophilic inflammatory cell infiltrates occurred at 10 mg/kg/day in the

heart valve, epididymides, eye sclera, and/or periocular tissue. Some instances of periocular inflammation were clearly an extension of peripheral glandular inflammation and, in general, the interior of the eye was unaffected. At 3 mg/kg/day, such infiltrates became minimal and were restricted to the periocular tissues; no such findings were seen at the 1 mg/kg/day. At the non-tolerated dose level, ophthalmology examination revealed hyporeflection and reduced pallor in the fundus of the eye. Also, at 10 mg/kg/day, mortality was associated with focal abscessation in the Harderian glands and/or skin/subcutis. Reactive alterations in affected doses groups included increased (myeloid) marrow cellularity, and extramedullary hematopoiesis in the liver (with some necrosis at the highest dose), spleen and/or adrenal glands.

In dogs dosed once weekly for 3 months, CC-90011 was well tolerated up to 0.25 mg/kg/dose, the highest dose level administered, with no signs of toxicity.

Safety pharmacology evaluations were performed to determine the potential cardiovascular and respiratory effects of CC-90011 in conscious Beagle dogs as part of a GLP 4-week repeat dose toxicity study. There were no CC-90011-related effects on electrocardiograms (ECGs), heart rate (HR), or respiratory rate up to 0.75 mg base/kg/dose on a QW schedule and 0.375 mg base/kg/dose on a twice weekly schedule (the highest doses with cardiovascular and respiratory endpoints evaluated). The effects of CC-90011 on hemodynamic and ECG parameters were also examined in anesthetized male Dunkin Hartley guinea pigs administered CC-90011 at doses of 0, 5, 10, 15, and 20 mg base/kg via a 10-minute infusion into the jugular vein. At 20 mg base/kg, CC-90011 caused a slight decrease in HR with a maximum suppression of 19% observed at 9 minutes into the 10-minute infusion period, as compared to vehicle. Heart rate remained decreased by 18% at the end of the monitoring period. A dose-dependent increase in QT and QT corrected based on Bazett's equation (QTcB) intervals was observed at 10, 15, and 20 mg base/kg; a maximum increase of QTcB interval by approximately 9%, 13%, and 16% at 10 to 18 minutes after infusion initiation was observed at 10, 15, and 20 mg base/kg respectively, as compared to time-matched vehicle. The QTcB interval remained increased by 10% at the end of the monitoring period. There were no remarkable CC-90011 related effects on arterial pressure, PR interval, QRS duration, or qualitative ECG parameters. Based on these results, the NOAEL for hemodynamic and ECG endpoints was 10 mg base/kg following intravenous administration. An in vitro human ether-à-go-go-related gene study was also performed and identified an IC_{50} of 3.4 μM.

CC-90011 was not mutagenic based on the results obtained from the in vitro mutagenicity (Ames) assays.

Overall, CC-90011 exhibits an acceptable safety profile in preclinical species for a clinical drug candidate in an advanced oncology setting and the toxicology program for CC-90011 adequately supports the conduct of clinical trials in oncology subjects.

1.2.5 Prior Clinical Experience of CC-90011

Clinical experience with CC-90011 in humans is based on 2 ongoing clinical Phase 1 studies, CC-90011-ST-001 (monotherapy) and CC-90011-SCLC-001 (combination therapy).

Study CC-90011-ST-001 is an open-label, Phase 1, multicenter, dose escalation (Part A) and expansion (Part B), first-in-human (FIH) clinical study (national clinical trial identifier:

NCT02875223) to assess the safety (including an assessment of maximum tolerated dose [MTD]), PK, and preliminary efficacy of oral CC-90011 in adult subjects with relapsed and/or refractory (R/R) advanced solid tumors and R/R advanced non-Hodgkin lymphomas.

Study CC-90011-SCLC-001 is an open-label, Phase 1b, multicenter, dose-finding study to assess the safety, tolerability, PK, PD, and preliminary efficacy of CC-90011 given in combination with cisplatin or carboplatin and etoposide, defined as Chemotherapy, followed by CC-90011 single agent in maintenance, and CC-90011 given in combination with Chemotherapy plus nivolumab followed by CC-90011 plus nivolumab in maintenance, to adult subjects with first line, extensive stage (ES) SCLC. The study consists of a dose-finding Chemotherapy Treatment Period, where increasing oral doses of CC-90011 are given in combination with standard dose of Chemotherapy with or without nivolumab and a Maintenance Treatment Period, following completion of the chemotherapy regimen, where CC-90011 at 60 mg is administered as a single agent or with nivolumab for responding subjects.

The most current summary of clinical data is available in the most current version of the IB and an overview of these data is described below.

1.2.5.1 Overview of Clinical Safety and Efficacy

1.2.5.1.1 Study CC-90011-ST-001

As of 11-Sep-2020, 50 subjects were enrolled in Part A of the study and received escalating oral doses of CC-90011 QW at 9 dose levels from 1.25 mg to 120 mg/dose and 16 subjects (14 subjects with low/intermediate-grade lung neuroendocrine tumors [NETs] [typical and atypical carcinoid] and 2 subjects with [redacted] neuroendocrine carcinomas [NECs] were enrolled in Part B of the study and received oral CC-90011 QW at 60 mg. The Part A of the study has been completed and the primary objectives were met. Seven out of the 47 evaluable subjects experienced a dose-limiting toxicity (DLT) and all DLTs were Grade 3 or 4 thrombocytopenia. Thrombocytopenia, an on-target effect, occurred at and beyond 60 mg QW and were successfully managed with dose interruption and/or dose reductions. The NTD was established at 120 mg QW with all 4 treated subjects experiencing Grade 3 (N = 2) or Grade 4 (N = 2) thrombocytopenia (requiring platelet transfusion). The MTD has been identified at 80 mg QW since the expanded cohort to 10 subjects identified 2 subjects with DLT, ie, one Grade 3 and one Grade 4 thrombocytopenia (requiring platelet transfusion). One subject at 60 mg QW experienced a Grade 4 thrombocytopenia requiring transfusion.

In Part A of the study (N = 50), the most frequently reported treatment-emergent adverse events (TEAEs) (in at least 10% of subjects) were thrombocytopenia (46.0%), vomiting and anemia (28.0% each), fatigue (26.0%), nausea, constipation and asthenia (22.0% each), diarrhea, pyrexia, and decreased appetite (20.0% each), musculoskeletal pain (16.0%), back pain (14.0%), neutropenia, abdominal pain, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and cough (12.0% each), and tumor pain, headache, and dyspnea (10.0% each). Overall, 24 (48.0%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (24.0%), neutropenia (8.0%), anemia (6.0%), and general physical health deterioration, increased ALT,

increased blood bilirubin, increased lipase, and hypophosphatemia (4.0% each). Grade 3 or 4 thrombocytopenia occurred from the dose level of 40 mg and Grade 3 or 4 neutropenia occurred from the dose level of 80 mg and only after clinically significant thrombocytopenia. Three (6.0%) subjects experienced at least one TEAE leading to discontinuation of study treatment (1 subject at 2.5 mg had Grade 3 portal acute vein thrombosis assessed as not related to study drug and 2 subjects at 120 mg had Grade 3 thrombocytopenia, assessed as related to study treatment). Overall, 33 (66.0%) subjects died during Part A mainly due to progression of malignant disease in this heavily treated population. No death due to drug-related toxicity occurred during the study.

CC-90011 demonstrated preliminary evidence of antitumor activity in this difficult-to-treat patient population with very few treatment options. Among 27 neuroendocrine neoplasm (NEN) subjects, 7 subjects have demonstrated prolonged stabilization of disease (stable disease [SD] > 4 months). Notably, 3 subjects with bronchial NEN had prolonged SD of > 6 months and 2 subjects with [redacted] NEN stayed over 6 months under study drug treatment due to clinical benefit. The R/R non-Hodgkin's lymphoma subject (transformed marginal zone lymphoma) experienced a complete metabolic response.

In Part B of the study (N = 17), the most frequently reported TEAEs (in at least 10% of subjects) were thrombocytopenia (70.6%), asthenia (41.2%), anemia (35.3%), constipation, diarrhea, and nausea (29.4% each), neutropenia and dysgeusia (23.5% each), decreased appetite, arthralgia, musculoskeletal pain, cough and epistaxis (17.6% each), and leucopenia, stomatitis, vomiting, fatigue, hepatic pain, bronchitis, lipase increased, hypokalemia, bone pain, neck pain, dizziness, peripheral sensory neuropathy, sciatica, confusional state, dyspnea, and pruritus (11.8% each). Overall, 13 (76.5.0%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (35.3%), neutropenia (17.6%), and asthenia (11.8%). No subject experienced TEAE leading to discontinuation of study treatment. Overall, 9 (52.9%) subjects died during Part B due to progression of malignant disease (N = 6), occurrence of an adverse event (AE) (N = 2), and unknown cause (N = 1). No death due to drug-related toxicity occurred during the study.

In the 14 subjects with low/intermediate-grade lung NET, a best response of SD was observed in 10 (71.4%) subjects, including 7 subjects with SD ≥ 4 months. The 2 subjects with [redacted] NEC progressed.

1.2.5.1.2 Study CC-90011-SCLC-001

As of 11-Sep-2020, safety and efficacy data are available for 19 enrolled subjects with first-line ES SCLC, who received escalating doses of oral CC-90011 at 20 mg (Cohort 1; N = 8) and 40 mg (Cohort 2; N = 7), and 60 mg (Cohort 3; N = 4), in combination with etoposide plus cisplatin (EP).

One subject, who received CC-90011 20 mg, and 2 subjects, who received CC-90011 60 mg plus EP experienced a DLT during Chemotherapy Treatment Period. No DLT was observed in the 6 evaluable subjects treated at the dose of 40 mg. The NTD was determined to be 60 mg and the CC-90011 recommended Phase 2 dose (RP2D) was 40 mg on Days 1 and 8 of each 21-day chemotherapy cycle.

During the Chemotherapy Treatment Period (N = 19), the most frequently reported TEAEs (in at least 20% of subjects) were anemia (78.9%), thrombocytopenia and neutropenia (68.4% each), asthenia (52.6%), nausea (42.1%), constipation (31.6%), blood alkaline phosphatase (ALP) increased (26.3%), and mucosal inflammation, pyrexia, diarrhea, decreased appetite, hyponatremia, dyspnea, and alopecia (21.1% each). Overall, 16 (84.2%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were neutropenia (63.2%), thrombocytopenia (42.1%), febrile neutropenia (15.8%), and anemia (10.5%).

As of 11-Sep-2020, the best objective response of PR was observed in 16 of the 19 treated subjects.

1.2.5.2.3 Study CC-90011-ST-002

Two SAEs of Grade 4 thrombocytopenia which were reported in the first 2 subjects participating in this ongoing study. On Cycle 1 Day 1 (C1D1), both subjects received their first dose of CC-90011 60 mg and nivolumab 480 mg, and on C1D8, they received their second dose of CC-90011 60 mg. Both subjects were treated with prior chemotherapy, and followed a similar course, with normal platelet count at baseline and a decrease in platelet count (within normal protocol limits) at C1D8. On C1D15, both subjects were diagnosed with Grade 4 thrombocytopenia for which they were hospitalized and recovered within a week. Both subjects received platelet transfusions and demonstrated an increase in platelet count over the course of a week. The events were assessed by the Investigator as related to CC-90011. Per protocol, study treatment was resumed upon resolution of the events with a dose reduction of CC-90011 to 40 mg.

On 14-Aug-2020, the Sponsor reviewed the 2 SAEs in the first 2 subjects with the treating Investigator and the Steering Committee. Thrombocytopenia occurred in both subjects around C1D15 and were consistent with observations from the early CC-90011 monotherapy studies. As a result of the first 2 subjects developing Grade 4 thrombocytopenia, which both followed a similar course, Celgene in agreement with the Steering Committee concluded that new subjects enrolled in Study CC-90011-ST-002 will receive CC-90011 at a reduced starting dose of 40 mg, unless otherwise determined during the ongoing safety evaluation in Section 7.3.1.1. The dose of nivolumab will remain at 480 mg.

1.2.5.2 Overview of Clinical Pharmacology

Pharmacokinetic results are available for 50 treated subjects from Part A of Study CC-90011-ST-001.

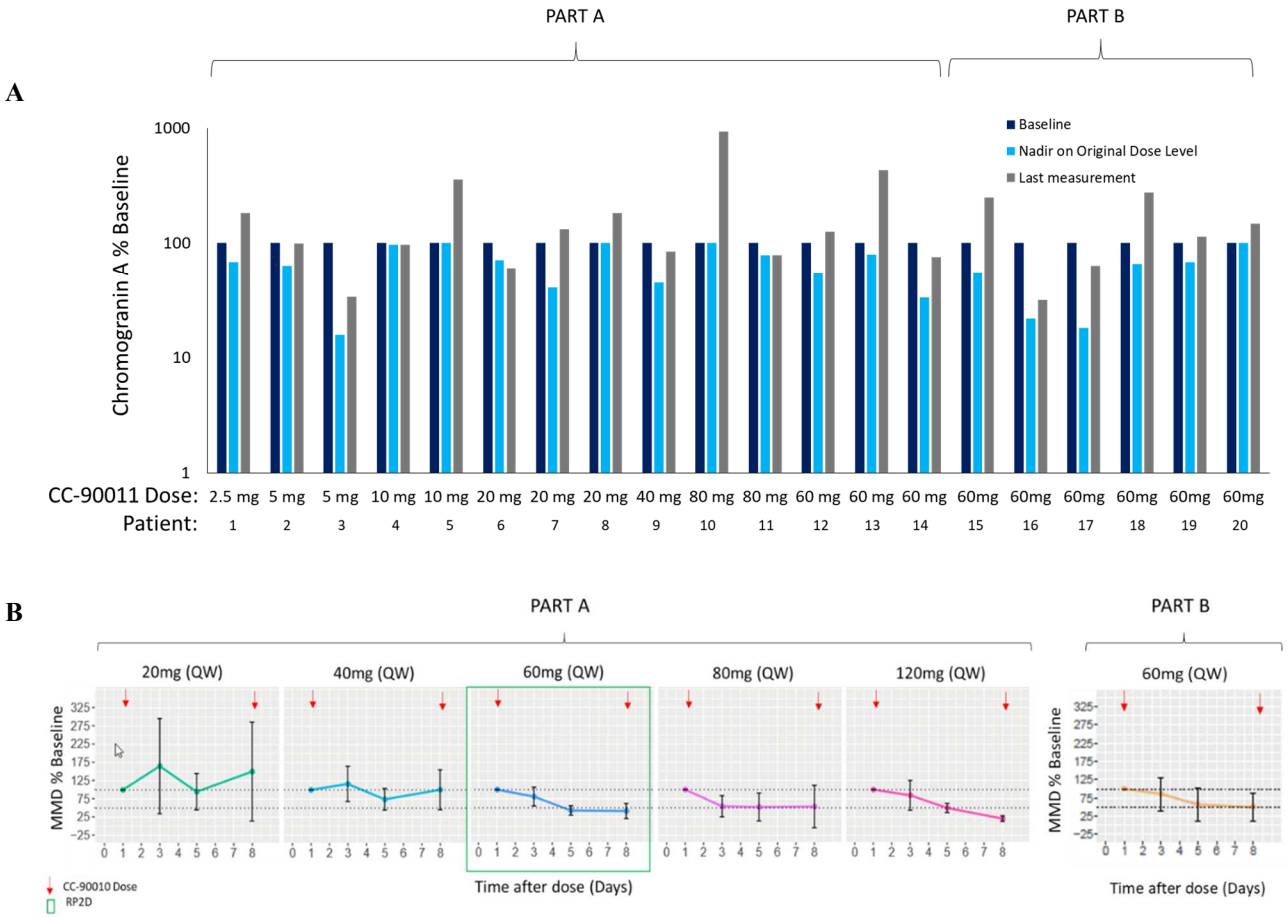
Median time to peak concentrations ranged from 2 to 4 hours post-dose across treatment groups. Drug accumulation was limited (range: 0% to 59% for area under the plasma concentration time curve from 0 to 24 hours [AUC_{0-24}] and maximum observed plasma concentration [C_{max}]) upon repeated QW dosing. Terminal half-life was estimated to be approximately 71 hours. Increase in CC-90011 plasma exposure (AUC_{0-24} and C_{max}) on Day 1 and Day 22 was approximately proportional to dose across the ~ 100-fold dose-range. Additional summary of PK data, by each dose group, is provided in the current version of the IB.

1.2.5.3 Overview of Clinical Pharmacodynamics

Preliminary PD analysis from CC-90011-ST-001 Clinical Trial revealed a decrease in chromogranin A (CgA) levels in response to CC-90011 at doses as low as 2.5 mg QW in subjects with NENs (Figure 2).

Additionally, CC-90011 decreased expression of monocyte to macrophage differentiation-associated (MMD) RNA by ≥ 50% in subject blood samples at doses ≥ 60 mg QW (Figure 2). These preliminary findings indicate that downregulation of MMD is a potential marker for pharmacodynamics by CC-90011 in the clinical setting.

Figure 2: Changes in Chromogranin A (A) and Monocyte to Macrophage Differentiation-associated (B) Over Time in Subjects Treated with CC-90011



Abbreviations: C1D1 = Cycle 1 Day 1; MMD = monocyte to macrophage differentiation-associated; QW = once weekly; RP2D = recommended phase 2 dose.

1.2.6 Nivolumab

Please refer to the Investigator's Brochure (IB), summary of product characteristics (SmPC), package insert, for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of nivolumab.

1.2.6.1 Duration of Treatment with Nivolumab:

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment (Schadendorf, 2017). Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment (Schadendorf, 2015).

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years (Gettinger, 2018). These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16% to 18% for squamous and non-squamous NSCLC respectively) (Felip, 2017).

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years (Spigel, 2017).

Collectively, these data suggest that there is minimal if any benefit derived from continuing immunotherapy treatment beyond two years in advanced tumors. Even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

1.3 Rationale

1.3.1 Study Rationale and Purpose

The use of ICIs in the treatment for lung cancer has proven efficacy as demonstrated by the increasing OS, PFS, ORR and longer DoR compared to chemotherapy alone. However, only limited number of subjects have long term benefit with ICI treatment.

The LSD-1 inhibition sequentially or in combination with cytoreductive therapy could improve disease-free survival by preventing the emergence of resistant clones through treatment of tumorigenic stem cells. This mechanism of action is applicable to many earlier stages of solid tumors where existing standard of care does not result in long term disease control for all patients. The LSD-1 could prove to have a role in treating tumors resistant to current immune check-point blockade, an area of high unmet need for multiple solid tumors where ICIs are either not effective, or where ICIs are currently employed.

CC-90011 has the potential to mitigate primary and acquired resistance to ICI, due to its expected reversal of the CSC phenotype and T cell exclusion in SCLC and sqNSCLC.

In addition, recognizing the multiple mechanisms of resistance, this study will examine biomarkers in blood and tissue that could be used to identify responsive patients and improve outcomes. SCLC and sqNSCLC have high expression of potential predictive biomarkers for CC-90011 (eg, SOX-2 and an LSD1-associated molecular signature), which will be evaluated for potential future use for patient enrichment.

This multi-cohort lung cancer study will evaluate the ability of CC-90011 to increase response rates in 3 different lung cancer populations: PD-1 inhibitor naïve (Cohort A, SCLC) and a PD-1 inhibitor “experienced” (Cohort B, SCLC; and Cohort C, sqNSCLC) when given in combination with nivolumab. Cohort A tests the hypothesis that CC-90011 could enhance nivolumab responses in SCLC “cold tumor” phenotype. In this cohort, the proportion of enrolled subjects who respond to treatment is expected to increase by the action of CC-90011. Tumors with higher expression of an LSD1-associated molecular signature and low TILs may have the best response to the combination of ICI with CC-90011, based on CC-90011 hypothesized mechanism of action of increasing T cell infiltration into tumors. Cohorts B and C tests whether CC-90011 can mitigate acquired resistance to ICI in SCLC as well as sqNSCLC. For these cohorts, the trial will be enrolling subjects who have an initial response or stable disease to ICI, but progress within the first 9 months after completion of the chemotherapy treatment.

For the purpose of this protocol, ICI means anti-PD-1 or anti-PD-L1 treatments.

1.3.2 Rationale for the Study Design

1.3.2.1 Combination of CC-90011 with Immune Checkpoint Inhibitors

The effectiveness of ICIs is grounded on a pre-existent anti-tumoral cellular immune response, which is usually recognized by the presence of tumor T-lymphocytic infiltrates that are, however, most often ineffective because of expression of co-inhibitory (or checkpoint) receptors such as PD-1, CTLA-4, and others. Blocking these checkpoint receptors or their ligands restores T cell function and leads to clinical responses.

PD-1 is expressed on activated CD8+ T cells, as well as B cells and natural killer cells, in the setting of chronic antigen exposure. PD-1 ligand (PD-L1) expression is induced by localized inflammatory stimuli, such as interferons released by the infiltrating T cells. Although PD-1 and PD-L1 checkpoint blockade can result in dramatic therapeutic responses, this therapy is effective only in a subset of subjects, and many of them are only partial responders to therapy (Nowicki, 2017). Subjects who do not respond to initial therapy with PD-1/PD-L1 blockade are referred to as having "primary resistance" to therapy (Sharma, 2017). Furthermore, a growing subset of subjects show robust initial response to therapy, but later have progressive disease. This phenomenon, in which the disease is either refractory to resumption of therapy or develops despite continuation of therapy, is known as "acquired resistance" to PD-1/PD-L1 blockade immunotherapy (O'Donnell, 2016). In all, almost four-fifths of patients either do not respond or lose their responsiveness to ICI. These limitations have made it necessary to explore combination treatment methods which are generally aimed at enhancing or activating antitumor immunity.

The tumor microenvironment can encompass multiple immunosuppressive mechanisms including dysfunctional T cells and lack of T cell infiltration or recognition by T cells, which prevent subjects to respond to anti-PD-1/PD-L1 therapy (Sharma, 2017; Zou, 2016). These mechanisms provide a basis for selecting appropriate combinations to complement the anti-PD-1/PD-L1 action. For example, the presence of T cytotoxic tumor infiltrates (defining the so-called "hot tumors") justifies targeting other checkpoint inhibitors and enhance anti-tumor immune response. With modest and immunosuppressed infiltrates, new therapy should be aimed at inhibitory mediators (such as TGF-β, IL-10, etc), immune suppressive cells (such as myeloid derived suppressor cells, regulatory lymphocyte T cells), or immune ignored cancer stem cells. Also, when T cells are excluded from the tumor bed and accumulate at the tumor border, then potentially effective combinations might be aimed at reactivating or supplanting T cell recruiting signals (eg, chemokines). Finally, when T cells are absent ("cold tumors"), then various modalities to increase tumor immunogenicity and restart antigen-presentation or T cell priming might prove useful.

Based on current understanding, CC-90011, [redacted] (unpublished data, current version of the Investigator Brochure), can be a combination partner for ICIs due to (1) its direct effects on tumor cells, [redacted] and (2) due to its potential immunomodulatory effects via its abilities to impact lymphocytic infiltrates and immunogenicity of tumors (see below). In addition, we have found that tumors which lack T cell infiltration (cold tumors) have higher mRNA

expression of LSD1 and an LSD1-associated molecule, which could be used to identify patients susceptible to the action of CC-90011 with ICI.

Preclinical data provide strong mechanistic rationale for the combination of CC-90011 and an ICI in SCLC. Although checkpoint inhibitors have demonstrated some efficacy in SCLC, the magnitude of benefit has been relatively modest, and only a subset of patients respond. These clinical results may be related to the low abundance of T cells in SCLC tumors. CC-90011 is expected to reverse this phenotype, allowing T cells to infiltrate the tumor.

Preclinical data in the literature and from Celgene, including survival data in mice with tumors, suggest that CC-90011 could induce pro-inflammatory and T cell permissive changes in the tumor microenvironment and, thus, enhance efficacy of checkpoint inhibitors, such as nivolumab.

Mouse tumor models have known limitations especially for evaluating immune oncology (IO) agents. Testing potential therapies in animal models of human disease is a key part of drug development, despite well-known limitations of such models (Ben-David, 2019; Day, 2015; Ochoa de Olza, 2018). A few main types of mouse models are used for IO studies, with advantages and disadvantages to each (Buque, 2018; Ochoa de Olza, 2018). Of these, syngeneic tumor models are often used because of the relative ease with which molecules can be tested. Variations in tumor response to immunotherapies, such as nivolumab, even in controlled laboratory studies with inbred mice, may be related to the gut microbiome (Gopalakrishnan, 2018; Matson, 2018; Ochoa de Olza, 2018; Pitt, 2016; Routy, 2018; Vetizou, 2015).

1.3.2.2 Direct Anti-Tumor Action of CC-90011 Mediated via SOX2

LSD1 appears to play a significant role in the development and progression of malignancies with stem cell features. Accumulating evidence suggests that transcription factor SOX2 drives cancer stemness, fuels tumor initiation, and contributes to tumor aggressiveness through major drug resistance mechanisms like epithelial-to-mesenchymal transition, adenosine triphosphate (ATP)-binding cassette drug transporters, anti-apoptotic or pro-survival signaling, lineage plasticity, and evasion of immune surveillance (Mamun, 2018). Cancer stem cells, which are quiescent and express drug efflux pumps, may avoid killing by cytotoxic agents. Cancer stem cells are believed to be immune privileged, at least in part by expression of immune-modulatory factors (Bruttel, 2014). By driving differentiation of stem cells, LSD1 inhibition may re-sensitize these cells. Inhibition or genetic silencing of LSD1 has been shown to promote differentiation and reduce proliferation, migration, and invasion in vitro (Augert, 2019; Lv, 2012) and to reduce tumor growth in preclinical models (Augert, 2019; Mohammad, 2015)

The SOX2 is the most frequently altered gene in human squamous cell carcinoma (skin, lung and esophageal carcinomas) (Mamun, 2018). The SOX2 gene expression is amplified in more than 20% of tumors, including 27% of SCLC tumors, and is associated with stemness and an un-differentiated state (Hayami, 2011; Rudin, 2012). The SOX2 protein expression is overexpressed in 60% to 90% of tumors, including gliomas, breast, lung, head and neck carcinoma, sarcoma, pancreatic ductal carcinoma, ovarian cancer, colorectal cancer, melanoma, gastric cancers, and medulloblastoma (Mamun, 2018). The SOX2 is frequently amplified and/or over-expressed in SCLC and is involved in the induction of pluripotent stem cells (Takahashi, 2006). [redacted]

CC-90011 may induce differentiation of CSCs. CSCs can be resistant to treatments, including checkpoint inhibitors (Bruttel, 2014). The LSD1 is key regulator of stemness (Zhang, 2018). SOX2 is over-expressed in some SCLC tumors and is a driver of SCLC cell growth (Rudin, 2012; Sholl, 2010; Zhang, 2018). LSD1 inhibitors can decrease SOX2 mRNA expression (Zhang, 2013). LSD1 prevents SETD7-Driven proteolysis of SOX2 (Zhang, 2018), providing another mechanism by which LSD1 inhibitors would decrease SOX2 protein levels.

Therefore, [redacted] CC-90011 may be a useful therapeutic approach for tumors with CSC involvement such as SCLC and sqNSCLC, which are known to have high expression of SOX2 (Karachaliou, 2013; Wuebben, 2017; Ying, 2016). Overexpression of LSD1 is associated with poor prognosis in NSCLC, and promotes tumor cell proliferation, migration and invasion in NSCLC (Lv, 2012). Inhibition of LSD1 inhibits SCLC cell proliferation (Takagi, 2017).

1.3.2.3 Immunomodulatory Activities of CC-90011

CC-90011 may increase the number of tumor T infiltrating lymphocytes (TIL). This could be related to the observation that LSD1 ablation can lead to activation of type 1 interferon and stimulate anti-tumor T cell immunity (Sheng, 2018); and it can also result in enhanced tumor immunogenicity and T cell infiltration in poorly immunogenic tumors. LSD1 inhibition can also result in re-expression of effector T cell-attracting chemokines (CCL5, CXCL9, and CXCL10) (Qin, 2019).

In addition, CC-90011 may inhibit CSC self-renewal and induce their differentiation. The CSCs are known to be resistant to chemotherapy and at least in part by their expression of immune-inhibitory factors to immunotherapy as well (Bruttel, 2014). A tumor without a CSC compartment would remain sensitive to killing by cytoreductive agents or immune regulators. This impact on CSC suggests that CC-90011 could also help mitigate acquired resistance (eg, responders that relapse after a period of response). However, given potential mechanisms of acquired resistance, such as loss of T cell function, lack of T cell recognition by downregulation of tumor antigen presentation, and development of escape mutation variants in the cancer (Sharma, 2017), it is expected that the other immune activities of CC-90011, increasing TIL, stimulating

immunogenicity and anti-tumor T cell immunity (Sheng, 2018), would also contribute to CC-90011 activity in relapsed subjects.

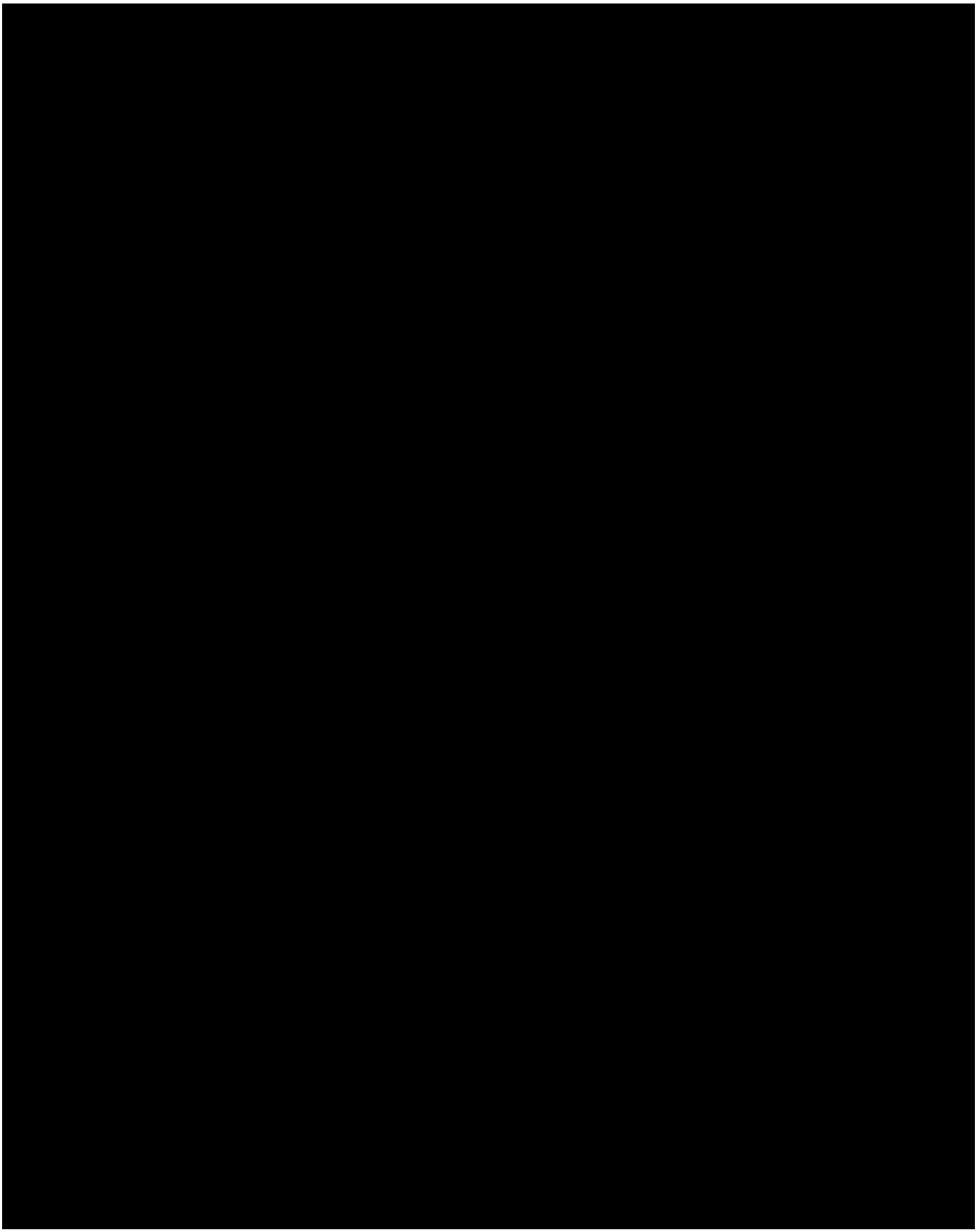
One of the best predictors of response to immunotherapy is the number and activity of tumor infiltrating CD8+ cytotoxic T lymphocytes recruited to the tumor site (Qin, 2019). Consistent with their biological role, tumor infiltrated lymphocytes have been associated with improved outcome in several tumor types, including melanoma, colorectal and breast cancer (Fridman, 2013). Tumor CD8+ T cell infiltration has been linked to antitumor activity of immune checkpoint inhibitors (ICI) in subjects with advanced melanoma or NSCLC (Sharma, 2017; Thomas, 2019)

High levels of tumor infiltrating immune cells are associated with improved overall survival in SCLC, irrespective of tumor stage, subject performance status, or type of treatment received (Wang, 2013). In SCLC, tumor responses were observed in all cases where pretreatment tumors were T cell inflamed. In extended or relapsed SCLC, pre-existing CD8+ T cell response may be predictive of benefit from ICI-based therapies (Thomas, 2019).

As an LSD1 inhibitor, CC-90011 may switch cold tumors (lacking T cells) into hot tumors (T cell infiltrated). Internal analyses of tumor data in The Cancer Genome Atlas (TCGA) identified > 100 genes which negatively correlate with T cell infiltration. Expression of LSD1 and an LSD1-associated molecule anti-correlated with T cells in tumors. The LSD1 complex regulates embryonic stem cells property and substitutes for SOX2 in reprogramming somatic cells to pluripotency (Yang, 2011). Approximately 50% of SCLC and approximately 33% of sqNSCLC had a gene expression pattern which may predict for LSD1 activity and thus response to CC-90011, when combined with anti-PD1 or anti-PD-L1.

CC-90011 may enhance tumor immunity in “cold” tumors. LSD1 expression is inversely associated with that of cytotoxic T cell-attracting chemokines and PDL1 (Qin, 2019). LSD1 knock-down increases inflammatory gene expression (Hanzu, 2013; Qin, 2019). LSD1 KO or inhibition increases T cell trafficking into tumors and check-point inhibitor efficacy in preclinical models (Qin, 2019; Sheng, 2018). LSD1 inhibitors upregulate PDL1 expression in cell lines (Qin, 2019).

Subsequently, LSD1 knockdown was shown to enhance efficacy of anti-PD1, as evidenced by decreased tumor size and increased mouse survival in syngeneic tumor models (Sheng, 2018). In a separate study, LSD1 inhibition plus an anti-PD-1 antibody significantly suppressed tumor growth and pulmonary metastasis and augmented CD8+ T cell infiltration into xenograft tumors of triple negative breast cancer (Qin, 2019). Thus, CC-90011 is expected to enhance response to ICI, such as anti-PD1, when used in combination.



[redacted]

1.3.4 Benefit/Risk Assessment Due to SARS-COV-2/COVID-19 Infection

In 2019, a new coronavirus was identified as the cause of a widespread disease outbreak. The virus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causes the disease called coronavirus disease 2019 (COVID-19), which can lead to severe disease including substantial mortality.

At this time, the risk of COVID-19 in subjects receiving CC-90011 is unknown. Current available clinical data from the ongoing CC-90011-ST-002 study suggest an overall favorable safety profile and no specific evidence of elevated risk of infection. However, since at least a theoretical risk of increased infection rates cannot be ruled out, clinical studies of CC-90011 have been further designed to minimize the overall risk to subjects; additional measures to mitigate risk associated specifically with COVID-19 will include the following:

- Continuous safety assessments will be utilized by the Investigators and Sponsor to determine whether additional safety measures are required. In addition, AEs and SAEs associated with confirmed or suspected SARS-CoV-2 infection will be collected from the date the subject signs informed consent until 100 days following discontinuation of study treatment. The event will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the subject is lost to follow-up), or for suspected cases, until SARS-CoV-2 infection is ruled-out. Adverse events and SAEs will be reviewed on an ongoing basis by the Medical Monitor (or designee) and Global Pharmacovigilance and Epidemiology representatives to monitor for any safety signals or trends. There will be prompt surveillance of SARS-CoV-2/COVID-19 infections in study subjects to ensure that the investigational study treatment do not pose an increased risk of SARS-CoV-2/COVID-19.
- The testing capability for SARS-CoV-2 to provide prompt results is not uniformly available. Due to these challenges, testing for SARS-CoV-2 will be deferred to local or regional policies. However, study subjects who test positive for SARS-CoV-2 during screening may be rescreened after meeting criteria in Section 6.1.1.
- Subjects with previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to screening are excluded until symptoms have completely resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the subject at a higher risk of receiving investigational treatment.
- Subjects currently in other interventional trials for COVID-19 may not participate in the study. If a study participant has received an investigational COVID-19 vaccine prior to screening, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the Investigator and the Medical Monitor. It is also advised to avoid overlap of study treatment and vaccine administration, if possible (for example, at least 2 days, preferably 7 days apart), given that adverse events related to vaccine administration may confound potential study treatment infusion reactions.
- SARS-CoV-2 may have short- and long-term impact on the study population, which may affect the safety profile and outcome of investigational products. Thus, serologic testing will be implemented at screening, during study treatment, after a documented or suspected SARS-CoV-2 infection, and at follow-up for potential future measurements of anti-SARS-CoV-2 serology.
- Dose delay and criteria to resume study treatment in cases when a subject develops confirmed or suspected SARS-CoV-2 is included in Section 7.4.5.

It is important to acknowledge the widespread impact of SARS-CoV-2 and the potential risks SARS-CoV-2 may have on this study population. However, there are limited treatment options available to individuals with advanced lung cancer who have a poor prognosis and few, if any, curative options. The absence of other available treatments supports the urgent need to develop therapeutic options for these serious diseases while not negating the implementation of mitigation measures to protect the safety of the study population.

The potential for direct benefit described within Section 1.3 warrants evaluating CC-90011 in combination with nivolumab in this Phase 2 clinical study with the risk mitigation described above.

1.4 Risk/Benefit Assessment

Please see Appendix G for the Risk Benefit Assessment document.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 4: Study Objectives

Primary Objective
The primary objective of the study is to evaluate in each individual cohort the overall response rate in subjects with SCLC or sqNSCLC treated with CC-90011 in combination with nivolumab.
Secondary Objective(s)
The secondary objectives are to evaluate in each individual cohort the following endpoints/outcomes in subjects with SCLC or sqNSCLC receiving CC-90011 in combination with nivolumab: • Evaluate the safety and tolerability • Evaluate the duration of response • Evaluate the time to response • Evaluate the Investigator-assessed progression-free survival • Evaluate the time to first subsequent therapy
Exploratory Objective(s)
The exploratory objectives for each individual cohort are to: • Evaluate the overall survival [redacted] • Explore the relationship between PK, PD biomarkers and/or clinical outcomes of CC-90011 in combination with nivolumab • Evaluate the disease control rate • Assess the pharmacokinetics and immunogenicity of nivolumab in small cell lung cancer and squamous non-small cell lung cancer cohort subjects • Assess the impact of SARS-CoV-2 serologic status on subjects and to support health authority requests

Abbreviations: LSD1 = lysine-specific histone demethylase 1 A; PD = pharmacodynamic; PK = pharmacokinetic; [redacted]; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; sqNSCLC = squamous non-small cell lung cancer; SCLC = small cell lung cancer; [redacted].

Table 5: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Overall response rate	The proportion of subjects in the treated population who had confirmed complete response (CR) or confirmed partial response (PR) as assessed by Investigator review per RECIST v1.1	Every 6 weeks post C1D1 for the first 24 weeks and then every 8 weeks until disease progression, new anticancer therapy, death or withdrawal by subject.
Secondary	Safety and tolerability	Safety and tolerability will be assessed from adverse events (using NCI CTCAE v5.0), laboratory tests, vital signs, ECOG performance status, concomitant medications, and dose modifications.	Signature of informed consent through 28 days after the last dose of CC-90011 and 100 days after the last dose of nivolumab.
	Duration of response	The time from the first occurrence of a confirmed documented response to the time of the first documented tumor progression, as determined by Investigator review per RECIST v1.1, or death from any cause, whichever comes first.	Every 6 weeks post C1D1 for the first 24 weeks and then every 8 weeks until disease progression, new anticancer therapy, death or withdrawal by subject.
	Time to response	The time from the first dose of the study drug to the date of the first confirmed documented response (CR or PR), as assessed by Investigator review per RECIST v1.1.	Every 6 weeks post C1D1 for the first 24 weeks and then every 8 weeks until disease progression, new anticancer therapy, death or withdrawal by subject.
	Progression-free survival	The time from first dose of study treatment to the date of the first objectively documented tumor progression as assessed by Investigator review per RECIST v1.1 or death from any cause, whichever occurs first.	Every 6 weeks post C1D1 for the first 24 weeks and then every 8 weeks until disease progression, new anticancer therapy, death or withdrawal by subject.
	Time to first subsequent therapy	The time from the first dose of the study drug to the date of the next cancer therapy or death.	From the first dose of study drug to the date of next cancer therapy or death due to any cause.
Exploratory	Overall survival	The time from first dose of the study drug to the date of death due to any cause.	From the first dose of the study drug to the date of death due to any cause.

Table 5: Study Endpoints

Endpoint	Name	Description	Timeframe
	Pharmacodynamics/ Biomarkers	[redacted]	[redacted]
	Pharmacokinetics	Assess the relationship between PK/PD biomarkers and clinical outcomes of CC-90011 in combination with nivolumab.	Cycle 1 and subsequent Cycles at specified timepoints.
	Disease control rate	The proportion of subjects in the treated population who had confirmed CR, confirmed PR, or stable disease (SD) for the minimum interval of 12 weeks as assessed by Investigator review per RECIST v1.1	Every 6 weeks post C1D1 for the first 24 weeks and then every 8 weeks until disease progression, new anticancer therapy, death or withdrawal by subject.
	Nivolumab Pharmacokinetics and Immunogenicity	Assess anti-nivolumab antibodies and explore relationship between pharmacokinetics, immunogenicity and selected efficacy and safety endpoints	Prespecified timepoints in treatment period
	SARS-CoV-2 serology	Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG) and the potential association between these measurements and selected endpoints related to safety, efficacy, and/or biomarkers	Baseline, every 6 months post C1D1, and at follow-up.

Abbreviations: [redacted]; ECOG = Eastern Cooperative Oncology Group; IgG = immunoglobulin G; [redacted]; NCI CTCAE = National Cancer Institute Common Terminology

Criteria for Adverse Events; ORR = overall response rate; [redacted]; PK = pharmacokinetic; [redacted]; RECIST = Response Evaluation Criteria in Solid Tumors; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

3 OVERALL STUDY DESIGN

3.1 Study Design

This is a Phase 2, multicenter, open-label, multi-cohort study to assess safety and efficacy of CC-90011 in combination with nivolumab in subjects with small cell lung cancer or squamous non-small cell lung cancer who have progressed after 1 or 2 lines of therapies.

Approximately 135 subjects total globally will be enrolled into one of the following cohorts in 2 stages:

- Cohort A: SCLC in ICI naïve subjects
- Cohort B: SCLC in ICI progressor subjects
- Cohort C: sqNSCLC in ICI progressor subjects

For the purpose of this protocol, ICI means anti-PD-1 or anti-PD-L1 treatments.

During Stage 1 of each cohort, a Data Review Team (DRT) will review all safety and preliminary efficacy data and will be responsible for conducting a futility review for go/no-go decision for Stage 2. The DRT will consist of the Celgene Medical Monitors, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives, as appropriate, and site investigator(s) and/or designees who have enrolled subjects in the Stage(s) 1 of the study. Data Review Team meetings will be held to review the data, monitor safety and make expansion decisions.

The primary endpoint is investigator assessed ORR.

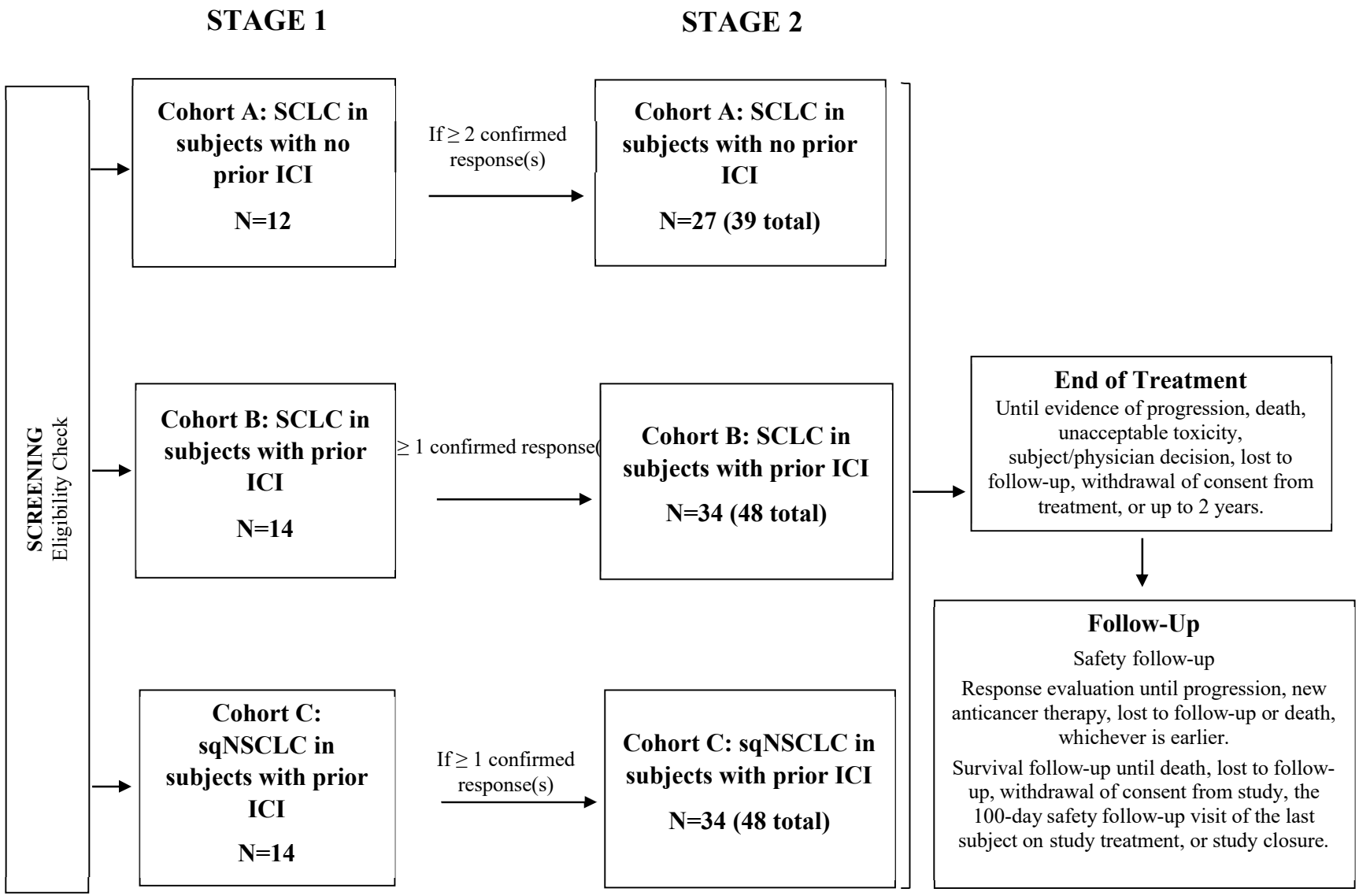
Based on safety/tolerability and preliminary efficacy data, the combination of CC-90011 and nivolumab could be expanded to add cohorts of subjects within other tumor types and the Sponsor may consider amending the Study design to investigate the efficacy of the combination versus the current standard of care in one or more tumor types.

All subjects will receive CC-90011 40 mg, unless otherwise determined during the ongoing safety evaluation (Section 7.3.1.1) PO weekly on Days 1, 8, 15, and 22 of every 28-day cycle and nivolumab 480 mg IV every 4 weeks. The decision to discontinue a subject, which will not be delayed or refused by the Sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

The study conduct will be overseen by a Steering Committee (SC) composed of selected Investigators who are taking part in the study. The SC will serve in an advisory capacity to the Sponsor.

The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 3: Overall Study Design



3.2 Study Duration for Subjects

Subjects may begin screening up to 28 days before first dose of study treatment. Treatment must begin within 3 days of enrollment. Subjects will be treated until death, progressive disease, unacceptable toxicity, withdrawal of consent from treatment, physician decision, or for up to 2 years. For subjects who progress with only brain metastasis, treatment with IP will be stopped, but may be continued after completion of, and recovery from local radiation treatment per the Investigator's judgement.

In the event of discontinuation of the study treatments, subjects will be followed in survival follow-up until death, withdrawal of consent from the entire study, lost to follow-up, the 100-day safety follow-up visit of the last subject on study treatment, or end of study.

Enrollment is expected to take approximately 18 months. The total study duration is estimated to be approximately 36 months from the enrollment of the first subject to the last subject last visit.

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 survival 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 prespecified in the protocol, whichever is the later date.

4 STUDY POPULATION

4.1 Number of Subjects

Approximately 135 subjects with SCLC or sqNSCLC will be enrolled globally. The total number of subjects to be enrolled in Stage 1 across all cohorts is approximately 40 subjects. In Stage 2, approximately 95 additional subjects will be enrolled across all cohorts.

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 with histological or cytological confirmation of extensive stage SCLC (ES SCLC) or Stage IIIb or IV sqNSCLC.
3) Subject has received 1 or 2 prior lines of therapies, defined as:
   a) Cohort A (SCLC, ICI naïve):
      - At least 1 prior treatment including a platinum-based chemotherapy doublet
      - A minimum of 3 cycles of platinum-based chemotherapy in first line treatment, unless stopped at 2 cycles due to treatment-related toxicity
   b) Cohort B (SCLC, ICI progressors):
      - At least 1 prior first or second line treatment includes an ICI
      - If treatment includes an ICI as maintenance therapy, at least 1 cycle of ICI in maintenance should have been completed
      - At least 1 prior treatment including a platinum-based chemotherapy doublet
      - A minimum of 3 cycles of platinum-based chemotherapy, with or without ICI, in first line treatment, unless stopped at 2 cycles due to treatment-related toxicity
      - Subject must have progressed during ICI therapy, defined as unequivocal progression on or within 3 months of the last dose of ICI therapy (if no subsequent therapy)
   c) Cohort C (sqNSCLC, ICI progressors):
      - At least 1 prior first or second line treatment includes an ICI
      - If treatment includes an ICI as maintenance therapy, at least 1 cycle of ICI in maintenance should have been completed
      - At least 1 prior treatment including a platinum-based chemotherapy doublet
      - A minimum of 3 cycles of platinum-based chemotherapy, with or without an ICI, in first line treatment, unless stopped at 2 cycles due to treatment-related toxicity
      - Subject must have progressed during ICI therapy, defined as unequivocal progression on or within 3 months of the last dose of ICI therapy (if no subsequent therapy)
4) Subject has progressed at the last line of therapy.
5) Subject has a measurable disease defined by RECIST v1.1.
6) Subject agrees to provide a tumor biopsy from primary or metastatic site prior to first dose and at a pre-specified timepoint during treatment. Core biopsy is required however, in the event a core biopsy may not otherwise be feasible in the opinion of the treating physician, an

endobronchial ultrasound-guided fine needle aspirate [EBUS-FNA]) biopsy, using the largest gauge needle, may be performed instead.

7) Subject has ECOG Performance Status of 0 to 1 (APPENDIX C).
8) Subject is able to swallow medication.
9) Subject must have the following laboratory values:
   a) Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
   b) Hemoglobin (Hgb) ≥ 9 g/dL (one-time blood transfusion is allowed)
   c) Platelet (Plt) Count ≥ 150 x 109/L
   d) White blood cells (WBC) ≥ 2 x 109L
   e) Serum AST/serum glutamic oxaloacetic transaminase (SGOT) or ALT/serum glutamic pyruvic transaminase (SGPT) ≤ 3 x upper limit of normal (ULN) or ≤ 5 x ULN if presence of liver metastases
   f) Total serum bilirubin ≤ 1.5 x ULN (≤ 3 x ULN, if Gilbert's syndrome or if indirect bilirubin concentrations are suggestive of extrahepatic source of the elevation)
   g) Creatinine clearance (CrCl) ≥ 60 mL/minute based on Cockcroft-Gault (APPENDIX D) or modification of diet in renal disease (MDRD) or ≥ 60 mL/min/1.73 m2
10) A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy or other medical condition does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months) and must:
   a) Have 2 negative pregnancy tests as verified by the Investigator prior to starting study treatments:
      – Have a negative serum pregnancy test (sensitivity of at least 25 mIU/mL) at Screening
      – Have a negative serum or urine pregnancy test within 72 hours prior to Cycle 1 Day 1 of study treatment. A urine pregnancy test must have a sensitivity of at least 25 mIU/mL.
   b) Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with 1 highly effective contraceptive method plus 1 barrier method during the following time periods related to this study: 1) from signing of ICF; 2) while taking study treatment; 3) during dose interruptions; and 4) for at least 45 days after the subject's last dose of CC-90011 or 5 months after the last dose of nivolumab, whichever is later.
      – Highly effective contraceptive methods are combined (containing estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, intravaginal, patch or implantable) bilateral tubal ligation; intra-uterine device; intrauterine hormone-releasing system, or vasectomized partner sterilization (note that vasectomized partner is a highly effective birth control method provided that partners is the sole sexual partner of the FCBP trial participant

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

and that the vasectomized partner has received medical assessment of the surgical success). Barrier methods are male or female latex or synthetic condom, diaphragm, cervical cap or sponge with spermicide.

c) Avoid conceiving or donating ova while on treatment and for 45 days after the last dose of CC-90011 or 5 months after the last dose of nivolumab, whichever is later.

d) Agree to ongoing pregnancy testing during the course of the study. This applies even if the subject practices true abstinence* from heterosexual contact.

11) Males must practice true abstinence* from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use a condom (a latex or non-latex synthetic condom is recommended) during sexual contact with a pregnant female or a FCBP while participating in the study, during dose interruptions, and for at least 105 days after the subject's last dose of CC-90011, even if he has undergone a successful vasectomy. Males must agree not to donate semen or sperm while on treatment and for at least 105 days following the last dose of CC-90011, whichever is later.

12) Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.

13) Subject is 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 any significant medical condition, including active or uncontrolled infection, or the presence of laboratory abnormalities, or psychiatric illness which places the subject at unacceptable risk if he/she were to participate in the study.

2) Subject has any condition that confounds the ability to interpret data from the study.

3) Subject has not recovered to Grade 2 or lower clinically significant toxicities related to the prior therapy (alopecia excluded).

4) Subject has received prior LSD1 therapies.

5) Subject has a history of severe hypersensitivity reactions to other monoclonal antibodies.

6) Subject with symptomatic and untreated or unstable central nervous system (CNS) metastases.

   a) Subject has recently been treated with whole brain radiation or stereotactic radiosurgery for CNS metastases must have completed therapy at least 2 weeks prior to Cycle 1 Day 1 and has a follow-up brain computed tomography (CT) or magnetic resonance imaging (MRI) demonstrating either stable or improving metastases 2 or more weeks after completion of radiotherapy.

   b) Subject must be asymptomatic and off steroids or on stable dose of steroids for at least 2 weeks (≤ 10 mg daily prednisone or equivalent) prior to first dose.

7) Subject has persistent diarrhea due to a malabsorptive syndrome (such as celiac sprue or inflammatory bowel disease) ≥ NCI CTCAE Grade 2, despite medical management), or any

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

other significant gastrointestinal (GI) disorder that could affect the absorption of the study treatments.

8) Subject with symptomatic or uncontrolled ulcers (gastric or duodenal), particularly those with a history of and/or risk of perforation and GI tract hemorrhages.
9) Subject with any hemorrhage/bleeding event > NCI CTCAE Grade 2 or haemoptysis > 1 teaspoon within 4 weeks prior to the first dose.
10) Subject has any of the following cardiovascular criteria:
    a) Evidence of acute or ongoing cardiac ischemia
    b) Current symptomatic pulmonary embolism
    c) Unstable angina pectoris or myocardial infarction ≤ 6 months prior to enrollment
    d) Heart failure of New York Heart Association Classification III or IV ≤ 6 months prior to enrollment
    e) Persistent or clinically meaningful ventricular arrhythmias prior to enrollment
    f) Cerebral vascular accident or transient ischemic attack ≤ 6 months prior to enrollment
    g) QT corrected based on Fridericia's equation (QTcF) ≥ 450 milliseconds (msec) on Screening ECG, a baseline prolongation of QTcF interval ≥ 450 msec (NCI CTCAE Grade ≥ 2)
    h) A history of additional risk factors for Torsades de pointes (TdP) (eg, heart failure, hypokalemia, family history of Long QT Syndrome)
    i) Uncontrolled hypertension (blood pressure ≥ 160/95 mm Hg)
11) Subject has known human immunodeficiency virus (HIV) infection.
12) Subject has known chronic active hepatitis B or C virus (HBV, HCV) infection.
    a) Subject who is seropositive due to HBV vaccination is eligible.
    b) Subject who has no active viral infection and is under adequate prophylaxis against HBV reactivation is eligible.
13) Subject has any other malignancy within 2 years prior to enrollment, with the exception of adequately treated in-situ bladder cancer, in-situ carcinoma of the cervix, uteri, non-melanomatous skin cancer, ductal in situ breast carcinoma, thyroid cancer, or early stage prostate cancer (all treatment of which should have been completed 6 months prior to enrollment).
14) Enrollment in any other clinical protocol or investigational study with an interventional agent or assessments that may interfere with study procedures.
15) Subject has medical conditions requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of enrollment.
    a) A brief (≤ 7 days) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
    b) Adrenal replacement steroid doses > 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.
    c) Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) are permitted.

16) Subject has active autoimmune diseases or history of autoimmune diseases that may relapse. Subjects with the following diseases are allowed to be enrolled after further screening: type I diabetes, hypothyroidism managed with hormone replacement therapy only, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis, or alopecia), or diseases not expected to recur in the absence of external triggering factors.
17) Subject is pregnant or nursing.
18) Subject has a history of persistent skin rash ≥ NCI CTCAE Grade 2 related to prior ICI therapy.
19) Subject has organ transplant history, including allogeneic stem cell transplant.
20) Subject has interstitial lung disease history.
21) Subject has received a live/attenuated vaccine within 30 days of first dose.
22) Subject who is currently in other interventional trials, including those for COVID-19, may not participate in Bristol Myers Squibb (BMS) or Celgene Corporation clinical trials until the protocol specific washout period is achieved. If a study subject has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the Investigator and the Medical Monitor.
23) Subject has previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to screening.
    a) Acute symptoms must have resolved and based on Investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the subject at a higher risk of receiving investigational treatment.

5 TABLE OF EVENTS

Table 6: Table of Events

Events	Screening Period[a]	Treatment Period								Follow-up Period		
		Cycle 1				Cycle 2		Subsequent Cycles	EOT[c]	Safety		Survival
	-28 to 1	Day 1[b]	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		28 days	100 days	Q2 months
Window (days)			± 1	± 1	± 1	± 1	± 1	± 7	± 1	+ 7	+ 7	± 14
STUDY ENTRY AND GENERAL ASSESSMENTS												
Informed consent form	X	-	-	-	-	-	-	-	-	-	-	-
Optional informed consent form to continue IP and research	X	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-
IRT Registration	X	X	-	-	-	X	-	X	X	-	-	-
Complete medical history	X	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-
Prior disease history	X	-	-	-	-	-	-	-	-	-	-	-
Prior disease therapies[a]	X	-	-	-	-	-	-	-	-	-	-	-
Histological or cytological confirmation	X	-	-	-	-	-	-	-	-	-	-	-

Table 6: Table of Events

Events	Screening Period[a]	Treatment Period								Follow-up Period		
		Cycle 1				Cycle 2		Subsequent Cycles	EOT[c]	Safety		Survival
	-28 to 1	Day 1[b]	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		28 days	100 days	Q2 months
Window (days)			± 1	± 1	± 1	± 1	± 1	± 7	± 1	+ 7	+ 7	± 14
Prior/ concomitant medication evaluation	X	Continuous, until 28 days after CC-90011 discontinuation or 100 days for nivolumab or EOT Visit, whichever occurs later										-
Prior/ concomitant procedures evaluation	X	Continuous, until 28 days after CC-90011 discontinuation or 100 days for nivolumab or EOT Visit, whichever occurs later										-
SAFETY ASSESSMENTS												
Adverse event evaluation	Continuous for all AEs (SAEs or non-serious AEs), including those associated with SARs-CoV-2 infection, starting after informed consent signature, until 28 days after CC-90011 discontinuation or 100 days for nivolumab or EOT Visit, whichever occurs later. All AEs (SAEs or non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event it otherwise explained, the event is deemed irreversible, the subject is lost to follow-up, or for suspected cases, until SARS-CoV-2 infection is ruled out.											-
Physical examination	X	X	-	-	-	X	-	X	X	X	-	-
Vital signs	X	X	X	X	X	X	X	X	X	X	X	-
Weight	X	X	-	-	-	X	-	X	X	X	X	-
Performance status (ECOG)	X	X	-	-	-	X	-	X	X	X	-	-
Height	X	-	-	-	-	-	-	-	-	-	-	-
12-lead ECG[d]	X	X[d]	X	-	-	X	-	Cycle 3	-	-	-	-
Hematology laboratory[e]	X	X	X	X	X	X	X	X	X	X	X	-

Table 6: Table of Events

Events	Screening Period[a]	Treatment Period								Follow-up Period		
		Cycle 1				Cycle 2		Subsequent Cycles	EOT[c]	Safety		Survival
	-28 to 1	Day 1[b]	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		28 days	100 days	Q2 months
Window (days)			± 1	± 1	± 1	± 1	± 1	± 7	± 1	+ 7	+ 7	± 14
Chemistry laboratory[f]	X	X	X	X	X	X	X	X	X	X	X	-
Thyroid function	X	X	-	-	-	-	-	Every 8 weeks	X	X	X	-
Coagulation laboratory	X	As clinically indicated										-
Serum β- hCG for FCBP	X	As clinically indicated										-
Urine β- hCG for FCBP[g]	-	X	-	-	-	X	-	X	X	X	X	-
Fertility counseling[h]	X	-	-	-	-	-	-	-	-	-	-	-
Contraceptive counseling for FCBP and males	X	X	-	-	-	-	-	-	X	X	X	-
EFFICACY AND OTHER ASSESSMENTS												
Efficacy assessments: CT scan/ MRI (chest, abdomen, pelvis)[i]	X	Every 6 weeks (± 7 days) for the first 24 weeks and then every 8 weeks (± 7 days) until disease progression, start of a new anticancer therapy, or withdrawal of consent by subject from the entire study.										-

Table 6: Table of Events

Events	Screening Period[a]	Treatment Period								Follow-up Period		
		Cycle 1				Cycle 2		Subsequent Cycles	EOT[c]	Safety		Survival
	-28 to 1	Day 1[b]	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		28 days	100 days	Q2 months
Window (days)			± 1	± 1	± 1	± 1	± 1	± 7	± 1	+ 7	+ 7	± 14
CT scan, with contrast, of the head or brain MRI with contrast[j]	X	As clinically indicated										
CC-90011 Pharmacokinetics (Refer to Table 7)	-	X	X	-	-	X	-	Cycle 3	-	-	-	-
Nivolumab Pharmacokinetics and Immunogenicity (Refer to Section 6.5.1)	-	X	-	-	-	X	-	Cycle 3 and then every 4th Cycle thereafter	-	-	-	-
[redacted]												
SARS-CoV-2 Serology[o] (Refer to Table 10)	X	Every 6 months during study treatment and approximately 4 weeks after a documented or suspected SARS-CoV-2 infection[o]							-	X	-	-

Table 6: Table of Events

Events	Screening Period[a]	Treatment Period								Follow-up Period		
		Cycle 1				Cycle 2		Subsequent Cycles	EOT[c]	Safety		Survival
	-28 to 1	Day 1[b]	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		28 days	100 days	Q2 months
Window (days)			± 1	± 1	± 1	± 1	± 1	± 7	± 1	+ 7	+ 7	± 14
INVESTIGATIONAL PRODUCT (IP)												
Administer CC-90011	-	Weekly administration on Days 1, 8, 15, 22 of each cycle							-	-	-	-
Dispense CC-90011	-	X	-	-	-	X	-	X	-	-	-	-
Administer nivolumab[n]	-	X	-	-	-	X	-	X	-	-	-	-
Provide, collect, and/or review medication diary for CC-90011[m]	-	X	X	X	X	X	X	X	X	-	-	-
Accountability of CC-90011	-	X	-	-	-	X	-	X	X	-	-	-
Accountability of nivolumab	-	X	-	-	-	X	-	X	X	-	-	-
FOLLOW-UP												
Survival follow-up	-	-	-	-	-	-	-	-	-	-	X	X
Disease therapy since IP discontinuation	-	-	-	-	-	-	-	-	-	X	X	X

Abbreviations: AE = adverse event; β- hCG = beta human chorionic gonadotropin; CT = computed tomography; [redacted]; [redacted]; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FCBP = female of child bearing

potential; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; [redacted]; [redacted]; Q2 = every two; Q4W = every 4 weeks; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] All screening assessments to be done within 28 days before enrollment. If screening assessments are performed within 72 hours of Day 1, safety, laboratory and physical examinations need not be repeated at Cycle 1 Day 1.

[b] Subjects should have first dosing initiated within 3 days of enrollment.

[c] End of treatment visit to be completed as soon as possible after IP discontinuation decision, within 28 days.

[d] ECG assessed locally per Investigator for immediate clinical decision. Triplicate ECGs to be collected on Cycle 1 Day 1 only at timepoints specified in Table 7 and Table 8. Single ECGs to be collected at screening, pre-dose on Cycle 1 Day 8, Cycle 2 Day 1, Cycle 3 Day 1, and as clinically indicated.

[e] Hematology tests will be performed pre-dose. All hematology tests will be performed locally and can be performed the day before next study treatment administration. Unscheduled hematology tests can be planned between each study visit.

[f] Chemistry tests will be performed pre-dose. All chemistry tests will be performed locally and can be performed the day before next study treatment administration. Unscheduled chemistry tests can be planned between each study visit.

[g] Urine (or serum) pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of IP, if the initial serum pregnancy test did not already occur with 72 hours of dosing (negative results required for IP administration).

[h] Fertility counseling including sperm banking for males, if appropriate.

[i] Imaging of pelvis if per local practice. Modality used at screening is to be used throughout the study if possible.

[j] For subjects who received prophylactic cranial irradiation (PCI), the brain imaging performed prior to initiation of PCI, must occur within 56 days prior to enrollment. For subjects who did not receive PCI, brain imaging must occur within 28 days prior to enrollment. Refer to Section 6.1 and Section 6.4.

[redacted]

Medication diary for CC-90011 should be provided at every Day 1 of every cycle. However, medication diary should be reviewed at each study visit, including Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, and Cycle 2 Day 15.

[n] Nivolumab Q4W dosing may be dosed within ± 3-day window but no less than 25 days from the previous dose.

[o] If a documented or suspected SARS-CoV-2 infection occurs within 4 weeks of the 6 month sampling time point, a single serum sample will be collected to satisfy the requirements for both every 6 month and approximately 4 week after infection time points.

6 PROCEDURES

Any questions regarding the protocol should be directed to the Sponsor's study physician or designee. The procedures conducted for each subject enrolled in the study are outlined in the Table of Events.

6.1 Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days of first dosing unless noted otherwise below.

Safety laboratory analyses and all assessments will be performed locally. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

Any questions regarding subject eligibility should be directed to the Sponsor or other Sponsor nominated representatives or designees for approval. Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

The baseline tumor assessment on chest, abdomen, and pelvis (pelvis if per local practice) is to be performed within 28 days prior to enrollment. For subjects who received prophylactic cranial irradiation (PCI), the brain imaging performed prior to initiation of PCI, must occur within 56 days prior to enrollment. For subjects who did not receive PCI, brain imaging must occur within 28 days prior to enrollment.

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

- Informed consent: Written informed consent must be obtained before performing any study specific tests or procedures. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment (or 56 days for the brain imaging performed prior to initiation of PCI as per practice for subjects treated with PCI) may be used for screening assessments rather than repeating such tests. Subject may be rescreened beyond the screening window and the subject will sign a new ICF at the time of rescreening.
- Optional informed consent for continuing IP beyond initial progression
- Inclusion/exclusion criteria assessment
- Interactive response technology (IRT) registration
- Demographics (initials, date of birth, sex, race, and ethnicity-if allowed by local regulations)
- Prior disease history (including but not limited to specific information regarding diagnosis, staging, histological or cytological confirmation of SCLC or sqNSCLC)
- Prior disease therapies: includes surgery, radiation, systemic or any other therapy for the subject's disease
- Complete medical history (all relevant medical conditions diagnosed/ occurring prior to screening should also be included)
- Prior and concomitant procedures (including all procedures occurring ≤ 28 days before screening)

- Prior and concomitant medication evaluation (including those taken ≤ 28 days before screening, except for those taken for disease)
- Physical examination (can be source documented only)
- Height and weight
- Vital signs (including blood pressure, temperature, and heart rate)
- ECOG Performance status
- Single 12-lead ECG, assessed locally for immediate clinical decision (see Table 8)
- Hematology panel including complete blood count (CBC) with differential, including RBC count, hemoglobin, hematocrit, white blood cell (WBC) count (with differential), and platelet count
- Chemistry panel including sodium, potassium, calcium, chloride, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase (ALT/SGPT), lactate dehydrogenase (LDH)
- Thyroid function (thyroid-stimulating hormone [TSH], free triiodothyronine [T3], free thyroxine [T4])
- Coagulation tests including, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
- [redacted]
- SARS-CoV-2 serology as listed in Table 10
- Efficacy assessments/tumor evaluation (see Section 6.4)
- [redacted]
- Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed at screening. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of IP, if the initial serum pregnancy test did not already occur with 72 hours of dosing (negative results required for IP administration)
- Contraceptive counseling: Explain to females of childbearing potential and male subjects the need for contraception
- Fertility counseling for men: Subjects will be informed that the effects of CC-90011 on spermatogenesis are unknown and they will be encouraged to collect and bank sperm if appropriate, prior to taking IP
- Adverse event assessment begins when the subject signs the ICF

6.1.1 Retesting During Screening Period

Subjects who become screen failures can be rescreened, as necessary, if it is reasonable to believe they will meet eligibility criteria during rescreening. If screening assessments are not within the

allowed Screening Period, the rescreened subject must reconsent to participation in the study by signing a new and current informed consent form.

Testing for asymptomatic SARS-CoV-2 infection, for example by reverse transcription-polymerase chain reaction (RT-PCR) or viral antigen is not required. However, some subjects may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, subjects may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved and
- In the opinion of the Investigator, there are no COVID-19-related sequelae that may place the participant at a higher risk of receiving investigational treatment, and
- Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local or regional guidelines

6.2 Treatment Period

The subject may be enrolled once all inclusion/exclusion criteria are verified and the subject is deemed to be eligible. The subject must start treatment within 3 days of enrollment. If screening assessments are performed within 72 hours of Day 1, safety, laboratory and physical examinations need not be repeated at Cycle 1 Day 1.

For all subsequent visits until Cycle 3, an administrative window of ± 1 days is permitted. For all visits starting with Cycle 3, an administrative window of ± 7 days is permitted. Study visits to the clinic will occur on Cycle 1 Days 1, 8, 15, 22, Cycle 2 Day 1, Cycle 2 Day 15, and Day 1 of all subsequent cycles. At each study visit, IP is to be administered in the clinic.

If the Investigator suspects a drug-related toxicity, an unscheduled visit with additional laboratory tests may be performed. Any assessments can be performed as clinically indicated.

Treatment cycles are 28 days in duration and will occur as described in 7.2.

The following evaluations will be performed at the frequency specified in the Table of Events, Table 6. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- IRT registration for subject enrollment and IP assignment
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Physical examination (source documented only)

- Vital signs (blood pressure, temperature, and heart rate): on-treatment vital sign measurements will be source documented and collected in the electronic case report form (eCRF). If an abnormal (out of range) value is reported at any given visit and is considered clinically significant, that parameter should also be collected in the eCRF as an adverse event (AE) if appropriate
- Weight
- Hematology panel including CBC with differential, including RBC count, hemoglobin, hematocrit, WBC count (with differential), and platelet count
- Chemistry panel including sodium, potassium, calcium, chloride, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), AST/SGOT or ALT/SGPT, LDH
- Thyroid function (TSH, free T3, free T4)
- ECOG performance status
- Paired triplicate 12-lead ECGs and blood samples for plasma concentrations collected at selected timepoints on Cycle 1 Day 1 as listed in Table 7. Single 12-lead ECG on Cycle 1 Day 8, Cycle 2 Day 1, Cycle 3 Day 1, and as clinically indicated in Table 8. ECGs assessed locally for immediate clinical decision.
- Adverse event evaluation (continuously)
- Efficacy assessment (see Section 6.4)
- Blood PK and immunogenicity collection as listed in Table 7 and Section 6.5.1
- [redacted]
- SARS-CoV-2 serology as listed in Table 10
- [redacted]
- Contraceptive counseling on Cycle 1 Day 1: Explain to females of childbearing potential and male subjects the need for contraception and the potential risks of fetal exposure. Reinforce importance of adherence to contraception and reevaluate abstinence and contraception methods used.
- Urine β-hCG for FCBP. Reinforce urine (or serum) pregnancy test requirement.
- CC-90011 and nivolumab administration
- Provide, collect, and/or review medication diary collection and review
- CC-90011 and nivolumab accountability on Cycle 3 Day 1 and every cycle thereafter on Day 1

6.2.1 End of Treatment

An end of treatment (EOT) evaluation will be performed for subjects who are withdrawn from treatment for any reason as soon as possible (within 7 days if feasible) after the decision to permanently discontinue treatment has been made.

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

- IRT registration for subject treatment discontinuation
- Physical examination (source documented only)
- Vital signs (blood pressure, temperature, and heart rate)
- Weight
- Concomitant medications evaluation
- Concomitant procedures evaluation
- ECOG performance status
- Adverse event evaluation (monitored through 28 days after the last dose of IP)
- Hematology panel including CBC with differential, including RBC count, hemoglobin, hematocrit, WBC count (with differential), and platelet count
- Chemistry panel including sodium, potassium, calcium, chloride, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), AST/SGOT or ALT/SGPT, LDH
- Thyroid function (TSH, free T3, free T4)
- Urine β-hCG (for females of childbearing potential)
- Efficacy assessment will be continued according to the schedule defined in the Table of Events, and does not need to be performed specifically for the EOT visit except as specified in Section 6.4

[redacted]

[redacted]

- Contraceptive counseling: Explain to females of childbearing potential and male subjects the need for contraception and the potential risks of fetal exposure. Reinforce importance of adherence to contraception and reevaluate abstinence and contraception methods used.
- Collection and review medication diary
- CC-90011 and nivolumab accountability

6.3 Follow-up Period

6.3.1 Safety Follow-up

All subjects will be followed for 28 days after the last dose of CC-90011 for AE reporting, as well as serious adverse events (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.1. An additional safety follow-up is required after 100 days from the last dose of nivolumab.

The following evaluations will be performed at the 28-day follow-up as specified in the Table of Events:

- Adverse event evaluation (monitored through 28 days after the last dose of CC-90011)

- Concomitant medications evaluation
- Concomitant procedures evaluation
- Physical examination (source documented only)
- Vital signs (blood pressure, temperature, and heart rate)
- Weight
- ECOG performance status
- Urine β-hCG (for females of childbearing potential)
- Hematology panel including CBC with differential, including RBC count, haemoglobin, haematocrit, WBC count with differential, and platelet count
- Chemistry panel including but not limited to sodium, potassium, calcium, chloride, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), AST/SGOT or ALT/SGPT, LDH
- Thyroid function (TSH, free T3, free T4)
- [redacted]
- SARS-CoV-2 serology as listed in Table 10
- Contraceptive counseling: Explain to females of childbearing potential and male subjects the need for contraception and the potential risks of fetal exposure. Reinforce importance of adherence to contraception and re-evaluate abstinence and contraception methods used.
- Follow-up disease anticancer therapies

The following evaluations will be performed at the 100-day follow-up as specified in the Table of Events:

- Adverse event evaluation (monitored through 100 days after the last dose of nivolumab). Every adverse event must be assessed by the Investigator regarding whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the eCRF.
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Vital signs (blood pressure, temperature, and heart rate)
- Weight
- Urine β-hCG (for females of childbearing potential)
- Hematology panel including CBC with differential, including RBC count, haemoglobin, haematocrit, WBC count with differential, and platelet count
- Chemistry panel including but not limited to sodium, potassium, calcium, chloride, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), AST/SGOT or ALT/SGPT, LDH
- Thyroid function (TSH, free T3, free T4)

- Contraceptive counseling: Explain to females of childbearing potential and male subjects the need for contraception and the potential risks of fetal exposure. Reinforce importance of adherence to contraception and re-evaluate abstinence and contraception methods used.
- Follow-up disease anticancer therapies

6.3.2 Efficacy Follow-up

All subjects who discontinue treatment for reasons other than disease progression, start of a new disease therapy, or withdrawal of consent from the entire study, will be followed for efficacy response assessments and new disease therapies as specified in Section 6.4.

6.3.3 Survival Follow-up

After the end of treatment visit, all subjects will be followed every 2 months (± 14 days) for survival/long-term follow-up until death, lost to follow-up, withdrawal by subject from entire study, the 100-day safety follow-up visit of the last subject on study treatment, or the End of Trial, whichever occurs first. Subsequent anticancer therapies should be collected at the same time schedule. Subsequent new anticancer therapy includes, but is not limited to, any systemic or local medication, surgery, radiation, or any other therapy intended to treat the subject's disease.

Survival/long-term 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.

Sponsor may request that survival data be collected on all treated subjects outside of the protocol defined window (refer to Section 5 and Section 6). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

6.4 Efficacy Assessment

Tumor assessments by CT scan or MRI of the chest, abdomen, and pelvis (pelvis if per local practice) should be performed at screening within 28 days prior to enrollment, and at every 6 weeks (± 7 days) post Cycle 1 Day 1 for the first 24 weeks and every 8 weeks (± 7 days) thereafter, until disease progression, start of new anticancer therapy, or withdrawal of consent by the subject from the entire study.

Brain imaging by CT scan with contrast or MRI should be performed at screening and as clinically indicated. For subjects who received PCI, the brain imaging performed prior to initiation of PCI, must occur within 56 days prior to enrollment. For subjects who did not receive PCI, brain imaging must occur within 28 days prior to enrollment.

To ensure sufficient ability to assess tumor response, the same imaging procedure should be used throughout the study for each subject, and these imaging studies must include all lesions assessed at baseline. Tumor assessments by CT scan or MRI should also be performed at any time if clinically indicated. Subjects who did not receive PCI treatment and with historical tumor scans evaluable per RECIST v1.1 performed within 28 days before enrollment need not repeat scans for the purposes of screening. Evaluation of response for therapeutic decisions should be performed using RECIST v1.1 guidelines by Investigator assessment.

All subjects with evidence of tumor response (CR or PR) should have their response confirmed with repeat assessments at the next scheduled scan, but no less than 4 weeks after initial response.

At the sponsor's discretion, scans may be collected for review.

Additional details and definitions of response for RECIST v1.1 are found in APPENDIX E.

6.4.1 Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD (Spigel, 2017).

Subjects will be permitted to continue study treatment beyond initial RECIST v1.1 defined progressive disease, up to a maximum of 24 months, 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 of study treatment
- Other treatment options, including no treatment and supportive care, have been discussed and subject has consented on the optional ICF to continue study treatment

A follow-up scan should be performed within 6 to 8 weeks of the original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject may remain on study treatment and continue to receive monitoring according to Table 6. The decision to continue treatment should be discussed with the Celgene Medical Monitor and documented in the study source documents.

For the subjects who continue study treatment beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of the initial PD. Study treatment should be discontinued permanently upon documentation of further progression, unless the clinical judgement of the investigator is that continuing treatment is in the subject's best interest and the Medical Monitor is in agreement upon discussion.

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

new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

6.5 Pharmacokinetics

For evaluation of the PK of CC-90011 in plasma, blood samples will be collected from all subjects at the timepoints listed in Table 7. An exploratory analysis of CC-90011 metabolites in plasma may be performed utilizing the plasma samples collected for PK evaluation. Time-matched triplicate ECGs will also be collected on Cycle 1 Day 1 at time points listed in Table 7.

The blood PK samples collected after CC-90011 administration should be collected from the arm contralateral to the arm used for nivolumab administration. If a peripheral IV catheter is used for nivolumab IV administration, the PK samples should be obtained from the opposite arm. In general, blood for PK samples should not be drawn from a central line. If a peripheral line is not accessible, blood for PK samples drawn from a central line must be collected after the lumen is flushed with saline, and the non-dosing lumen of a dual/triple lumen catheter should be used.

All pre-dose samples should be collected before administration of CC-90011 (preferably within 30 minutes). If it is known that a CC-90011 dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed CC-90011 dose.

Detailed information regarding the collection, handling, and shipment of blood for the assessment of pharmacokinetics is provided in the study Laboratory Manual.

Table 7: Schedule of Pharmacokinetic Blood Sample and Triplicate Time-matched ECG Collection

Time in Hours Relative to CC-90011 Dose[a]	Collection Window	Cycle 1			Cycle 2 and Cycle 3
		Day 1		Day 8	Day 1
		PK	Triplicate ECGs[a]	PK	PK
0 (pre-dose)	Within 30 minutes prior to dosing	X	X	X	X
1	±10 minutes	X	-	-	-
2	±15 minutes	X	X	-	-
3	±20 minutes	X	X	-	-
4	±20 minutes	X	X	-	-

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetics.

[a] Triplicate ECGs to be collected on Cycle 1 Day 1 only.

6.5.1 Collection of Blood Samples for Nivolumab Pharmacokinetics and Immunogenicity

Subjects enrolled in all 3 cohorts will have blood samples collected to measure PK and anti-nivolumab antibodies (ADA). Blood samples for the analysis of ADA should be drawn from the arm not used for infusion of study drug. Detailed instructions for the collection, processing, handling, labeling, storage, and shipment of PK and ADA samples will be provided in the laboratory manual. All samples will be collected pre-dose (approximately within 30 minutes prior to infusion) on the following visits, for up to 2 years:

- Cycle 1 Day 1: pre-dose
- Cycle 2 Day 1: pre-dose
- Cycle 3 Day 1: pre-dose
- Every 4th cycle after Cycle 3 (i.e. Cycle 7, Cycle 11, Cycle 15 etc) Day 1: pre-dose

6.6 12-lead Electrocardiograms

12-lead ECGs will be recorded at the visits as outlined in Table 8. The 12-lead ECGs (12-lead at 25 mm/sec reporting rhythm, ventricular rate, PR interval, QRS complex, QT interval, and QT corrected based on Fridericia's equation [QTcF] interval) should be performed before any other blood is drawn and after the subject has been in the supine position for at least 5 minutes.

Investigators will make immediate clinical decisions based on their interpretation of the ECG results and provide their overall assessment of the ECG in the eCRF. Clinically significant changes from baseline will be recorded in the AE section of the eCRF.

The ECG outputs will also be uploaded to the central ECG laboratory for the Sponsor's definitive analysis and interpretation.

Table 8: Schedule of Electrocardiogram Collection

Time in Hours Relative to Study Dose	Screening	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 3 Day 1
	Single ECG	Triplicate ECG[a]	Single ECG	Single ECG	Single ECG
0 (pre-dose)	X	X	X	X	X
2	-	X	-	-	-
3	-	X	-	-	-
4	-	X	-	-	-

Abbreviation: ECG = electrocardiogram.

[a] Timepoints matched with blood PK collection. Three ECGs within 2 minutes at each nominal time point should be collected.

6.7 Biomarkers, Pharmacodynamics, Pharmacogenomics

[redacted]

6.7.1 Other Assessment

Serum will be collected for potential future measurements of anti-SARS-CoV-2 antibodies by serology (anti-SARS-CoV-2 total or immunoglobulin G [IgG]) to explore potential association with safety, efficacy, and/or immune biomarkers (Table 10).

[redacted]

[redacted]

Table 10: SARS-CoV-2 Samples Schedule

Visits	SARS-CoV-2 serology
Screening	X
Every 6 months during study treatment	X
Approximately 4 weeks after a documented or suspected SARS-CoV-2 infection[a]	X[a]
28-day Safety Follow-up	X

[a] If a documented or suspected SARS-CoV-2 infection occurs within 4 weeks of the 6 month sampling time point, a single serum sample will be collected to satisfy the requirements for both every 6 month and approximately 4 week after infection time points.

6.8 Additional and Optional Research

Additional and optional research as described below may be performed using left-over samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using deoxyribonucleic acid (DNA) or RNA and may lead to the development of new diagnostic tests.

6.8.1 Additional Research

Additional research related to the study drug and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.

6.8.2 Optional Research

Optional research not related to the study drug or the subject's disease may be performed. The subject's decision to participate in this optional research will not impact their ability to participate in the main study.

6.9 Subject Reported Outcomes

Not Applicable.

7 DESCRIPTION OF STUDY TREATMENTS

Study treatment is CC-90011 in combination with nivolumab and is referred as the investigational product (IP) or as investigational medicinal product (IMP).

Celgene Corporation (Celgene) will supply CC-90011 and nivolumab for administration and labeled appropriately as investigational product for this study.

Additional information may be included on the label as needed or applicable. Label(s) for IP will contain information as required per local health authority.

7.1 Description of Investigational Product(s)

7.1.1 CC-90011

The study Sponsor will supply the CC-90011 capsules for oral administration. The capsules will be supplied in high-density polyethylene bottles with child-resistant caps, labeled appropriately for investigational use as per the regulations of the relevant country health authority.

CC-90011 is stored in room temperature (below 25°C [77°F]) and must be used within the individually assigned expiry date on the label. Subjects should not extensively handle CC-90011 capsules and should maintain storage in the packaging until ingestion.

Refer to the Pharmacy Manual for details regarding oral administration, accountability, storage and disposal. Please also refer to the IB for other details regarding CC-90011.

7.1.2 Nivolumab

The study sponsor will provide nivolumab 100 mg vials in cartons, labeled appropriately for investigational use as per the regulations of the relevant country health authority.

Refer to the Pharmacy Manual for details regarding administration, accountability, storage and disposal. Please also refer to the IB for other details regarding nivolumab.

For details regarding product storage, preparation, and administration, please refer to supply labels, current Investigator Brochure, Pharmacy Manual or Summary of Product Characteristics (SmPC)/United States Package Insert.

7.2 Treatment Administration and Schedule

CC-90011 should be administered first, before nivolumab administration, if possible.

No pre-medication is required. Supportive care per the institution's normal standard of care including concomitant medications can be provided at the investigator's discretion.

7.2.1 CC-90011

CC-90011 will be given orally (PO) at a dose of 40 mg, unless otherwise determined during the ongoing safety evaluation (Section 7.3.1.1), on a once weekly basis in a continuous 28-day cycle.

CC-90011 will be administered with at least 240 mL of water. Subjects should fast for a minimum of 4 hours prior CC-90011 administration and refrain from any food intake for up to 1 hour after dosing. Subjects should abstain from food or other medication intake for at least 1 hour after each dose. Grapefruit juice should be avoided during study treatment.

CC-90011 will be administered at home except on the following study visits: Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2 Day 1, Cycle 2 Day 15, and Day 1 of all subsequent cycles.

7.2.2 Nivolumab

Nivolumab will be administered intravenously at a dose of 480 mg every 4 weeks per local practice as a 30 minute or a 60-minute infusion as per local practice.

There will be no dose escalations or reductions of nivolumab allowed. For Q4W dosing cycles, subjects may be dosed within a ± 3-day window, but no less than 25 days from the previous dose. Premedications are not recommended for the first dose of nivolumab.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 7.

Doses of study drug(s) may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed.

Please refer to the current Investigator Brochure and/or Pharmacy Manual for further details regarding storage, preparation, and administration of nivolumab.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

No premedication is required. Supportive care per the institution's normal standard of care including concomitant medications can be provided at the Investigator's discretion.

7.2.3 Missed Doses

All efforts should be made to administer study treatment on all the scheduled days of each treatment cycle. Any missed doses during that period should not be taken after the last scheduled day of administration but should be returned by the subject for IP accountability.

If a subject vomits within 1 hour of taking a dose of CC-90011 and the whole unbroken capsule is visible in the vomit, the subject can take a replacement dose within 1 hour of vomiting. However, if the subject vomits more than 1 hour after taking a dose of CC-90011, or the whole unbroken capsule is not visible in the vomit, the subject should not take a replacement dose.

If a subject miss or forgets to take the scheduled dose of CC-90011, the subject can take the dose should it be less than 24 hours than the scheduled dose. If more than 24 hours since the scheduled dose, the dose should be skipped, and administration resumed at the next planned date.

7.2.4 Definition of an Overdose

Overdose, as defined for this protocol, refers to CC-90011 and nivolumab dosing. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CC-90011 and/or nivolumab assigned to a given subject, regardless of any associated adverse events or sequelae:

- PO any amount over the protocol-specified dose

- 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 eCRF. Refer to Section 10.1 for the reporting of adverse events associated with overdose.

7.3 Safety Evaluation

7.3.1 Initial Safety Evaluation

A safety evaluation will be conducted to assess the safety of CC-90011 with nivolumab after 6 subjects (without distinction of cohorts) have completed at least 2 Cycles. A Bayesian method will be used to monitor for the rate of thrombocytopenia Grade 4 and neutropenia Grade 3 to 4 events. The expected rate of thrombocytopenia Grade 4 is 20% and the expected rate of neutropenia Grade 3 to 4 is 12% from CC-90011 alone. No serious overlapping toxicities are expected for the combination of CC-90011 with nivolumab. No immune-related adverse events (irAEs) have been observed in the first-in-human study with CC-90011.

After the enrollment of 6 successive subjects completing 2 cycles, or sooner per Section 7.3.2, the following stopping criteria based on the posterior distributions of the rate of thrombocytopenia Grade 4 and neutropenia Grade 3 to 4 events with a noninformative Jeffreys prior distribution of Beta (1/2, 1/2) will be evaluated:

1) Probability (rate of thrombocytopenia Grade 4 > 0.2|data from 6 subjects) > 0.95 or
2) Probability (rate of neutropenia Grade 3 to 4 > 0.12|data from 6 subjects) > 0.95

If any of these stopping criteria are met, the starting dose of CC-90011 will be reduced to the next lower dose level 40 mg. The first criterion is equivalent to observing 3 or more thrombocytopenia events Grade 4 out of 6 and the second criterion is equivalent to observing 3 or more neutropenia events Grade 3 to 4. Enrollment will not be paused during this evaluation.

Once the starting dose is reduced to 40 mg, the same rule will be applied. If any of these stopping criteria are met for the 6 subjects treated at 40 mg, the starting dose of CC-90011 will be reduced to the next lower dose level 20 mg.

Once the initial 6 subjects at a given dose level do not trigger the dose reduction rule, subjects' safety data will be closely monitored on an ongoing basis and individual dose delays and/or reduction recommendations will be followed. In case the starting dose is reduced to a lower dose level, it will be ensured that the sample size at the selected dose meets the planned number of subjects.

7.3.1.1 Safety Evaluation for CC-90011 Starting Dose of 40 mg

As of 14 Aug 2020, the Sponsor, in agreement with the Steering Committee made the decision to reduce the starting dose of CC-90011 to 40 mg, as per Section 7.3.2. Implementation of this dose reduction was not considered an urgent safety measure. The same stopping criteria as specified in Sections 7.3.1 and 7.3.2 will be applied to the reduced starting dose of 40 mg.

To further evaluate if the RP2D of 60 mg that was established in the first-in-human study can be safely administered in this study and in order to maximize the potential efficacy of CC-90011 and level of target engagement (see FIH data, Figure 2), re-escalation to 60 mg may be considered after review of the overall data and AEs/SAEs by the Sponsor in agreement with the Steering Committee. Specifically, if in the first 2 cycles, there are no reports of Grade 4 thrombocytopenia or Grade 3 or 4 neutropenia, in any of the 6 subsequent subjects (without distinction of cohorts) who received 40 mg, then re-escalation of the starting dose to 60 mg for subsequent subjects may be considered.

If the starting dose is re-escalated to 60 mg, an additional 4 subjects (without distinction of cohorts) will be treated so that 6 subjects in total (including the 2 subjects in which Grade 4 thrombocytopenia [n=2] and Grade 3 neutropenia [n=1] was reported) will have received 60 mg. There will be staggered dosing, where the second subject to receive 60 mg will not be dosed until at least 15 days after the first subject has been treated and safety has been reviewed. This sentinel dosing scheme may or may not be continued for the rest of the 60 mg subjects, depending on the findings in the first subject and the overall safety profile to date.

The stopping criteria in Sections 7.3.1 and 7.3.2 will be applied to these 6 subjects. Therefore, if in the first 2 cycles, there are no reports of Grade 4 thrombocytopenia and 1 or less reports of Grade 3 or 4 neutropenia, in any of the 4 subsequent subjects who received 60 mg, then 60 mg will be declared as the starting dose of CC-90011 and the dose to continue with in this study. If in the first 2 cycles, there is at least 1 report of Grade 4 thrombocytopenia or at least 2 reports of Grade 3 or 4 neutropenia, in any of the 4 subsequent subjects who received 60 mg, then 40 mg will be declared as the starting dose of CC-90011 and the dose to continue with in the study.

7.3.2 Definition of Stopping Criteria

If any of these stopping criteria described in Section 7.3.1 are met for the 6 subjects treated at 20 mg, the trial will be stopped.

Events to be monitored with special interest and which may trigger the above stopping criteria include but are not limited to:

- Serious adverse events (SAEs) related to IPs of the same nature or organ system
- Clinically significant SAEs related to IPs of the same nature or organ system which would prevent further dosing of an individual subject

Review of the AEs and SAEs, and any decision to pause enrollment, or modify the dose and/or schedule of the cohorts, will be determined by the Sponsor in agreement with Steering Committee. Decisions to pause enrollment or stop cohorts or modify the dose and/or schedule of the cohorts of the study will be communicated promptly to Investigators, to the Institutional Review Boards

(IRBs)/Ethics Committees (ECs) (as applicable), and will be implemented in a protocol amendment which will be submitted to the appropriate regulatory authorities.

7.4 Dose Adjustment of Study Treatments

Any toxicity, unless the event can clearly be determined to be unrelated to the study treatments, could be managed according to the recommended guidance listed in Table 12, Table 13, and Table 14.

If the Investigator suspects a drug related toxicity, an unscheduled visit with additional laboratory assessments may be performed.

If any subject continues to experience unacceptable toxicity after permitted IP adjustments, 1 or both IPs will be discontinued permanently.

7.4.1 Permitted Dose Reduction for CC-90011

Permitted dose reductions for CC-90011 are described in Table 11.

Table 11: Permitted Dose Reduction for CC-90011

Starting Dose	First Reduction	Second Reduction
60 mg	40 mg	20 mg
40 mg	20 mg	None
20 mg	None	None

7.4.2 Criteria for CC-90011 Dose Adjustment

Recommendations on the dose adjustments for hematologic and nonhematologic toxicities are listed in Table 12 and Table 13. Permitted dose reductions are listed in Table 11. CC-90011 may be interrupted up to 4 weeks.

7.4.2.1 Recommended Dose Adjustment Guidelines for CC-90011

Table 12 and Table 13 list the recommended dose adjustment guidelines for study treatments related to hematologic toxicities and non-hematologic toxicities respectively.

Table 12: Recommended Dose Adjustment Guidelines for CC-90011 Related Hematologic Toxicities

Toxicity	Action
Grade 2 thrombocytopenia	Hold until resolution to Grade ≤ 1 or baseline Follow complete blood count (CBC) at least every 7 days When resolution to Grade ≤ 1 or baseline, study treatment can be reintroduced at the same dose level In case of repeat occurrence of Grade 2 or worse, hold until recovery to ≤ Grade 1 and study treatment can be reintroduced at the lower dose level (if available).

Table 12: Recommended Dose Adjustment Guidelines for CC-90011 Related Hematologic Toxicities

Toxicity	Action
Grade 3 thrombocytopenia	Hold until resolution to Grade ≤ 1 or baseline Follow complete blood count (CBC) at least every 3 to 4 days If resolution to Grade ≤ 1 or baseline occurs ≤ 8 days, study treatment can be reintroduced at the same dose level. If AE resolution occurs > 8 days, study treatment can be reintroduced at the lower dose level. In case of repeat occurrence of Grade 3 or worse, hold until recovery to ≤ Grade 1; study treatment can be reintroduced at the next lower dose level (if available).
Grade 4 thrombocytopenia	Hold study treatment until recovery to Grade ≤ 1 or baseline Repeat CBC within 24 to 48 hours Follow CBC at least every 3 to 4 days Study treatment can be reintroduced at the lower dose level, if available In case of repeat occurrence of Grade 4, hold until recovery to ≤ Grade 1; study treatment can be reintroduced at the next lower dose level (if available).
Grade 3 neutropenia	Hold until resolution to Grade ≤ 1 Follow CBC at least every 3 to 4 days If AE resolution to Grade ≤ 1 occurs ≤ 8 days, study treatment can be reintroduced at the same dose level. If AE resolution occurs > 8 days, study treatment can be reintroduced at next lower dose level lower, if available. Use of growth factors (GCSF, GMCSF) is permitted at the discretion of the Investigator. In case of repeat occurrence of Grade 3 or worse, hold until recovery to ≤ Grade 1; study treatment can be reintroduced at the next lower dose level (if available).
Grade 4 neutropenia	Hold until resolution to Grade ≤ 1 Follow CBC at least every 3 to 4 days Study treatment can be reintroduced at the lower dose level, if available Use of growth factors (GCSF, GMCSF) is permitted at the discretion of the Investigator In case of repeat occurrence of Grade 4, hold until recovery to ≤ Grade 1; study treatment can be reintroduced at the next lower dose level (if available).
Febrile neutropenia	Hold further dosing until recovery to Grade ≤ 1 and when febrile neutropenia resolves, then resume dosing study treatment at 1 dose level lower, if available. Follow CBC at least every 3 to 4 days. Use of growth factors (GCSF, GMCSF) is permitted at the discretion of the Investigator If recurrence of febrile neutropenia, discontinue treatment.
Any hematological toxicity requiring interruption for > 4 weeks	Discontinue study treatments.

AE = adverse event; GCSF = granulocyte-colony stimulating factor; GMCSF = granulocyte-macrophage colony stimulating factor.

Table 13: Recommended Dose Adjustment Guidelines for CC-90011 Related to Non-hematologic Toxicities

Toxicity	Grade	Action
Gastrointestinal		
Diarrhea, nausea, vomiting	Grade 1 or 2	Implement prophylactic antiemetic regimen according to local guidelines. Maintain current CC-90011 dose schedule without dose modification. If persistence or (re)occurrence despite appropriate prophylaxis, dose-reduce 1 dose level (see dose reduction table) at the next scheduled dose administration.
	Grade 3 or 4	Implement prophylactic antiemetic regimen according to local guidelines. Hold dose until event improves to ≤ Grade 2. Reintroduce at a lower dose. If (re)occurrence to Grade 3 or 4 despite appropriate prophylaxis, hold dosing until event improves to Grade ≤ 2. Reintroduce at a lower dose. In addition, consider other supportive treatment per local guidelines.
Other adverse events		
	Grade 3	Hold dose until event improves to Grade ≤ 2. At the next scheduled CC-90011 dose administration, dose-reduce 1 dose level (see dose reduction table). If recurrence to Grade 3, reduce the dose. If a second recurrence of Grade 3 occurs, permanently discontinue. During continued treatment, if adverse event (AE) has not resolved to ≤ Grade 2 (or baseline) by the next scheduled dose, skip dose; consider dose reduction with the next scheduled dose.
	Grade 4	Stop CC-90011 until resolution to < Grade 2 (or baseline). Discuss with Medical Monitor. Reintroduce at a reduced dose. If recurrence to Grade 4, permanently discontinue in agreement with Medical Monitor.

7.4.3 Criteria for Nivolumab Dose Management

For nivolumab dose adjustment, follow local practice, package labels or SmPC, and management algorithms (see APPENDIX F). Adverse event management of nivolumab should follow CTCAE v5.0.

Guidelines for permanent discontinuation or withholding of nivolumab doses are described in Table 14. Interrupt or slow the rate of infusion in subjects with mild or moderate infusion reactions. Discontinue nivolumab in subjects with severe or life-threating infusion reactions.

Table 14: Recommended Treatment Modifications for Nivolumab

Adverse Reaction	Severity*	Dose Modification
Gastrointestinal		
Colitis or Diarrhea	Grade 2	Delay dose
	Grade 3	Delay dose[a]
	Grade 4	Permanently discontinue
Renal		
Serum Creatinine Increased	Grade 2 or 3	Delay dose[b]
	Grade 4	Permanently discontinue
Pulmonary		
Pneumonitis	Grade 2	Delay dose[b]
	Grade 3 or 4	Permanently discontinue
Hepatic		
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased	AST or ALT m> 3 x and ≤ 5 x upper limit of normal (ULN) or T. Bili > 1.5 x and ≤ 3 x ULN, regardless of baseline value	Delay dose[a]
	AST or ALT > 5 x ULN or T.bili > 3 x ULN, regardless of baseline value	Permanently discontinue
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue
Endocrinopathy		
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose[c]
	Grade 4	Delay dose or permanently discontinue[d]
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose[e]
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue[f]

Table 14: Recommended Treatment Modifications for Nivolumab		
Adverse Reaction	**Severity***	**Dose Modification**
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose[g]
	Grade 4	Delay dose or permanently discontinue[h]
Hyperthyroidism or hypothyroidism	Grade 2 or 3	Delay dose[i]
	Grade 4	Delay dose or permanently discontinue[j]
Skin		
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose[k]
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose[l]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Neurological		
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue
Encephalitis	Any Grade encephalitis	Delay dose[m]
	Any Grade drug-related encephalitis	Permanently discontinue
Myelitis	Any Grade myelitis	Delay dose[m]
	Any Grade drug-related myelitis	Permanently discontinue
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose[a]
	Grade 3 or 4	Permanently discontinue
Cardiac		
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose[a]
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated	Permanently discontinue
Other Clinical AE		
Pancreatitis: Amylase or Lipase Increased	Grade 3 with symptoms	Delay dose[n]
	Grade 4	Permanently discontinue

Table 14: Recommended Treatment Modifications for Nivolumab		
Adverse Reaction	**Severity***	**Dose Modification**
Uveitis	Grade 2 uveitis	Delay dose[o]
	Grade 3 or 4 uveitis	Permanently discontinue
Other Drug-Related AE (not listed above)	Grade 2 non-skin AE, except fatigue	Delay dose[b]
	Grade 3 AE First occurrence lasting ≤ 7 days	Delay dose[b]
	Grade 3 AE First occurrence lasting > 7 days	Permanently discontinue
	Recurrence of Grade 3 AEs of any duration	Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
Other Lab Abnormalities		
Other Drug-Related Lab Abnormality (not listed above)	Grade 3	Delay dose Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding
	Grade 4	Permanently discontinue Exceptions: The following events do not require discontinuation of study drug: Grade 4 neutropenia ≤ 7 days Grade 4 lymphopenia or leukopenia Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)		

Table 14: Recommended Treatment Modifications for Nivolumab		
Adverse Reaction	**Severity***	**Dose Modification**
Hypersensitivity	Grade 3 or 4	Permanently discontinue (Refer to Section 7.4.4 on Treatment of Related Infusion Reactions)

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0).

[a] Dosing may resume when AE resolves to baseline.

[b] Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.

[c] Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement.

[d] Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, subject may not require discontinuation of study drug.

[e] Dosing may resume after adequately controlled with hormone replacement.

[f] Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, subject may not require discontinuation of study drug.

[g] Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value or is adequately controlled with glucose-controlling agents.

[h] Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, subject may not require discontinuation of study drug.

[i] Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement or other medical management.

[j] Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controls with physiologic hormone replacement or other medical management, subject may not require discontinuation of study drug.

[k] Dosing may resume when rash reduces to ≤ 10% body surface area.

[l] Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤ 10% body surface area.

[m] After workup for differential diagnosis (ie, infection, tumor-related), if AE is not drug related, then dosing may resume when AE resolves.

[n] Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when subject becomes asymptomatic.

[o] Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If subject requires oral steroids for uveitis, then permanently discontinue study drug.

Subjects who require a delay of nivolumab should be reevaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when retreatment criteria are met.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the Celgene Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.

7.4.4 Treatment of Related Infusion Reactions due to Nivolumab

Infusion reactions related to nivolumab treatment may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported as per Section 10 and reported as an SAE if it meets the criteria for an SAE. Infusion reactions should be graded according to NCI CTCAE v5.0 guidelines.

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

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

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

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDS), narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours):

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

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

7.4.5 Dose Delay and Criteria to Resume in Case of SARS-CoV-2 Infection

Study treatment with CC-90011 and nivolumab should be delayed for a SARS-CoV-2 infection that is either confirmed or suspected. Subjects with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after all of the following:

- at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen), and
- resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), and
- evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and
- consultation by the Medical Monitor

For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

7.5 Method of Treatment Assignment

An interactive response technology will be used to track subject assignments. Subjects who enter screening will be assigned a 7-digit number consisting of the 3-digit site number plus an incrementing number at a site.

7.6 Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP 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.

7.7 Investigational Product Accountability and Disposal

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

Accountability for IP that is administered during the course of the study is the responsibility of the Investigator or designee. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secure and temperature-controlled location. The investigational site must maintain accurate records demonstrating dates and amounts of IP received, to whom it was administered (subject-by-subject accounting), and accounts of any CC-90011 or nivolumab accidentally or deliberately destroyed or returned. Unless otherwise notified, all bottles and vials, both used and unused, must be saved for drug accountability. The investigational product should be disposed of in accordance with the institutional/regional requirements after drug accountability

has been completed by the monitor. The Investigator must return all unused bottles and vials of IP to the Sponsor at the end of the study, or the IP may be destroyed at the clinical site with the permission of the Sponsor. For either scenario, the outcome must be documented on the drug accountability log. The Sponsor will provide direction for the outcome of all unused bottles and vials.

7.8 Investigational Product Compliance

Only the pharmacist, Investigator, or the Investigator's designee will dispense CC-90011. 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 doses dispensed/administered in the appropriate study records.

Subjects will use diary cards to record their weekly self-administration of CC-90011 at home. The person completing the diary card will sign/initial and date the cards in accordance with good documentation practice. These will be reviewed by study staff each time the subject visits the clinic (please refer to Table 6). Entries will be clarified, as necessary, so that appropriate information can be captured on the eCRFs. Study site personnel will perform a CC-90011 administration compliance check and record this information on the subject's source documentation and on the appropriate eCRF (please refer to Table 6).

Accurate recording of nivolumab IV administration will be made in the appropriate section of the subject's eCRFs 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.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator.

All concomitant treatments, including blood and blood products, used from 28 days prior to enrollment until 28 days after the last dose of CC-90011 and 100 days after the last dose of nivolumab, must be reported on the eCRF.

For information regarding other drugs that may interact with IP and affect its metabolism, pharmacokinetics, or excretion, please see the Investigators Brochure, local package insert, and/or SmPC.

The Investigator will instruct subjects to notify the study staff about any new medications taken after signing the ICF. All medications and significant non-drug therapies (herbal medicines, physical therapy, etc) and any changes in dosing with existing medications will be documented on the eCRFs.

8.1 Permitted Concomitant Medications and Procedures

Most concomitant medications and therapies deemed necessary for the care of the subject is allowed. All concomitant medications, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids will be recorded on the eCRF.

The following are permitted concomitant medications and procedures:

- Subjects with ≥ Grade 1 diarrhea should promptly initiate treatment, as per recommendation of their treating physician and local guidelines, with diphenoxylate/atropine (Lomotil), or loperamide (Imodium) or an alternative over-the-counter remedy for diarrhea. Premedication with antidiarrheal medication for subsequent doses of study treatment may be appropriate and should be discussed with Sponsor's study physician.
- Antiemetics will be withheld until subjects have experienced NCI CTCAE ≥ Grade 1 nausea or vomiting. Subjects may then receive prophylactic antiemetics at the discretion of the Investigator and per local guidelines, including dexamethasone.
- Therapeutic use of granulocyte growth factors is allowed at any time for subjects experiencing febrile neutropenia or Grade 3/4 neutropenia. Routine prophylaxis with granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor is allowed at the Investigator's discretion after one or more occurrences of neutropenia and/or febrile neutropenia.
- Routine infectious disease prophylaxis is not required. However, antibiotic, antiviral, anti-pneumocystis, antifungal, or other prophylaxis may be implemented during the study at the discretion of the Investigator.
- Brain irradiation or other localized treatment for brain metastasis for subjects who progress with only brain metastasis, in the absence of other sites of progression, is allowed. During the brain irradiation CC-90011 and nivolumab will be held during the treatment and may be resumed at the Investigator's discretion.

- Focal palliative radiotherapy for treatment of cancer-related symptoms (eg, localized bone pain) is allowed during study treatment at the discretion of the Investigator, provided this is not indicative of disease progression, in which case the subject should be discontinued from study treatment.
- Subjects may receive physiologic replacement doses of glucocorticoids (up to the equivalent of 10 mg daily prednisone) as maintenance therapy. They may also receive glucocorticoids as treatment for immune-related adverse events.
  - Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted in the absence of active autoimmune disease. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- As a precautionary measure, it is recommended that subjects avoid prolonged exposure to ultraviolet light, wear protective clothing and sunglasses, and use ultraviolet-blocking topical preparations while taking study treatment.
- COVID-19 vaccines that are not live are permitted during the study and after the last dose of study treatment. Overlap of study treatment and vaccine administration, should be avoided, if possible (for example, at least 2 days, preferably 7 days apart), given that adverse events related to vaccine administration may confound potential study treatment infusion reactions.

8.2 Prohibited Concomitant Medications and Procedures

The following medications are prohibited or restricted at Screening and during the study:

- Other investigational therapies must not be used while the subject is on the study.
- Treatment with bisphosphonates (eg, pamidronate, zoledronate) or other agents (eg, denosumab) used to prevent progression of bone metastases.
- Anticancer therapy (chemotherapy, biologic or investigational therapy, and surgery) other than the study treatments must not be given to subjects while the subject is on the study. If such treatment is required, the subject must be discontinued from the study.
- Drug-drug interactions have not been investigated in clinical studies. In vitro studies have shown that CC-90011 is primarily metabolized by CYP3A4/5. Hence, drugs that are known strong inducers or inhibitors of this enzyme should not be co-administered with CC-90011. Should use of these drugs become necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-90011. Grapefruit juice should also be avoided during study treatment.
  - Examples of these drugs are (not inclusive):
  - CYP3A4/5 inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin
  - CYP3A4/5 inducers: rifampin and carbamazepine
  - A more exhaustive list of CYP inhibitors and inducers of potential clinical relevance is provided at the following link: https://drug-interactions.medicine.iu.edu/Clinical-Table.aspx

- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are allowed if they are used as supportive care.
- Any live / attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose.
- Refer to the approved product labeling for nivolumab for complete information regarding drug-drug interactions.

8.2.1 Medications to be used with Caution

In view of the potential for thrombocytopenia, nonsteroidal anti-inflammatory drugs and aspirins (aspirin dose ≤ 150 mg is allowed) should be avoided if possible and paracetamol or acetaminophen, should be administered instead.

Treatment with chronic, therapeutic dosing of anticoagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors, thrombin antagonists) and short-term, prophylactic dosing of anticoagulants may be considered in subjects if medically indicated (eg, hospitalized subjects, post-operatively) under careful consideration by the Investigator.

8.3 Required Concomitant Medications and Procedures

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Overview

This is a Phase 2, multicenter, open-label, multi-cohort study to assess safety and efficacy of CC-90011 in combination with nivolumab in subjects with SCLC who progressed after one or two lines of therapy, with or without an ICI. The primary objective of the statistical analysis is to evaluate the overall response rate (ORR) of subjects treated with CC-90011 in combination with nivolumab in 3 cohorts:

- Cohort A: SCLC in ICI naïve subjects
- Cohort B: SCLC in ICI progressor subjects
- Cohort C: sqNSCLC in ICI progressor subjects

The sections below provide an overview of the proposed statistical considerations and analyses. The final statistical analysis methods will be documented in detail in the statistical analysis plan (SAP).

9.2 Study Population Definitions

9.2.1 Enrolled Population

The enrolled population will consist of all subjects who signed the informed consent form and obtained a subject number.

9.2.2 Treated Population

The treated population will consist of all subjects who enroll and take at least 1 dose of either CC-90011 or nivolumab.

9.2.3 Per Protocol Population

The per protocol population will include all subjects who have met all the eligibility criteria with no important protocol deviations, received at least 1 dose of either CC-90011 or nivolumab, and have at least 1 baseline and post baseline efficacy assessment. This definition will be further clarified and detailed in the final SAP prior to database lock.

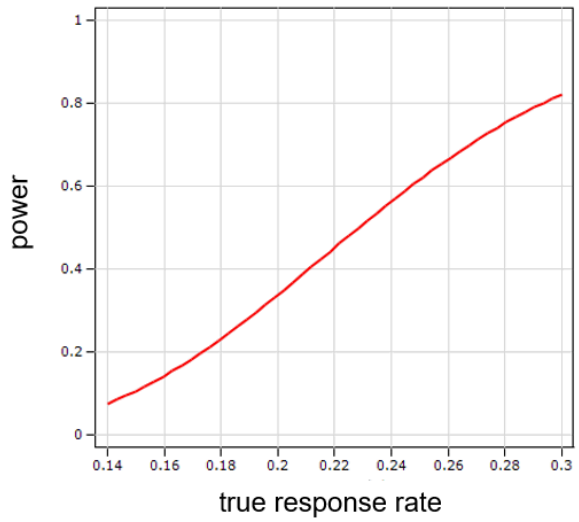
9.3 Sample Size and Power Considerations

In Cohort A, the sample size for the combination is based on an expected ORR for nivolumab monotherapy of 14% while target ORR for the combination is 30%. To achieve at least 80% power with one-sided type 1 error 0.1, 39 subjects will be enrolled according to a 2-stage group sequential design based on a binomial test. In Stage 1, 12 subjects will be enrolled and treated with CC-90011 in combination with nivolumab. If there are 2 or more subjects responding, Cohort A will continue to enroll an additional 27 subjects. If 1 or less subjects respond in Stage 1, Cohort A will stop for futility. This futility boundary was determined by rho spending function with $\rho = 0.1$. Enrolment will be held between Stage 1 and 2, unless response is documented prior to enrolment of all 12 subjects.

After 39 subjects are treated, if 9 or more subjects respond to the treatment, the null hypothesis would be rejected in favor of CC-90011 in combination with nivolumab treatment. Figure 4 below depicts the study power under various true response rates and sample sizes.

Figure 4: Cohort A - Study Power Under Various True Response Rates and Sample Sizes

(A) Power vs. ORR



(B) Power vs. Sample size

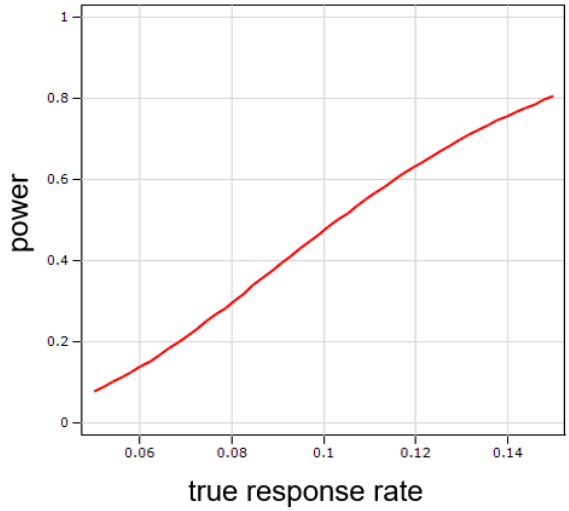
sample size	power
16	0.51
20	0.56
24	0.59
28	0.77
32	0.72
36	0.74
39	0.82

In Cohort B and C, the sample size for the combination are based on an expected ORR for nivolumab monotherapy of 5% while the target ORR for the combination is 15%. To achieve at least 80% power with one-sided type 1 error 0.1, 48 subjects will be enrolled according to a 2-stage group sequential design based on a binomial test. In Stage 1, 14 subjects will be enrolled and treated with CC-90011 in combination with nivolumab. If there are 1 or more subjects responding, Cohort B and C will continue to enroll an additional 34 subjects each. If 0 subjects respond in Stage 1, Cohort B and C will stop for futility. This futility boundary was determined by rho spending function with $\rho = 0.1$. Enrolment will be held in each cohort between Stage 1 and 2, unless response is documented prior to enrolment of all 14 subjects.

After 48 subjects are treated, if 5 or more subjects respond to the treatment, the null hypothesis would be rejected in favor of CC-90011 in combination with nivolumab treatment. Figure 5 below depicts the study power under various true response rates and sample sizes.

Figure 5: Cohorts B and C – Study Power Under Various True Response Rates and Sample Sizes

(A) Power vs. ORR



(B) Power vs. Sample size

sample size	power
24	0.5
28	0.62
32	0.73
36	0.72
40	0.68
44	0.75
48	0.8

In case of any deviation from the planned sample size, the futility boundary will be adjusted based on the rho spending function with $\rho = 0.1$.

9.4 Background and Demographic Characteristics

Demographic and baseline disease characteristics will be summarized by cohort for the enrolled population, treated population and per protocol population. Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, maximum), while age group, gender, race and other categorical variables will be provided using frequency tabulations (count, percent). Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).

9.5 Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site and by country will be provided. Important protocol deviations and protocol deviations will be summarized using frequency tabulations. Supportive corresponding subject listings will also be provided.

9.6 Efficacy Analysis

All efficacy analyses will be primarily performed in the treated population by cohort. Key efficacy analyses will be performed in the per protocol population as supportive evidence to assess the robustness of the efficacy findings.

9.6.1 Primary Endpoint

Overall Response Rate

The Overall Response Rate is defined as the proportion of subjects in the treated population who had confirmed complete response or confirmed partial response as assessed by Investigator review per RECIST v1.1. The point estimate of ORR will be summarized along with a 95% CI using exact binomial method proposed by Clopper and Pearson (Clopper, 1934) in the treated population. Similar analyses will be performed for the per protocol population.

9.6.2 Secondary Endpoint

Safety and tolerability

Safety and tolerability will be assessed from adverse events (using NCI CTCAE v5.0), laboratory tests, vital signs, ECOG performance status, concomitant medications, and dose modifications.

Duration of response

The duration of response is defined as the time from the first occurrence of a confirmed documented response (CR or PR) to the time of progression, as determined by Investigator review per RECIST v1.1, or death from any cause, whichever comes first. If progression is not documented, duration of response will be censored at the date of the last tumor assessment. Duration of response will be summarized based on Kaplan-Meier method.

Time to response

The time to response is defined as the time from the first dose of study drug to the date of the first confirmed documented response (CR or PR), as assessed by Investigator per RECIST v1.1. The time to response will be summarized for responders (confirmed CR or PR) using descriptive statistics.

Progression-free survival

Progression-free survival is defined as the time from the first dose of the study drug to the date of the first objectively documented tumor progression as assessed by Investigator review per RECIST v1.1 or death from any cause, whichever occurs first. Subjects who are alive without documented progression will be censored at the date of their last response assessment. The PFS will be summarized based on Kaplan-Meier method.

Time to first subsequent therapy

The time to first subsequent therapy is defined as the time in days from the date of first dose of study drug to the date of the next cancer therapy or death. Subjects who neither receive the next therapy nor die at a data cut-off date will be censored at the last known time that the subject was alive or the clinical cut-off date whichever is earlier. The time to first subsequent therapy will be summarized based on Kaplan-Meier (KM) method.

9.7 Safety Analysis

Adverse events, including treatment-emergent adverse events (TEAEs), laboratory assessments, ECG results, ECOG performance status, vital signs, exposure to study treatment, assessment of concomitant medications, and pregnancy testing for females of childbearing potential will be summarized for the treated population by cohort.

Adverse events observed will be classified using the Medical Dictionary for Regulatory Activities (MedDRA), system organ class (SOC) and preferred term (PT). In the by-subject analysis, a subject having the same AE more than once will be counted only once. All adverse events will also be summarized by SOC, PT, and NCI CTCAE grade (Version 5.0). Adverse events leading to discontinuation of study treatment, those classified as Grade 3 or 4, IP-related AEs, and SAEs (including deaths) will be tabulated separately. By-subject listings of all AEs, TEAEs, SAEs (including deaths), and their attribution will be provided.

Clinical laboratory results will be summarized descriptively by cohort and visit, which will also include a display of changes from baseline. Shift tables demonstrating the changes (low/normal/high) from baseline to worst postbaseline laboratory value will be displayed in cross-tabulations by cohort. Similar shift tables demonstrating the change of NCI CTCAE grades from baseline to the worst post-baseline severity grade during the Treatment Period will also be presented by cohort for applicable analytes. Listings of abnormal clinical laboratory data according to NCI CTCAE severity grades (if applicable), abnormal flags (low or high) and clinical significance of the latter will be provided.

Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by cohort and visit. Shift tables demonstrating the changes from baseline to the worst post-baseline value will be displayed in cross-tabulations by cohort. Vital sign measurements will be listed by subject and by visit.

ECG parameters and changes from baseline will be summarized by cohort and visit using descriptive statistics. Post-baseline abnormal QT corrected (QTc), (QTcF) will be summarized using frequency tabulations for the following 5 categories:

- QTc > 450 msec
- QTc > 480 msec
- QTc > 500 msec
- QTc increase from baseline > 30 msec
- QTc increase from baseline > 60 msec

Shift from baseline to worst post-baseline qualitative assessment of abnormality (ie, “Normal”, “Abnormal, not clinically significant”, and “Abnormal, clinically significant” or “Normal” and “Abnormal”) will be displayed in cross–tabulations by cohort. A listing of ECG parameters by subject and by visit will be provided.

9.8 Interim Analysis

No formal interim analysis will be performed, however, at the end of Stage 1 of each cohort, a Data Review Team (DRT) will review all safety and preliminary efficacy data and will conduct a futility review for go/no-go decision for Stage 2.

In Stage 1 of Cohort A, 12 subjects will be enrolled and treated with CC-90011 in combination with nivolumab. If 1 or less subjects respond in Stage 1, Cohort A will stop for futility. In Stage 1

of Cohort B and C, 14 subjects will be enrolled and treated with CC-90011 in combination with nivolumab. If 0 subjects respond in Stage 1, Cohort B and C will stop for futility.

The DRT will consist of the Celgene Medical Monitors, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives, as appropriate, and site investigator(s) and/or designees who have enrolled subjects in the Stage(s) 1 of the study. DRT meetings will be held as needed to review the data, monitor safety and make expansion decisions.

9.9 Other Topics

9.9.1 Steering Committee

The conduct of this trial will be overseen by a Steering Committee (SC), presided over by the coordinating Principal Investigator and if possible, the representative Regional Investigators from European countries participating in this study. The SC will serve in an advisory capacity to the Sponsor. Operational details for the SC will be detailed in a separate SC charter.

9.9.2 Safety Evaluation

A safety evaluation will be conducted to assess the safety of CC-90011 with nivolumab after 6 subjects (without distinction of cohorts) have completed at least 2 Cycles. A Bayesian method will be used to monitor for the rate of thrombocytopenia grade 4 and neutropenia Grade 3 to 4 events. The expected rate of thrombocytopenia Grade 4 is 20% and the expected rate of neutropenia Grade 3 to 4 is 12% from CC-90011 alone. No serious overlapping toxicities are expected for the combination of CC-90011 with nivolumab.

After the enrollment of 6 successive subjects completing 2 cycles, the following stopping criteria based on the posterior distributions of the rate of thrombocytopenia Grade and neutropenia Grade 3 to 4 events with a noninformative Jeffreys prior distribution of Beta (1/2, 1/2) will be evaluated:

1) Probability (rate of thrombocytopenia Grade 4 > 0.2|data from 6 subjects) > 0.95 or
2) Probability (rate of neutropenia Grade 3 to 4 > 0.12|data from 6 subjects) > 0.95

If any of these stopping criteria are met, the starting dose of CC-90011 will be reduced to the next lower dose level. Enrollment will not be paused during this evaluation. See Section 7.3 for more details.

Review of the AEs and SAEs, and any decision to pause enrollment, or modify dose and/or schedule of the cohorts, will be determined by the Sponsor in agreement with Steering Committee. Decisions to pause enrollment or stop cohorts or modify dose and/or schedule of the cohorts of the study will be communicated promptly to Investigators, to the IRBs/ECs (as applicable), and to the appropriate regulatory authorities.

9.9.3 Exploratory Analysis

A separate biomarker analysis plan will be developed prior to the sample analysis.

9.9.3.1 Subgroup Analysis

Appropriate subgroup analyses will be conducted by age, gender, region, and baseline prognostic factors as exploratory analyses, when possible.

9.9.4 Pharmacokinetic Analysis

The PK population includes all subjects who have at least 1 evaluable concentration data to calculate the summary statistics of concentrations. The evaluable subjects in the PK population will be included in the PK data analysis.

Summary statistics (number of subjects [N], mean, standard deviation, coefficient of variance [CV%], geometric mean, geometric CV%, median, minimum, and maximum) may be provided for drug concentration data from all evaluable subjects. Results may be presented in tabular and/or graphic formats as appropriate. Data permitting, a population pharmacokinetic approach may be utilized to characterize the PK of CC-90011 by pooling the PK data across cohorts and other studies. The relationship between CC-90011 dose, plasma exposures, and selected clinical endpoints (eg, measures of toxicities, efficacy, and/or biomarkers) may also be explored.

Methodology for exploratory analyses including immunogenicity of nivolumab in Cohort C is described in the statistical analysis plan.

10 ADVERSE EVENTS

10.1 Monitoring, Recording and Reporting of Adverse Events

An 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 investigational product 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 7.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product 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-90011 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-90011 and until 100 days after the last dose of nivolumab as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to CC-90011 or nivolumab. All SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date the subject signed informed consent until 100 days following discontinuation of study treatment.

All adverse events (serious/non-serious) will be recorded on 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.

The SAE is recorded within the eCRF and the data is transmitted electronically to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety and ensuring the event is recorded on the eCRF as well.

Progressive disease is considered a study endpoint and will not be recorded as an AE. However, any sign, symptom, or manifestation of progressive disease will be considered as an AE (if they meet any of the seriousness criteria they will be considered as an SAE).

10.1.1 Immune-Mediated Adverse-Events

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

10.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1 Seriousness

An 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 start 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 not 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 the IP, action taken regarding the IP, 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 Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0); https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- 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 the IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	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:	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 IP 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 IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of 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 (returned to baseline), recovered with sequelae, or death (due to the SAE).

All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the subject is lost to follow-up or for suspected cases, until SARS-Cov-2 infection is ruled-out.

10.2.7 Detecting Immune-Mediated Adverse-Events

Every adverse event must be assessed by the Investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the subject's case report form

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 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 a serious adverse event.

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 partner of childbearing potential of a male subject are immediately reportable events.

10.4.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 45 days of the subject's last dose of CC-90011, or within 5 months of the subject's last dose of nivolumab, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an 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.

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 within 24 hours of the Investigator's knowledge of the event.

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 to the IP should also be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

10.4.2 Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.5 Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of CC-90011 or until 100 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 IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the CRF, but do not require reporting to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/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.

The SAE is recorded within the eCRF, and the data is transmitted electronically to Celgene Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the eCRF as well.

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-90011 based on the Investigator Brochure and of events suspected of being related to nivolumab based on the Investigator Brochure.

In the United States, 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 trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

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

- Any AE suspected of being related to the use of IP 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.)

11 DISCONTINUATIONS

11.1 Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

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

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

The decision to discontinue a subject from treatment 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.

All subjects discontinued from the protocol prescribed treatment for any reason should undergo End of Treatment procedures.

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 from entire study
- Death
- Physician decision
- Lost to follow-up
- Study terminated by Sponsor
- 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

12.1 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

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 International Council on Harmonisation (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 Good Clinical Practice 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 informed consent form (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.

The IP 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;
- GCP 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 eCRFs 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 case report forms (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 institution 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 Investigators' 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 or remote 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 Good Clinical Practice 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 Good Clinical Practice 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, FDA, 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.

15.3 Product Quality Complaint

Issues that call into question IMP safety, purity, potency, quality and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to your study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all BMS or Celgene Corporation supplied IMP, non-investigational IMP or auxiliary medicinal products suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labelling, and IMP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by the site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps). When reporting, provide as much product information as possible. Suspected IMP quality issues will be investigated, and a response will be provided back to the investigational site.

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 the study Steering Committee (when applicable) and contribution to abstract, presentation and/or publication development.

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18 APPENDICES

APPENDIX A TABLE OF ABBREVIATIONS

Table 15: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
[redacted]	[redacted]
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
ATP	Adenosine triphosphate
AUC_{0-24}	Area Under the Plasma Concentration Time Curve from 0 to 24 hours
β-hCG	β-subunit of human chorionic gonadotropin
BUN	Blood urea nitrogen
CBC	Complete blood count
CgA	Chromogranin A
CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus disease2019
C_{max}	Maximum plasma concentration
CR	Complete response
CrCl	Creatine Clearance
CRF	Case report form
CSC	Cancer stem cells
CT	Computed tomography
[redacted]	[redacted]
[redacted]	[redacted]
CV%	Coefficient of variance
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DOR	Duration of response
DNA	Deoxyribonucleic acid
DRT	Data review team
[redacted]	[redacted]

Table 15: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
EMA	European Medicines Agency
EOT	End of treatment
EP	Etoposide plus cisplatin
ES SCLC	Extensive stage small cell lung cancer
ESMO	European Society of Medical Oncology
[redacted]	[redacted]
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
[redacted]	[redacted]
FIH	First-in-human
GCP	Good Clinical Practice
GFI1b	Growth factor independence 1b
GI	Gastrointestinal
GLP	Good laboratory practice
[redacted]	[redacted]
H3K4	Histone H3 lysine 4
H3K27	Histone H3 lysine 27
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HR	Heart rate Hazard ratio
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration, 50%
ICF	Informed consent form

Table 15: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ICH	International Council on Harmonisation
ICI	Immune checkpoint inhibitor
IgG	Immunoglobulin G
IMG	Immunogenicity
IMP	Investigational medicinal product
IP	Investigational product
IRB	Institutional Review Board
irAE	Immune-related adverse events
IRT	Interactive Response Technology
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
LSD1	Lysine-specific histone demethylase 1 A
MedDRA	Medical Dictionary for Regulatory Activities
MHC1	Major histocompatibility complex 1
MMD	Monocyte to macrophage differentiation-associated
mOS	Median overall survival
mPFS	Median progression-free survival
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
msec	Milliseconds
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NECs	Neuroendocrine carcinomas
NEN	Neuroendocrine neoplasm
[redacted]	[redacted]
NETs	Neuroendocrine tumors
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PCI	Prophylactic cranial irradiation

Table 15: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
PD	Pharmacodynamics
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
[redacted]	[redacted]
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
Plt	Platelet
PO	Orally
PQC	Product quality complaint
PR	Partial response
[redacted]	[redacted]
PT	Preferred term
Q2W	Once every 2 weeks
QD	Daily
QOD	Every other day
QTc	QT corrected
QTcB	QT corrected based on Bazett's equation
QTcF	QT corrected based on Fridericia's equation
QW	Once weekly
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
R/R	Relapsed and/or Refractory
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Steering committee
SCLC	Small cell lung cancer
SD	Stable disease

Table 15: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
shRNA	Short hairpin RNA
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
SOX2	SRY (sex determining region Y)-box 2
sqNSCLC	Squamous non-small cell lung cancer
STD10	Severely toxic dose 10%
SUSAR	Suspected unexpected serious adverse reaction
T3	Triiodothyronine
T4	Thyroxine
TdP	Torsades de pointes
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent therapy
TIL	T infiltrating lymphocytes
TSH	Thyroid-stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
UV	Ultraviolet
WBC	White blood cell

APPENDIX B VETERANS AFFAIRS LUNG STUDY

Table 16: Veterans Affairs Lung Study Group Staging

Limited stage disease	Extensive stage disease
Disease confined to one hemithorax (includes ipsilateral, contralateral, and/or supraclavicular nodes)	Disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases.

(Kalemkerian, 2012).

APPENDIX C PERFORMANCE STATUS CRITERIA

Table 17: Eastern Cooperative Oncology Group Performance Status

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

(Oken, 1982).

APPENDIX D CALCULATED CREATININE CLEARANCE (COCKCROFT AND GAULT, 1976)

This formula should be used for calculating creatinine clearance (CrCl) from local laboratory results only.

(A). Weight-Based Formula for Calculated Creatinine Clearance for Men

For serum creatinine concentration in mg/dL:

CrCl (mL/min) = [(140 – age*) X (weight in kg) X 1.0] / [72 X serum creatinine (mg/dL)]

For serum creatinine concentration in µmol/L:

CrCl(mL/min) = [(140 – age*) X (weight in kg) X 1.0] / [0.81 X serum creatinine (µmol/L)]

(B). Weight-Based Formula for Calculated Clearance for Women

For serum creatinine concentration in mg/dL:

CrCl (mL/min) = [(140 – age*) X (weight in kg)] X 0.85] / [72 X serum creatinine (mg/dL)]

For serum creatinine concentration in µmol/L:

CrCl (mL/min) = [(140 – age*) X (weight in kg) X 0.85] / [0.81 X serum creatinine (µmol/L)]

* Age in years.
Source: (Cockcroft, 1976)

APPENDIX E THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The following information is extracted/summarized from (New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version 1.1). Please refer to the primary reference for further information (Eisenhauer, 2009).

Definitions

At screening, tumor lesions/lymph nodes will be categorized as measurable or non-measurable.

Measurable Disease

Tumor Lesions. Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Tumor Response Evaluation

Target lesions

When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the measurable criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-

target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the eCRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-target lesions

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present," "absent," or "unequivocal progression."

Response Criteria

Target and non-target lesions are evaluated for response separately, and then the tumor burden as a whole is evaluated as the overall response.

Target Lesion Response

Target lesions will be assessed as follows:

- Complete Response (CR). Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR). At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD). At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD). Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
- Non-target Lesion Response
- Non-target lesions will be assessed as follows:
- Complete Response (CR). Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD. Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD). Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the Subject Also Has Measurable Disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial

worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Subject Has Only Non-Measurable Disease: This circumstance arises in some Phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so: therefore, the increase must be substantial.

Overall Response

Overall response should be assessed according to Table 18 for subjects with target lesions, and Table 19 for subjects with only non-target lesions.

Table 18: Time Point Response: Subjects with Target (± Non-target) Disease

Target Lesions Response	Non-target Lesion Response	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 19: Time Point Response: Subjects with Non-target Disease Only

Nontarget Lesions Response	New Lesions	Overall Response
CR	No	CR
Non-CR/ non-PD	No	Non-CR/ non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

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

Symptomatic Deterioration

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

APPENDIX F NIVOLUMAB ADVERSE EVENT MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

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

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

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

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

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

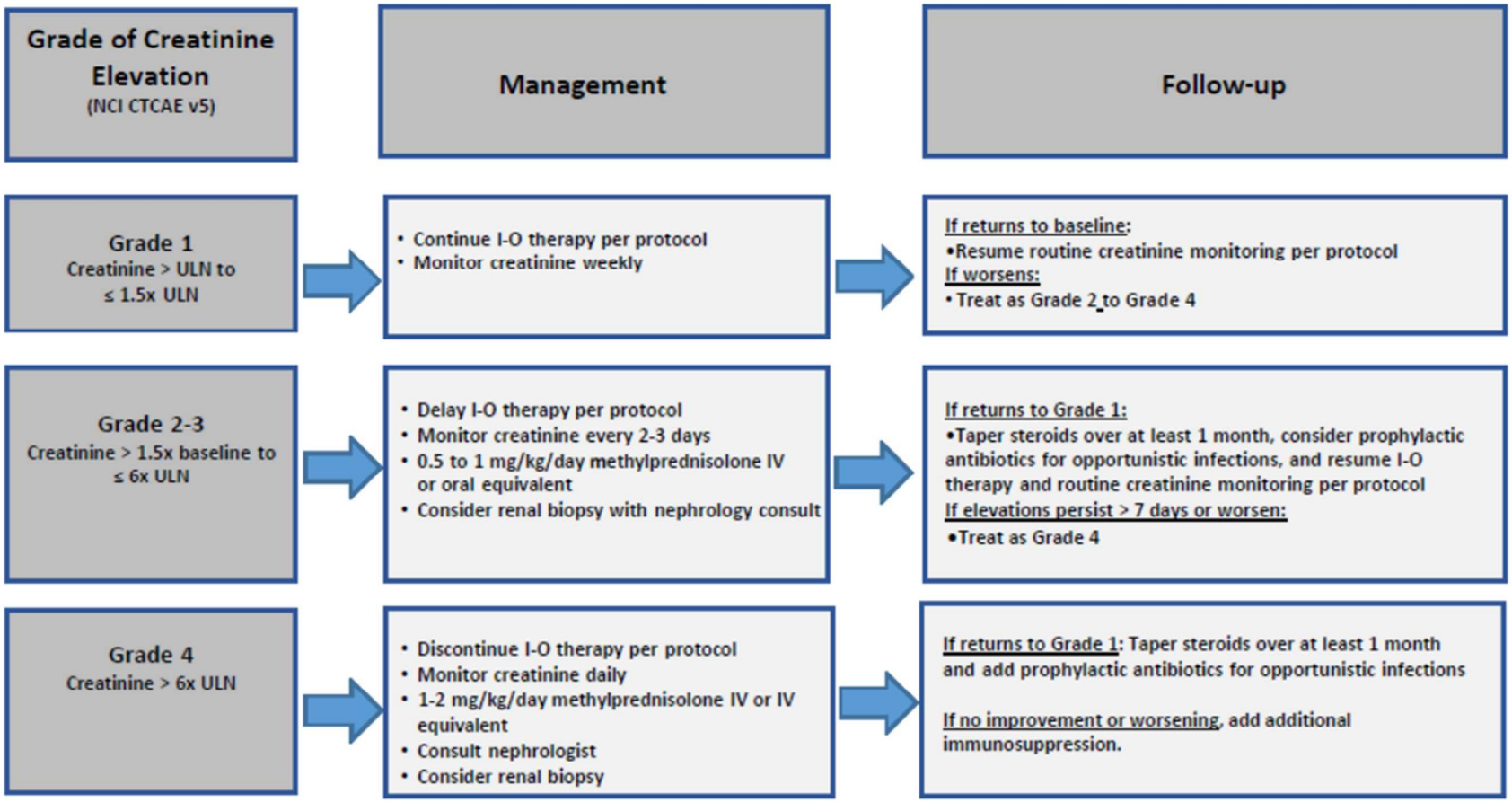
Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

Renal Adverse Event Management Algorithm

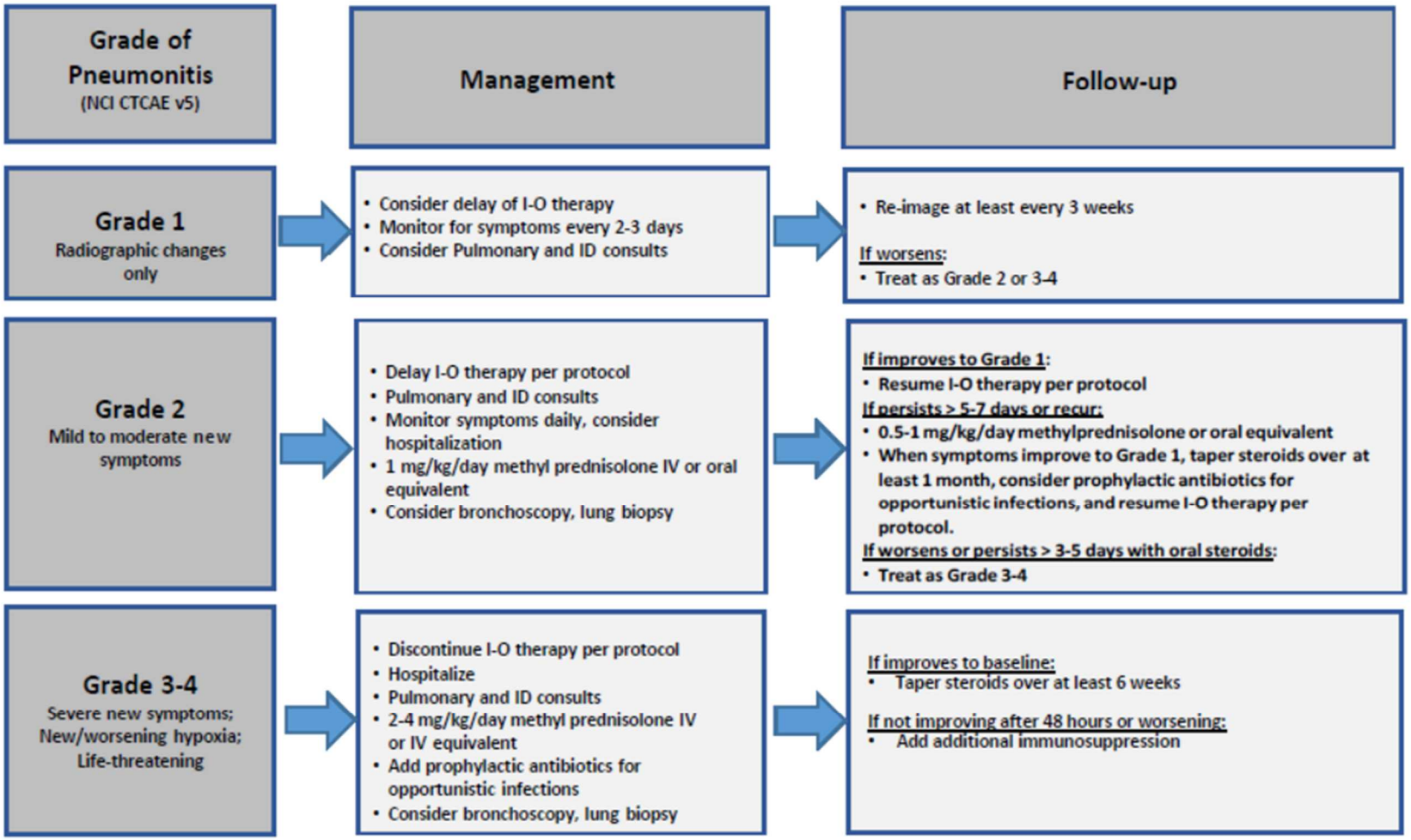
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

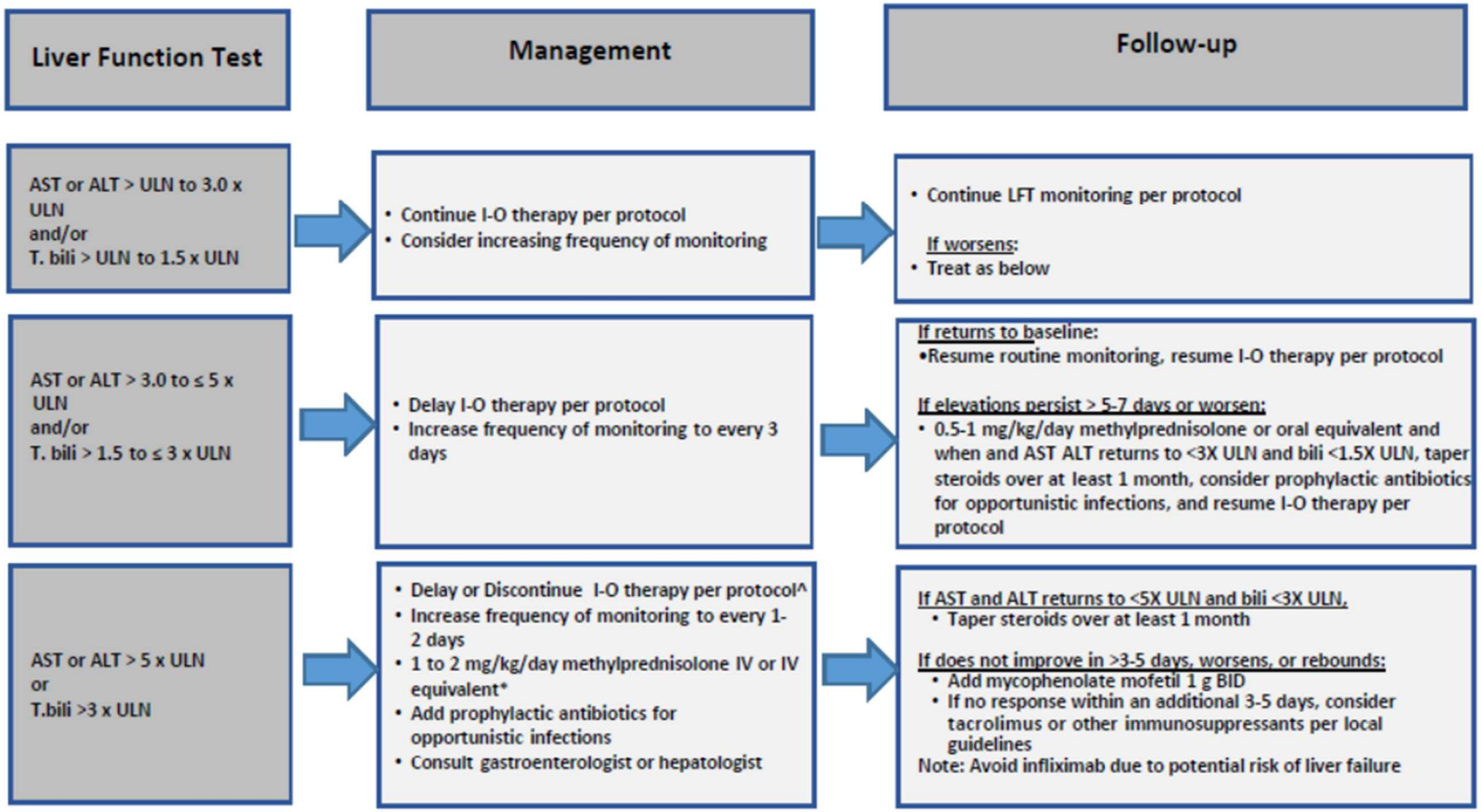
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

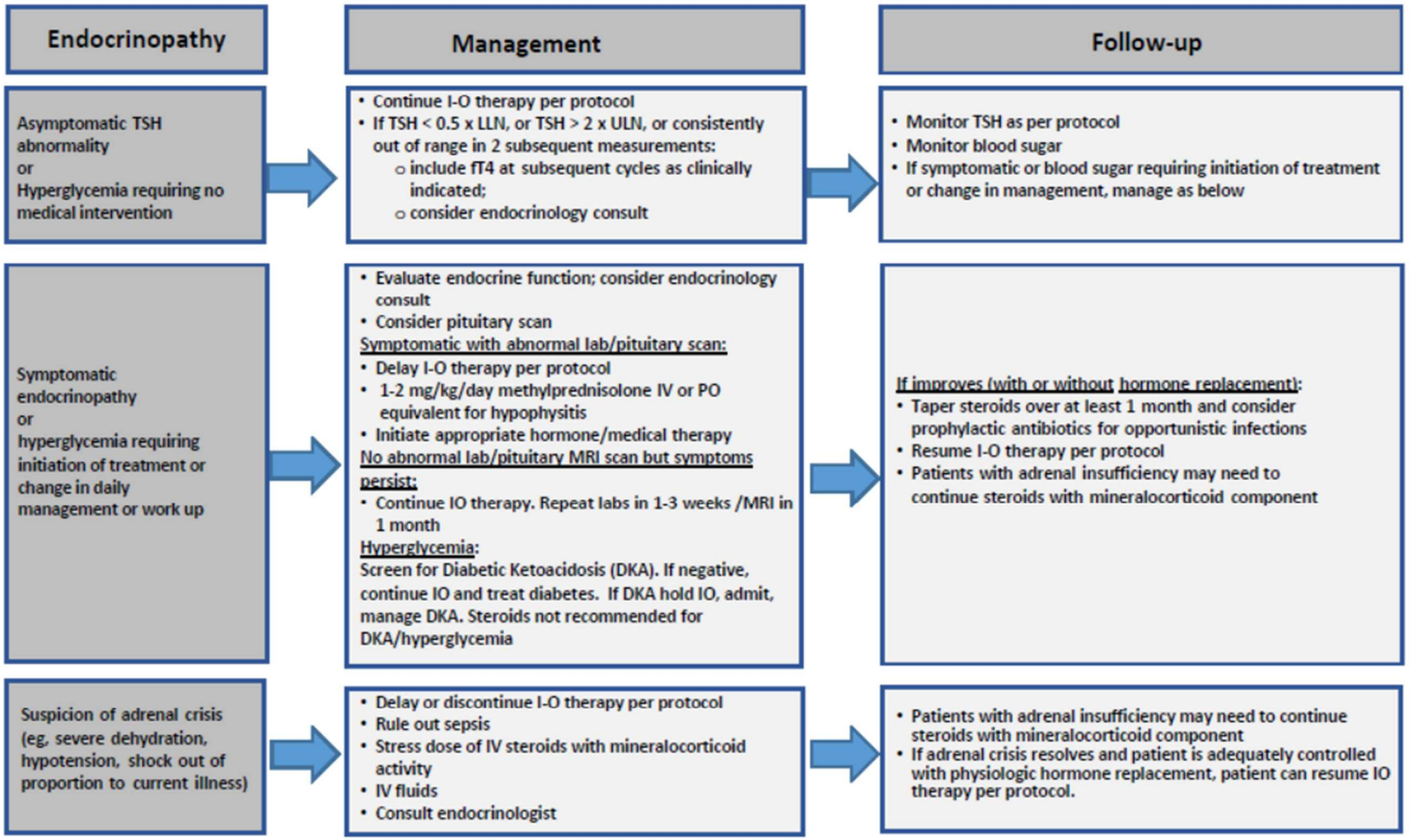
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

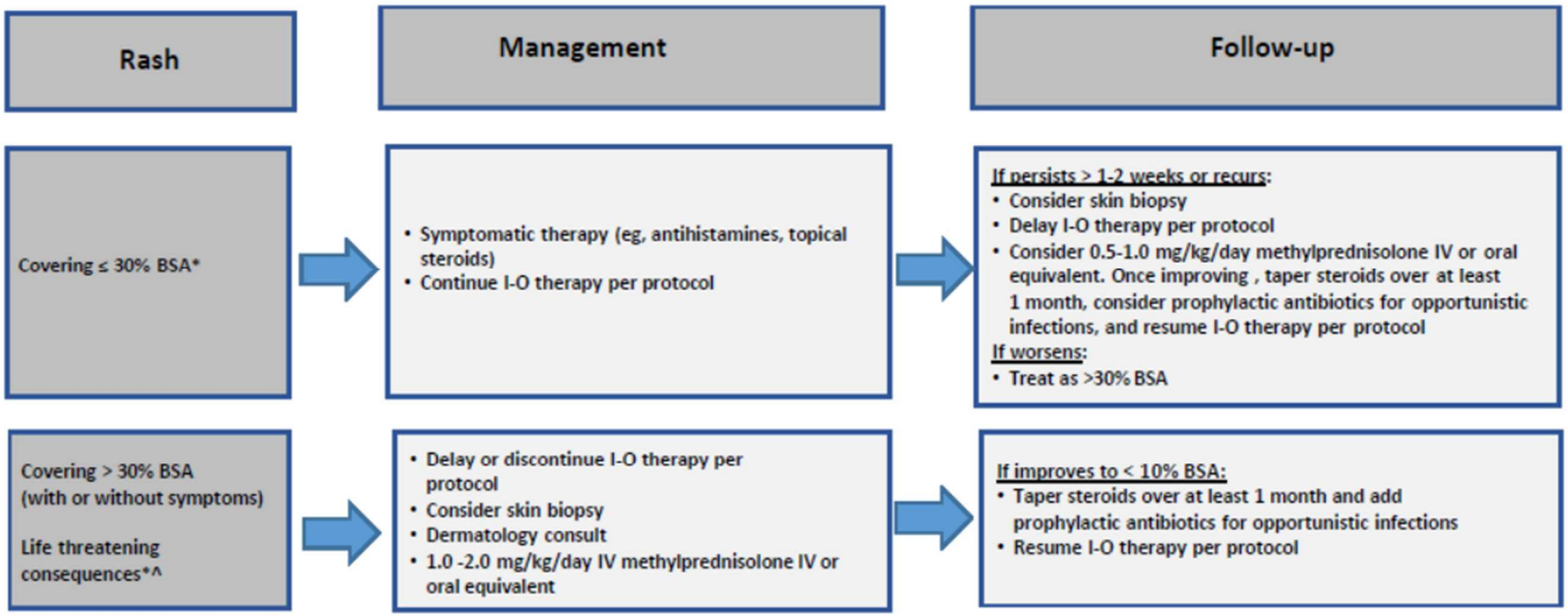
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



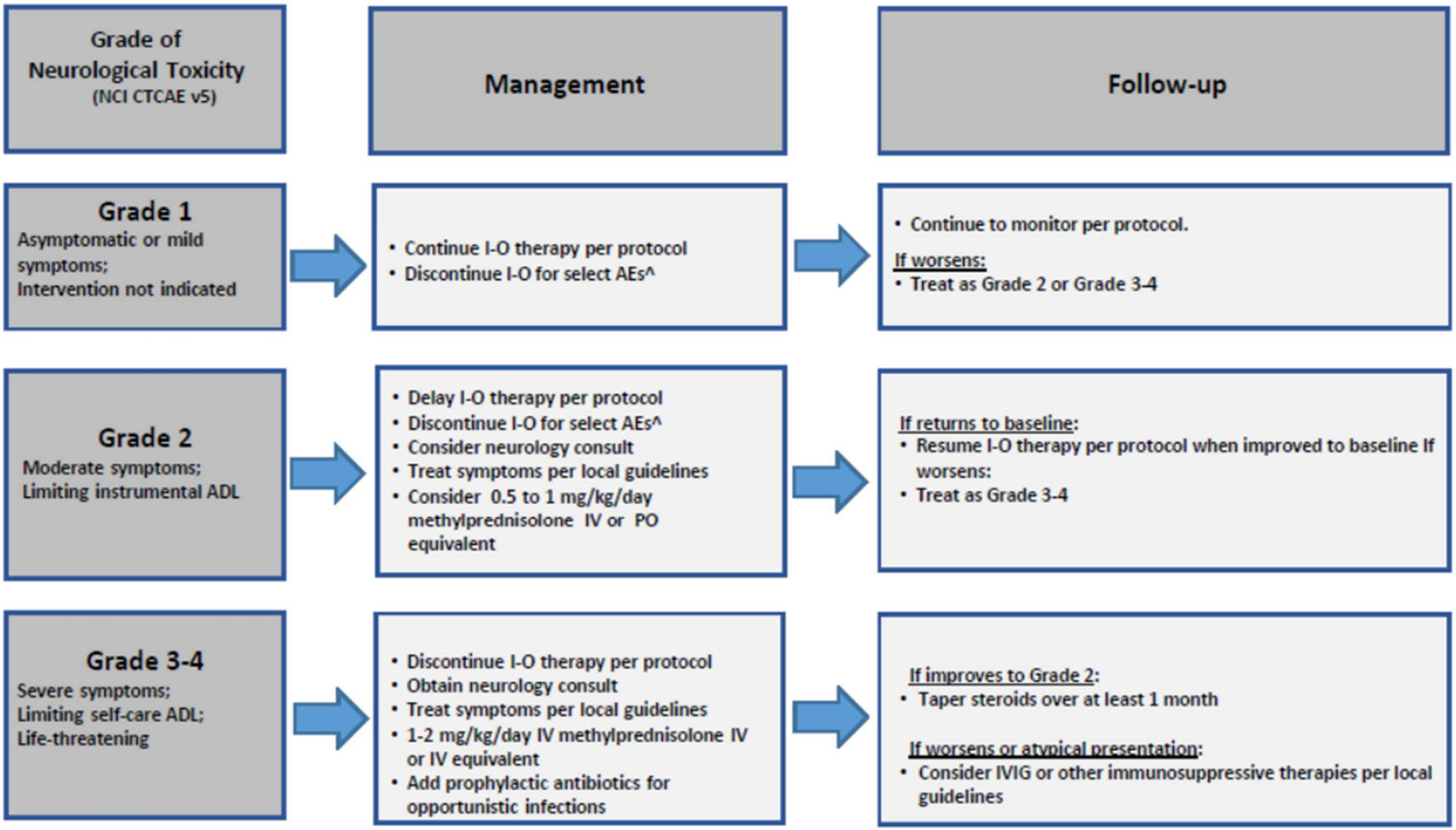
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

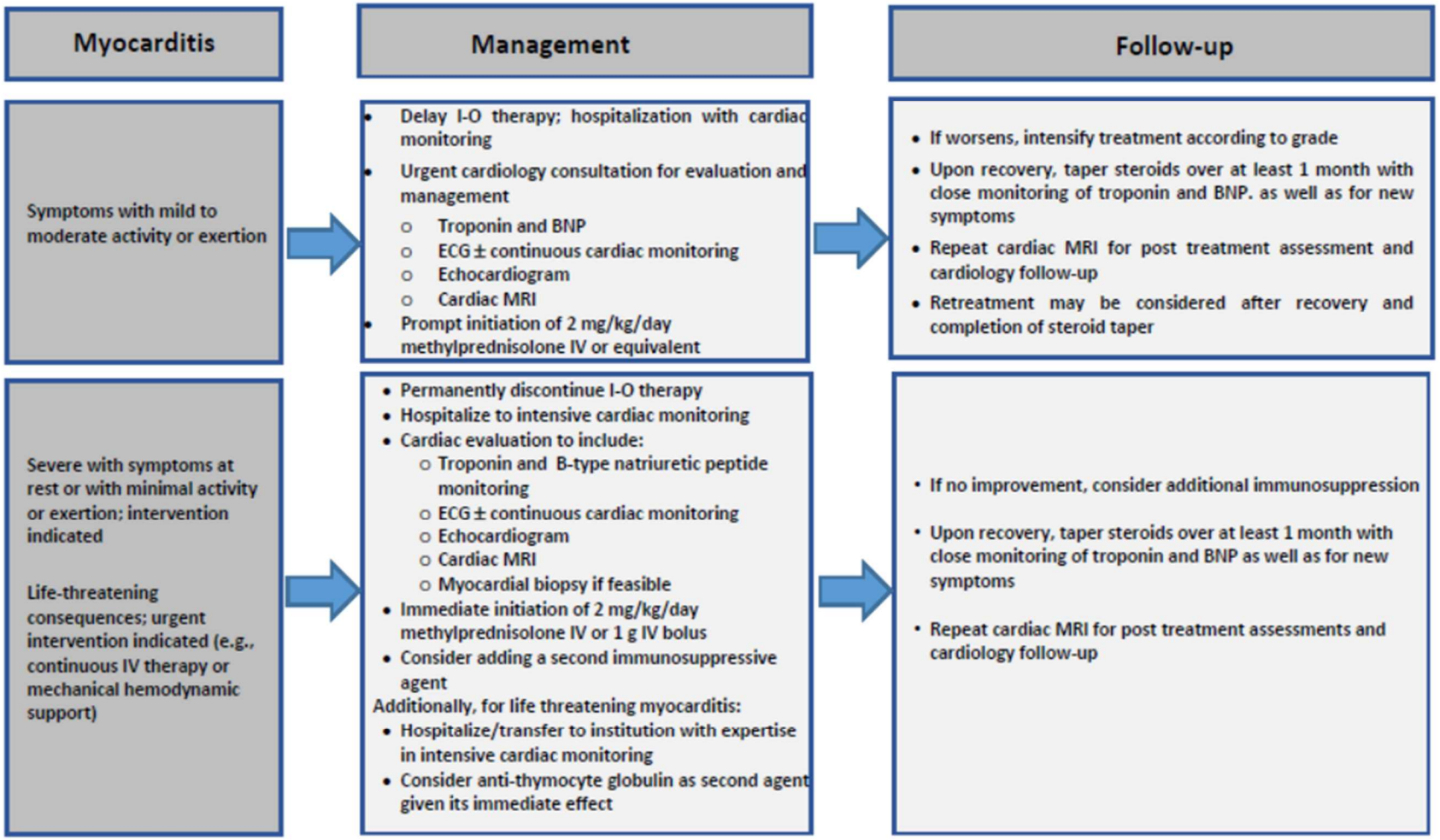


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

APPENDIX G RISK BENEFIT ASSESSMENT

BENEFIT AND RISK ASSESSMENT

STUDY TITLE:	A Phase 2 multicenter, open-label, multi-cohort study to assess safety and efficacy of CC-90011 in combination with nivolumab in subjects with advanced cancers
PROTOCOL NUMBER:	CC-90011-ST-002(also known as CA069-P05)
EudraCT NUMBER	2019-004194-95
VERSION:	4.0
Date:	23 Mar 2022

1 POTENTIAL BENEFITS

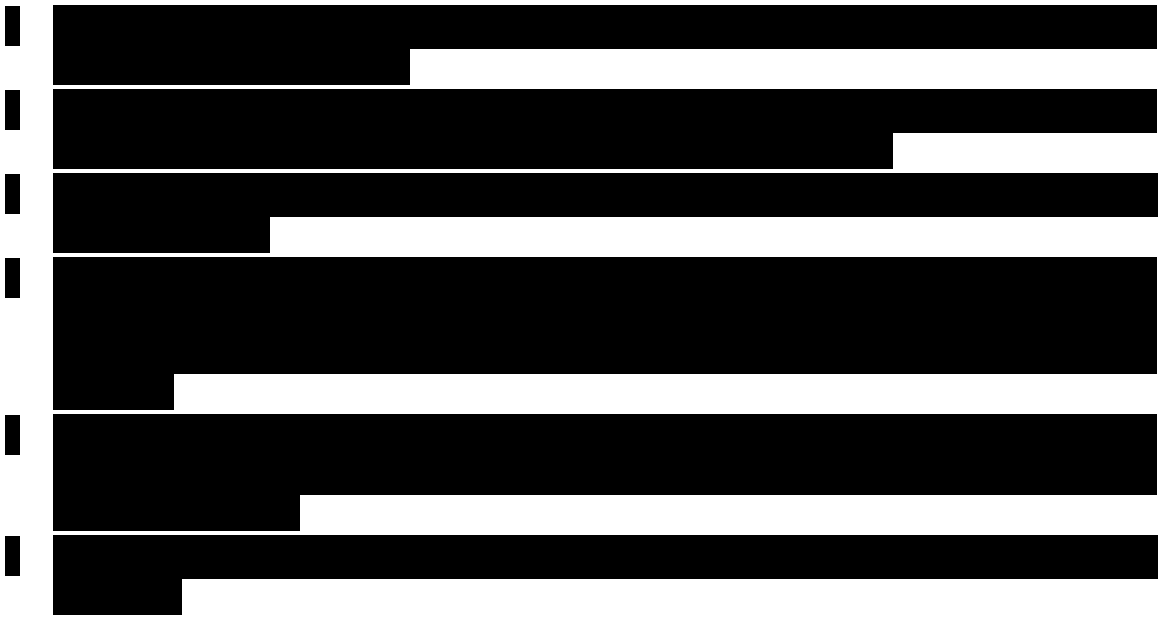
This is a Phase 2, multicenter, open-label, multi-cohort study designed to assess the safety and efficacy of CC-90011 in combination with nivolumab in subjects with small cell lung cancer or squamous non-small cell lung cancer who have progressed after 1 or 2 lines of therapy.

The primary objective is to evaluate in each individual cohort the overall response rate (ORR) in subjects with small cell lung cancer (SCLC) or squamous non-small cell lung cancer (sqNSCLC) treated with CC-90011(also known as BMS-986363) in combination with nivolumab.

The secondary objectives are to evaluate in each individual cohort the following endpoints/outcomes in subjects with SCLC or sqNSCLC receiving CC-90011 in combination with nivolumab:

- Safety and tolerability
- Duration of response (DoR)
- Time to response (TTR)
- Progression-free survival (PFS) assessed by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Overall survival (OS)
- Time to first subsequent therapy (TFST)

The exploratory objectives in each individual cohort are to:



- Explore the relationship between pharmacokinetics (PK), pharmacodynamic (PD) biomarkers and/or clinical outcomes of CC-90011 in combination with nivolumab
- Evaluate the disease control rate
- Assess the pharmacokinetics and immunogenicity of nivolumab in SCLC and sqNSCLC cohort subjects

- Assess the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serologic status on subjects and to support health authority requests

For the purpose of this protocol, immune checkpoint inhibitor (ICI) means anti-PD-1 or anti-PD-L1 treatments.

Approximately 135 subjects total globally will be enrolled into one of the following cohorts in 2 stages:

- Cohort A: SCLC in ICI naïve subjects
- Cohort B: SCLC in ICI progressor subjects
- Cohort C: sqNSCLC in ICI progressor subjects

Small cell lung cancer (SCLC)

SCLC accounts for up to 13% to 15% of all lung cancer diagnoses, with 250,000 cases diagnosed annually worldwide. It is the sixth most-common cause of cancer-related mortality (Govindan, 2006; Jemal, 2007; Lozano, 2012). SCLC is an aggressive high-grade neuroendocrine tumor associated with a short doubling time, a high growth fraction, and early development of widespread metastases, which contribute to the extremely poor disease prognosis (Sabari, 2017). These aspects of SCLC, as well as the limited success of current treatments, perhaps due to cancer stem cells (CSCs), highlight the unmet medical need for the development of new therapeutics for SCLC, particularly in relapsed disease.

In contrast to the rapidly changing status of non-small cell lung cancer (NSCLC), where significant inroads have been made with targeted agents and immunotherapies, SCLC is a recalcitrant tumor without significant treatment advances in the limited stage (LS) setting for 30 years (Oronsky, 2017; van Meerbeeck, 2011). For these reasons, alternative approaches to the treatment of SCLC are needed.

Current treatment for first line extensive stage SCLC

Standard first-line treatment for ES SCLC consists of platinum-based chemotherapy, mainly 4 to 6 cycles of cisplatin or carboplatin plus etoposide (Fruh, 2013; Kalemkerian, 2018). In patients with ES SCLC, response rates of 60% to 70% can be achieved with combination chemotherapy alone. Despite the initial chemosensitivity, almost all patients relapse and have limited or no response to subsequent therapy.

Many strategies have been evaluated to improve the treatment regimen for ES SCLC, including the addition of a third agent. However, they have shown modest survival benefit with increased toxicity.

The introduction of immune checkpoint inhibitors (ICI) has provided an important advancement. On 18 Mar 2019, the United States Food and Drug Administration (FDA), and on 06 Sep 2019, the European Medicines Agency (EMA), approved atezolizumab, an anti-PD-L1, in combination with carboplatin plus etoposide, followed by maintenance atezolizumab as first line treatment for

ES SCLC. The addition of an anti-PD-L1 to chemotherapy resulted in 0.9 months improvement in mPFS, and a 2-month benefit in mOS, from 10.3 to 12.3 months. However, the confirmed overall response rate (ORR) was similar in both groups, 60.2% versus 64.4%, with 5 patients (2.5%) having a completed response (CR) in the atezolizumab group and two patients (1%) with a CR in the chemotherapy alone group (Horn, 2018). Similar results from a clinical trial of durvalumab (anti-PD-L1) in addition to the standard chemotherapy, cisplatin or carboplatin plus etoposide in first line ES SCLC were recently presented (Paz-Ares, 2019).

Despite the recent approval of atezolizumab as first-line treatment for ES SCLC, and the positive but still modest results with the addition of durvalumab, overall attempts to improve long-term survival rates have failed to yield significant advantages. Given the efficacy of immunotherapy in SCLC is observed in a minority of subjects, a predictive biomarker study is warranted for finding patients most likely to benefit (Ahn, 2019).

Despite the rationale to combine chemotherapy with ICI, based on immunogenic cell death induction and immunogenicity of tumor cells modulation by chemotherapy, the benefit observed are modest (Ahn, 2019). Explanation of this resistance could be found in the nature the SCLC tumor with characteristics of a "cold tumor": limited PD-L1 expression, decreased major histocompatibility complex 1(MHC1) expression, activation or accumulation of suppressors cells, myeloid derived suppressor cells, regulatory lymphocytes, ineffective priming or activation of dendritic cells and lymphocytes T cells, and finally low rate of immune cell infiltration (Hamilton, 2019). Modifying one of these characteristics by using CC-90011 would have the potential to enhance ICI activity.

Most patients relapse despite the initial chemosensitivity indicating the inability to eradicate residual tumor cells and suggesting the existence of cancer stem cells (CSC) that are resistant to radiation and cytotoxic therapy. The CSC theory is a key component of cancer cell biology and is hypothesized to be associated with aggressive cancer spread and metastatic progression, as well as resistance to therapy (Codony-Servat, 2016). After relapse, these patients have a median survival of only 4 to 5 months when treated with further systemic therapy (Owonikoko, 2012). Therefore, exploring treatment strategies that target CSC and address this mechanism of resistance appears to be essential (Nunes, 2018).

Current treatment for second- and third-line extensive stage SCLC

Subsequent systemic therapy provides significant palliation in many patients; however, the likelihood of response is highly dependent on the time from initial therapy to relapse. While there are numerous systemic therapy options for patients who have relapsed 6 months or less after initial therapy, the likelihood of response is low, and duration of response is very limited. Recommended subsequent systemic therapies for these patients include topotecan, cyclophosphamide, doxorubicin and vincristine (CAV), and bendamustine (Cheng, 2007; Kalemkerian, 2018).

In third-line treatment, both nivolumab and pembrolizumab were approved by FDA for subjects with ES SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. Nivolumab has demonstrated an ORR of 12%. Responses were durable

for 6 months or longer in 77%, 12 months or longer in 62%, and 18 months or longer in 39% of the 13 responding patients (Antonia, 2016).

Activity of ICIs after progression on platinum-based chemotherapy is modest with low response rates and low progression-free and overall survival rates, thus prompting the testing of combination therapy as a potential modality to enhance ICI efficacy and improve outcomes in SCLC patients. However, the durable DoR observed is supporting the use of ICIs in second line but understanding how to enhance efficacy and enrich subject selection are key.

Squamous Non-Small Cell Lung Cancer (sqNSCLC)

Non-small cell lung cancer accounts for 80% to 90% of lung cancers. Squamous histology account for approximately 20% to 30% and is associated with shorter survival than non-squamous histology (Cheng, 2016; Lortet-Tieulent, 2014; Soldera, 2017).

Advanced squamous non-small cell lung cancer (sqNSCLC) remains a recalcitrant disease. While non-squamous NSCLC has benefited from advances in chemotherapy doublets (pemetrexed and platinum), VEGF targeted therapy (bevacizumab) and tumor profiling with actionable mutations for therapeutic interventions (ie, EGFRmut, ALK, BRAF, ROS1), the same has not occurred in the setting of sqNSCLC. Together, these factors make sqNSCLC an especially challenging disease to manage (Socinski, 2016) such that new therapies, especially ICI and combinations, could have a large impact.

Current Treatment for First Line Squamous Non-Small Cell Lung Cancer

Platinum-based doublet chemotherapy (cisplatin or carboplatin) has been the standard first-line treatment for sqNSCLC for decades. Taxanes (including paclitaxel, albumin-bound paclitaxel [*nab*®]-paclitaxel or docetaxel) or gemcitabine commonly complete the standard chemotherapy backbone as the initial systemic therapy for patients with advanced sqNSCLC without major comorbidities and with a performance status of 0 to 2 (Scarpace, 2015).

More recently, the introduction of ICIs in combination with first line platinum doublets has resulted in improvements in ORR, PFS and OS. This has resulted in the FDA approval of pembrolizumab, an anti-PD-1 and atezolizumab.

Current Treatment for Second Line Squamous Non-Small Cell Lung Cancer

Three anti-PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, and atezolizumab) have been approved by the FDA and the EMA as second-line treatment based on Phase 3 studies demonstrating improved survival rates, longer duration of response, and fewer adverse events in comparison to docetaxel. However, these therapies were evaluated in immunotherapy-naïve patients, prior to approval of ICIs in the first line setting.

Treatment options are limited for sqNSCLC patients who are intolerant to immunotherapy or for patients whose disease has progressed on anti-PD-1/PD-L1 therapy. In this case, retreatment with platinum-based doublet chemotherapy, docetaxel (with or without ramucirumab), or gemcitabine is recommended (Planchard, 2019).

As switching to another PD-l/PD-L1 inhibitor is not routinely recommended after a patient progresses on PD-1/PD-L1 inhibitor (Ettinger, 2018), there are several combinations involving ICIs that are being investigated in patients who progressed during or after an ICI therapy.

CC-90011

[redacted] Lysine-specific histone demethylase 1A is an eraser of the epigenetic code, thereby regulating the expression of many genes important in cancer progression and cell proliferation (Hoffmann, 2012; Lynch, 2012; Scoumanne, 2007). LSD1 over-expression promotes proliferation, migration, and tumor invasion (Lv, 2012) and has been documented in many human solid tumors including bladder, breast, colorectal, prostate and SCLC (Hayami, 2011; Kahl, 2006; Kauffman, 2011; Serce, 2012). Moreover, LSD1 over-expression has been correlated with poor prognosis in hepatocellular carcinoma, neuroblastoma, prostate cancer, non small cell lung cancer, and estrogen receptor negative breast cancer (Chen, 2015; Kahl, 2006; Lim, 2010; Lv, 2012; Schulte, 2009; Zhao, 2012).

LSD1 is required for normal differentiation in adult as well as embryonic cells (Wang, 2007). The importance of LSD1 in normal differentiation suggests that aberrant gene expression resulting from dysregulation of LSD1 may result in alterations in pathways associated with a stem-cell like phenotype. Moreover, LSD1 plays a part in stem cell maintenance, regulation of epithelial-to-mesenchymal transition (Adamo, 2011; McDonald, 2011), and has been shown to be an essential regulator of leukemia stem cell potential (Harris, 2012). LSD1 is a master regulator of normal stem cell phenotype, which is required for regulation of pluripotency genes, such as the transcription factor SRY (sex determining region Y)-box 2 (SOX2) and NANOG (Whyte, 2012), and which represses expression of lineage commitment genes (Adamo, 2011). In mouse embryonic stem cell lines, 2 experiments, ribonucleic acid (RNA) interference–mediated knockdown of LSD1 expression and treatment by small molecule LSD1 inhibitor, have demonstrated inhibition of the proliferation of pluripotent cancer cells including teratocarcinoma, embryonic carcinoma, and seminoma or embryonic stem cells that express the stem cell markers OCT4 and SOX2, while displaying minimum growth-inhibitory effects on non- pluripotent cancer or normal somatic cells (Wang, 2011).

[redacted]

Nivolumab

Nivolumab is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab monotherapy (OPDIVO™) was first approved on 04 Jul 2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and EU, and has been approved for several other indications (eg, metastatic NSCLC, advanced RCC, cHL, SCCHN, urothelial carcinoma, HCC, RCC, adjuvant treatment of melanoma).

Study Rationale and Purpose

For the purpose of this protocol, ICI means anti-PD-1 or anti-PD-L1 treatments.

The use of ICIs in the treatment for lung cancer has proven efficacy as demonstrated by the increasing OS, PFS, ORR and longer DoR compared to chemotherapy alone. However, only limited number of subjects have long term benefit with ICI treatment.

The LSD-1 inhibition sequentially or in combination with cytoreductive therapy could improve disease-free survival by preventing the emergence of resistant clones through treatment of tumorigenic stem cells. This mechanism of action is applicable to many earlier stages of solid tumors where existing standard of care does not result in long term disease control for all patients. The LSD-1 could prove to have a role in treating tumors resistant to current immune check-point blockade, an area of high unmet need for multiple solid tumors where ICIs are either not effective, or where ICIs are currently employed.

CC-90011 has the potential to mitigate primary and acquired resistance to ICI, due to its expected reversal of the CSC phenotype and T cell exclusion in SCLC and sqNSCLC.

In addition, recognizing the multiple mechanisms of resistance, this study will examine biomarkers in blood and tissue that could be used to identify responsive patients and improve outcomes. SCLC and sqNSCLC have high expression of potential predictive biomarkers for CC- 90011 (eg, SOX-2 and an LSD1-associated molecular signature), which will be evaluated for potential future use for patient enrichment.

In this study, cohort A tests the hypothesis that CC-90011 could enhance nivolumab responses in SCLC “cold tumor” phenotype. In this cohort, the proportion of enrolled subjects who respond to treatment is expected to increase by the action of CC-90011. Tumors with higher expression of an LSD1-associated molecular signature and low tumor T infiltrating lymphocytes (TILs) may have the best response to the combination of ICI with CC-90011, based on CC-90011 hypothesized mechanism of action of increasing T cell infiltration into tumors. Cohorts B and C tests whether CC-90011 can mitigate acquired resistance to ICI in SCLC as well as sqNSCLC. For these cohorts,

the trial will be enrolling subjects who have an initial response or stable disease to ICI, but progress within the first 9 months after completion of the chemotherapy treatment.

Combination of CC-90011 with Immune Checkpoint Inhibitors

The effectiveness of ICIs is grounded on a pre-existent anti-tumoral cellular immune response, which is usually recognized by the presence of tumor T-lymphocytic infiltrates that are, however, most often ineffective because of expression of co-inhibitory (or checkpoint) receptors such as PD-1, CTLA-4, and others. Blocking these checkpoint receptors or their ligands restores T cell function and leads to clinical responses.

PD-1 is expressed on activated CD8+ T cells, as well as B cells and natural killer cells, in the setting of chronic antigen exposure. PD-1 ligand (PD-L1) expression is induced by localized inflammatory stimuli, such as interferons released by the infiltrating T cells. Although PD-1 and PD-L1 checkpoint blockade can result in dramatic therapeutic responses, this therapy is effective only in a subset of subjects, and many of them are only partial responders to therapy (Nowicki, 2017). Subjects who do not respond to initial therapy with PD-1/PD-L1 blockade are referred to as having “primary resistance” to therapy (Sharma, 2017). Furthermore, a growing subset of subjects show robust initial response to therapy, but later have progressive disease. This phenomenon, in which the disease is either refractory to resumption of therapy or develops despite continuation of therapy, is known as “acquired resistance” to PD-1/PD-L1 blockade immunotherapy (O'Donnell, 2016). In all, almost four-fifths of patients either do not respond or lose their responsiveness to ICI. These limitations have made it necessary to explore combination treatment methods which are generally aimed at enhancing or activating antitumor immunity.

The tumor microenvironment can encompass multiple immunosuppressive mechanisms including dysfunctional T cells and lack of T cell infiltration or recognition by T cells, which prevent subjects to respond to anti-PD-1/PD-L1 therapy (Sharma, 2017; Zou, 2016). These mechanisms provide a basis for selecting appropriate combinations to complement the anti-PD-1/PD-L1 action. For example, the presence of T cytotoxic tumor infiltrates (defining the so-called “hot tumors”) justifies targeting other checkpoint inhibitors and enhance anti-tumor immune response. With modest and immunosuppressed infiltrates, new therapy should be aimed at inhibitory mediators (such as TGF-β, IL-10, etc), immune suppressive cells (such as myeloid derived suppressor cells, regulatory lymphocyte T cells), or immune ignored cancer stem cells. Also, when T cells are excluded from the tumor bed and accumulate at the tumor border, then potentially effective combinations might be aimed at reactivating or supplanting T cell recruiting signals (eg, chemokines). Finally, when T cells are absent (“cold tumors”), then various modalities to increase tumor immunogenicity and restart antigen-presentation or T cell priming might prove useful.

Based on current understanding, CC-90011, a potent and selective reversible inhibitor of LSD1 can be a combination partner for ICIs due to (1) its direct effects on tumor cells, as inhibition of LSD1 reduces cell proliferation and stem cell maintenance while promoting cell differentiation and reducing tumor growth in preclinical models (Mohammad, 2015); and (2) due to its potential immunomodulatory effects via its abilities to impact lymphocytic infiltrates and immunogenicity of tumors. In addition, we have found that tumors which lack T cell infiltration (cold tumors) have

higher mRNA expression of LSD1 and an LSD1-associated molecule, which could be used to identify patients susceptible to the action of CC-90011 with ICI.

Preclinical data provide strong mechanistic rationale for the combination of CC-90011 and an ICI in SCLC. Although checkpoint inhibitors have demonstrated some efficacy in SCLC, the magnitude of benefit has been relatively modest, and only a subset of patients respond. These clinical results may be related to the low abundance of T cells in SCLC tumors. CC-90011 is expected to reverse this phenotype, allowing T cells to infiltrate the tumor. Preclinical data in the literature and from Celgene, including survival data in mice with tumors, suggest that CC-90011 could induce pro-inflammatory and T cell permissive changes in the tumor microenvironment and, thus, enhance efficacy of checkpoint inhibitors, such as nivolumab.

Direct Anti-Tumor Action of CC-90011 Mediated via SOX2

LSD1 appears to play a significant role in the development and progression of malignancies with stem cell features. Accumulating evidence suggests that transcription factor SOX2 drives cancer stemness, fuels tumor initiation, and contributes to tumor aggressiveness through major drug stemness, fuels tumor initiation, and contributes to tumor aggressiveness through major drug resistance mechanisms like epithelial-to-mesenchymal transition, adenosine triphosphate (ATP)-binding cassette drug transporters, anti-apoptotic or pro-survival signaling, lineage plasticity, and evasion of immune surveillance (Mamun, 2018). Cancer stem cells, which are quiescent and express drug efflux pumps, may avoid killing by cytotoxic agents. Cancer stem cells are believed to be immune privileged, at least in part by expression of immune-modulatory factors (Bruttel, 2014). By driving differentiation of stem cells, LSD1 inhibition may re-sensitize these cells. Inhibition or genetic silencing of LSD1 has been shown to promote differentiation and reduce proliferation, migration, and invasion in vitro (Augert, 2019; Lv, 2012) and to reduce tumor growth in preclinical models (Augert, 2019; Mohammad, 2015)

The SOX2 is the most frequently altered gene in human squamous cell carcinoma (skin, lung and esophageal carcinomas) (Mamun, 2018). The SOX2 gene expression is amplified in more than 20% of tumors, including 27% of SCLC tumors, and is associated with stemness and an un-differentiated state (Hayami, 2011; Rudin, 2012). The SOX2 protein expression is overexpressed in 60% to 90% of tumors, including gliomas, breast, lung, head and neck carcinoma, sarcoma, pancreatic ductal carcinoma, ovarian cancer, colorectal cancer, melanoma, gastric cancers, and medulloblastoma (Mamun, 2018). The SOX2 is frequently amplified and/or over-expressed in SCLC and is involved in the induction of pluripotent stem cells (Takahashi, 2006).

In agreement with these findings, the LSD1 inhibitor CC-90011 can downregulate SOX2 and decrease proliferation and colony formation in SCLC cell lines. CC-90011 induced significant dose-dependent tumor growth inhibition in multiple cell line-derived xenografts and PDXs in vivo at doses ranging from 2.5 to 10 mg/kg QD, while being well tolerated in all models tested.

CC-90011 may induce differentiation of CSCs. CSCs can be resistant to treatments, including checkpoint inhibitors (Bruttel, 2014). The LSD1 is key regulator of stemness (Zhang, 2018). SOX2 is over-expressed in some SCLC tumors and is a driver of SCLC cell growth (Rudin, 2012; Sholl,

2010; Zhang, 2018). LSD1 inhibitors can decrease SOX2 mRNA expression (Zhang, 2013). LSD1 prevents SETD7-Driven proteolysis of SOX2 (Zhang, 2018), providing another mechanism by which LSD1 inhibitors would decrease SOX2 protein levels.

Therefore, inhibition of LSD1 by CC-90011 may be a useful therapeutic approach for tumors with CSC involvement such as SCLC and sqNSCLC, which are known to have high expression of SOX2 (Karachaliou, 2013; Wuebben, 2017; Ying, 2016). Overexpression of LSD1 is associated with poor prognosis in NSCLC, and promotes tumor cell proliferation, migration and invasion in NSCLC (Lv, 2012). Inhibition of LSD1 inhibits SCLC cell proliferation (Takagi, 2017).

Immunomodulatory Activities of CC-90011

CC-90011 may increase the number of tumor T infiltrating lymphocytes (TIL). This could be related to the observation that LSD1 ablation can lead to activation of type 1 interferon and stimulate anti-tumor T cell immunity (Sheng, 2018); and it can also result in enhanced tumor immunogenicity and T cell infiltration in poorly immunogenic tumors. LSD1 inhibition can also result in re-expression of effector T cell-attracting chemokines (CCL5, CXCL9, and CXCL10) (Qin, 2019).

In addition, CC-90011 may inhibit CSC self-renewal and induce their differentiation. The CSCs are known to be resistant to chemotherapy and at least in part by their expression of immune- are known to be resistant to chemotherapy and at least in part by their expression of immune-inhibitory factors to immunotherapy as well (Bruttel, 2014). A tumor without a CSC compartment would remain sensitive to killing by cytoreductive agents or immune regulators. This impact on CSC suggests that CC-90011 could also help mitigate acquired resistance (eg, responders that relapse after a period of response). However, given potential mechanisms of acquired resistance, such as loss of T cell function, lack of T cell recognition by downregulation of tumor antigen presentation, and development of escape mutation variants in the cancer (Sharma, 2017), it is expected that the other immune activities of CC-90011, increasing TIL, stimulating immunogenicity and anti-tumor T cell immunity (Sheng, 2018), would also contribute to CC-90011 activity in relapsed subjects.

One of the best predictors of response to immunotherapy is the number and activity of tumor infiltrating CD8+ cytotoxic T lymphocytes recruited to the tumor site (Qin, 2019). Consistent with their biological role, tumor infiltrated lymphocytes have been associated with improved outcome in several tumor types, including melanoma, colorectal and breast cancer (Fridman, 2013). Tumor CD8+ T cell infiltration has been linked to antitumor activity of immune checkpoint inhibitors (ICI) in subjects with advanced melanoma or NSCLC (Sharma, 2017; Thomas, 2019).

High levels of tumor infiltrating immune cells are associated with improved overall survival in SCLC, irrespective of tumor stage, subject performance status, or type of treatment received (Wang, 2013). In SCLC, tumor responses were observed in all cases where pretreatment tumors were T cell inflamed. In extended or relapsed SCLC, pre-existing CD8+ T cell response may be predictive of benefit from ICI-based therapies (Thomas, 2019).

As an LSD1 inhibitor, CC-90011 may switch cold tumors (lacking T cells) into hot tumors (T cell infiltrated). Internal analyses of tumor data in The Cancer Genome Atlas (TCGA) identified > 100 genes which negatively correlate with T cell infiltration. Expression of LSD1 and an LSD1-associated molecule anti-correlated with T cells in tumors. The LSD1 complex regulates embryonic stem cells property and substitutes for SOX2 in reprogramming somatic cells to pluripotency (Yang, 2011). Approximately 50% of SCLC and approximately 33% of sqNSCLC had a gene expression pattern which may predict for LSD1 activity and thus response to CC-90011, when combined with anti-PD1 or anti-PD-L1.

CC-90011 may enhance tumor immunity in “cold” tumors. LSD1 expression is inversely associated with that of cytotoxic T cell-attracting chemokines and PDL1 (Qin, 2019). LSD1 knock-down increases inflammatory gene expression (Hanzu, 2013; Qin, 2019). LSD1 KO or inhibition increases T cell trafficking into tumors and check-point inhibitor efficacy in preclinical models (Qin, 2019; Sheng, 2018). LSD1 inhibitors upregulate PDL1 expression in cell lines (Qin, 2019).

Subsequently, LSD1 knockdown was shown to enhance efficacy of anti-PD1, as evidenced by decreased tumor size and increased mouse survival in syngeneic tumor models (Sheng, 2018). In a separate study, LSD1 inhibition plus an anti-PD-1 antibody significantly suppressed tumor growth and pulmonary metastasis and augmented CD8+ T cell infiltration into xenograft tumors of triple negative breast cancer (Qin, 2019). Thus, CC-90011 is expected to enhance response to ICI, such as anti-PD1, when used in combination.

2 POTENTIAL RISKS AND PRECAUTIONS

Pre-clinical data – CC-90011

Exploratory and GLP-compliant repeated-dose toxicity studies of oral CC-90011 for up to 3 months in mice and dogs following several dosing schedules (mouse = QD, QDx5/week, and QODx3/week; dog = QW, BIW, and Q2W) were conducted to 1) assess the systemic exposure and toxicities over a range of dose levels and dose schedules, 2) to aid in dose and dose schedule selection for clinical trials, and 3) to further characterize CC-90011-related toxicity.

In 4-week studies, treatment-related mortality was observed at 45 mg base/kg/dose in mice following a QDx5/week dose schedule; and at ≥ 0.375 mg base/kg/dose in dogs following a QW dose schedule. The cause of mortality in mice was not determined; the moribund condition of dogs was due to CC-90011-related GI toxicity and ensuing septicemia.

In mice dosed at up to 45 mg base/kg/dose for 4 weeks, there was dose-proportional marrow toxicity, evidenced by a myeloid shift and/or marrow hypocellularity. The marrow space was replaced by fibrosis in the sternum and/or femur, with hyperostosis of endosteal, periosteal, and trabecular bone surfaces of affected sternebrae. Collectively, these changes persisted through a recovery period at the highest dose only. Some increase in marrow megakaryocytes (without peripheral correlate) was noted at all doses, also persisting at the highest dose. Marrow toxicity occurred in concert with declines in peripheral red cell mass (RBC count, hemoglobin, and hematocrit), and declines in platelet, reticulocyte and/or leukocyte counts along with significant are particularly sensitive). Depletion of splenic marginal zone lymphocytes was observed in all but the lowest dose groups but did not persist through a recovery period.

In dogs dosed for 4 weeks, findings were more clearly inflammatory in nature. The predominant finding centered on GI inflammation which in some instances was ulcerative and associated with secondary septicemia and mortality at higher doses. Changes in the bone marrow (BM) reflected peripheral demand, with myeloid hypercellularity and variable evidence of marrow toxicity reflected in the peripheral blood as either a decrease or increase in peripheral leukocyte numbers; unlike mice, no reactive bone alterations were noted.

In one 4-week dog study, there was mortality at ≥ 0.375 mg base/kg/dose, with morbidity generally attributed to gastric inflammation and/or ulceration. Slight to marked, acute to subacute inflammation was observed variably in the esophagus, stomach, small and/or large intestines, and/or rectum of dogs dying early. Findings that correlated with these microscopic changes included dehydration, abnormal feces (liquid, red), red vomitus, decreased food consumption and body weight, hypoactivity, fever, and/or GI tract discomfort. Related clinical pathology findings included decreased albumin, albumin:globulin ratio, calcium, and inorganic phosphorous; increased monocytes, large unstained cells, and neutrophils; and decreased red cell mass, platelets, reticulocytes, and eosinophils. Other findings in these animals were attributed to generalized inflammation and/or septicemia secondary to mucosal ulceration in the GI tract (inflammation in multiple lymph nodes, subcutaneous edema, acute inflammation in the heart or liver), and/or physiologic stress, including extramedullary hematopoiesis in the spleen and an increased myeloid:erythroid ratio in the sternal marrow. In surviving animals, only minimal to moderate

acute inflammation of the intestines and/or rectum was observed at ≤ 0.75 mg/kg/dose, with complete recoverability following a 4-week non-dosing interval. In a 4-week study at lower doses (0.125 or 0.25 mg base/kg/dose QW or 0.5 mg/kg/dose Q2W), there was no mortality, and findings were of lower severity, with acute inflammation in the cecum, ileum, and/or gut-associated lymphoid tissue of dogs from the highest dose-groups from each dosing-interval. Changes were minimal when dosed Q2W, becoming marked when dosed QW. Other findings included minimal extramedullary hematopoiesis in animals from the highest dose groups of either dosing regimen.

All CC-90011-related findings in mice and dogs demonstrated evidence of partial to complete reversibility following a 4-week treatment-free period.

In mice dosed daily for up to 3 months at up to 10 mg/kg/dose, further evidence of CC-90011-related systemic inflammation was observed. Inflammation affected multiple tissues, with instances of mortality (10 mg/kg/dose level) being associated with more severe inflammatory foci. Specifically, scattered neutrophilic inflammatory cell infiltrates occurred at 10 mg/kg/day in the heart valve, epididymides, eye sclera, and/or periocular tissue. Some instances of periocular inflammation were clearly an extension of peripheral glandular inflammation and, in general, the interior of the eye was unaffected. At 3 mg/kg/day, such infiltrates became minimal and were restricted to the periocular tissues; no such findings were seen at the 1 mg/kg/day. At the nontolerated dose level, ophthalmology examination revealed hyporeflection and reduced pallor in the fundus of the eye. Also, at 10 mg/kg/day, mortality was associated with focal abscessation in the Harderian glands and/or skin/subcutis. Reactive alterations in affected dose groups included increased (myeloid) marrow cellularity, and extramedullary hematopoiesis in the liver (with some necrosis at the highest dose), spleen and/or adrenal glands.

In dogs dosed QW for 3 months, CC-90011 was well tolerated up to 0.25 mg/kg/dose, the highest dose level administered, with no signs of toxicity.

Safety pharmacology evaluations were performed to determine the potential effects of CC-90011 on CV-related endpoints and respiratory rates. In an in vivo CV study in male Dunkin Hartley guinea pigs, an increase of QTcB interval of up to 16% at 10 to 18 minutes after infusion initiation was observed. CC-90011 caused a slight decrease in HR with a maximum suppression of 19% at 9 minutes into the 10-minute infusion. There were no remarkable CC-90011 related effects on arterial pressure, PR interval, QRS duration, or qualitative ECG parameters. The NOAEL in guinea pigs was 10 mg base/kg after IV infusion, with a mean plasma concentration of 2362 ng/mL at the end of the 10-minute infusion. This NOAEL plasma concentration was approximately 3000-fold higher than the predicted Cmax at the clinical starting dose of 1.25 mg base (0.80 ng/mL). In the 4-week oral gavage pivotal toxicity study in the dog, no CC-90011-related abnormalities in rhythm or waveform morphology or on HR, RR interval, PR interval, QRS duration, QT interval, or QTc interval were found at any dose level with CV and respiratory endpoints evaluated (ie, < 1.5 mg base/kg/dose). Therefore, the NOEL for CV and respiratory changes were 0.75 mg base/kg/dose (QW) and 0.375 mg base/kg/dose (BIW), the highest dose levels with CV and

respiratory endpoints evaluated. Steady state Cmax values at 0.75 mg base/kg/dose QW were 36.2 ng/mL (males) and 40.8 ng/mL (females); and at 0.375 mg base/kg/dose BIW were 17.7 ng/mL (males) and 19.0 ng/mL (females). These NOEL plasma concentrations were approximately 20- to 50-fold higher than the predicted Cmax at the clinical starting dose of 1.25 mg base (0.80 ng/mL). In the clinical CC-90011-ST-001 Part A study, the human mean Cmax taken on Day 22 was 0.42 ng/mL at the starting dose of 1.25 mg, and 20.43 ng/mL at the RP2D (60 mg).

The IC50 of the hERG cardiac potassium ion channel current was 3.4 μM CC-90011 (Hill coefficient = 1.2), indicating moderate inhibition. Together, the hERG and CV safety pharmacology data suggest CV-related risk to patients is low.

Potential CNS-related effects were monitored in the GLP-compliant repeat-dose dog and mouse studies and no clinical observations were considered CNS-related.

CC-90011 was non- mutagenic based on the results obtained from the in vitro mutagenicity assays.

Overall, CC-90011 exhibits an acceptable safety profile in preclinical species for a clinical drug candidate in an advanced oncology setting and the toxicology program for CC-90011 adequately supports the conduct of clinical trials in oncology subjects.

Clinical data

CC-90011

Clinical experience with CC-90011 in humans is based on 2 ongoing clinical Phase 1 studies, CC-90011-ST-001 (monotherapy) and CC-90011-SCLC-001 (combination therapy).

Study CC-90011-ST-001 is an open-label, Phase 1, multicenter, dose escalation (Part A) and expansion (Part B), first-in-human (FIH) clinical study to assess the safety (including an assessment of maximum tolerated dose [MTD]), PK, and preliminary efficacy of oral CC-90011 in adult subjects with relapsed and/or refractory (R/R) advanced solid tumors and R/R advanced non-Hodgkin lymphomas.

Study CC-90011-SCLC-001 is an open-label, Phase 1b, multicenter, dose-finding study to assess the safety, tolerability, PK, PD, and preliminary efficacy of CC-90011 given in combination with cisplatin or carboplatin and etoposide, defined as Chemotherapy, followed by CC-90011 single agent in maintenance, and CC-90011 given in combination with Chemotherapy plus nivolumab followed by CC-90011 plus nivolumab in maintenance, to adult subjects with first line, extensive stage (ES) SCLC. The study consists of a dose-finding Chemotherapy Treatment Period, where increasing oral doses of CC-90011 are given in combination with standard dose of Chemotherapy with or without nivolumab and a Maintenance Treatment Period, following completion of the chemotherapy regimen, where CC-90011 up to 60 mg is administered as a single agent or with nivolumab for responding subjects.

Study CC-90011-ST-001

As of 11 Sep 2020, 50 subjects were enrolled in Part A of the study and received escalating oral doses of CC-90011 QW at 9 dose levels from 1.25 mg to 120 mg/dose and 17 subjects (14 subjects with low/intermediate-grade lung neuroendocrine tumors [NETs] [typical and atypical carcinoid]

and 2 subjects with prostate neuroendocrine carcinomas [NECs], and 1 subject with MZL were enrolled in Part B of the study and received oral CC-90011 QW at 60 mg. The Part A of the study has been completed and the primary objectives were met. Seven out of the 47 evaluable subjects experienced a DLT and all DLTs were Grade 3 or 4 thrombocytopenia. Thrombocytopenia, an on-target effect, occurred at and beyond 60 mg QW and were successfully managed with dose interruption and/or dose reductions. The NTD was established at 120 mg QW with all 4 treated subjects experiencing Grade 3 (N = 2) or Grade 4 (N = 2) thrombocytopenia (requiring platelet transfusion). The MTD has been identified at 80 mg QW since the expanded cohort to 10 subjects identified 2 subjects with DLT, ie, one Grade 3 and one Grade 4 thrombocytopenia (requiring platelet transfusion). One subject at 60 mg QW experienced a Grade 4 thrombocytopenia requiring transfusion.

In Part A of the study (N=50), the most frequently reported treatment emergent adverse events (TEAEs) (in at least 10% of subjects) were thrombocytopenia (46.0%), vomiting (28.0%), anemia (28.0%), fatigue (26.0%), nausea, constipation and asthenia (22.0% each), diarrhea, pyrexia, and decreased appetite (20.0% each), musculoskeletal pain (16.0%), back pain (14.0%), neutropenia, abdominal pain, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and cough (12.0% each), and tumor pain, headache, and dyspnea (10.0% each). Overall, 24 (48.0%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (24.0%), neutropenia (8.0%), anemia (6.0%), and general physical health deterioration, increased ALT, increased blood bilirubin, increased lipase, and hypophosphatemia (4.0% each). Grade 3 or 4 thrombocytopenia occurred from the dose level of 40 mg and Grade 3 or 4 neutropenia occurred from the dose level of 80 mg and only after clinically significant thrombocytopenia. Three (6.0%) subjects experienced at least one TEAE leading to discontinuation of study treatment (1 subject at 2.5 mg had Grade 3 portal acute vein thrombosis assessed as not related to study drug and 2 subjects at 120 mg had Grade 3 thrombocytopenia, assessed as related to study treatment). Overall, 33 (66.0%) subjects died during Part A mainly due to progression of malignant disease in this heavily treated population. No death due to drug-related toxicity occurred during the study.

CC-90011 demonstrated preliminary evidence of antitumor activity in this difficult-to-treat patient population with very few treatment options. Among 27 neuroendocrine neoplasm (NEN) subjects, 7 subjects have demonstrated prolonged stabilization of disease (stable disease [SD] > 4 months). Notably, 3 subjects with bronchial NEN had prolonged SD of > 6 months and 2 subjects with prostate NEN stayed over 6 months under study drug treatment due to clinical benefit. The R/R non-Hodgkin's lymphoma subject (transformed marginal zone lymphoma) experienced a complete metabolic response.

In Part B of the study (N = 17), the most frequently reported TEAEs (in at least 10% of subjects) were thrombocytopenia (70.6%), asthenia (41.2%), anemia (35.3%), constipation, diarrhea, and nausea (29.4% each), neutropenia and dysgeusia (23.5% each), decreased appetite, arthralgia, musculoskeletal pain, cough and epistaxis (17.6% each), and leucopenia, stomatitis, vomiting, fatigue, hepatic pain, bronchitis, lipase increased, hypokalemia, bone pain, neck pain, dizziness, peripheral sensory neuropathy, sciatica, confusional state, dyspnea, and pruritus (11.8% each).

Overall, 13 (76.5.0%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (35.3%), neutropenia (17.6%), and asthenia (11.8%). No subject experienced TEAE leading to discontinuation of study treatment. Overall, 9 (52.9%) subjects died during Part B due to progression of malignant disease (N = 6), occurrence of an adverse event (AE) (N = 2), and unknown cause (N = 1).

No death due to drug-related toxicity occurred during the study.

In the 14 subjects with low/intermediate-grade lung NET, a best response of SD was observed in 10 (71.4%) subjects, including 7 subjects with SD ≥ 4 months. The 2 subjects with [redacted] NEC and the MZL subject progressed.

The study demonstrates that CC-90011 is well-tolerated in the heavily pretreated subjects with advanced tumors. The majority of treatment emergent adverse events (TEAEs) were mild or moderate in severity, transient, and manageable by dose adjustments and/or supportive treatment.

Study CC-90011-SCLC-001

As of 11 Sep 2020, safety and efficacy data are available for 19 enrolled subjects with first line ES SCLC, who received escalating doses of oral CC-90011 at 20 mg (Cohort 1; N = 8) and 40 mg (Cohort 2; N = 7), and 60 mg (Cohort 3; N = 4), in combination with etoposide plus cisplatin (EP).

One subject, who received CC-90011 20 mg, and 2 subjects, who received CC-90011 60 mg plus EP experienced a DLT during Chemotherapy Treatment Period. No DLT was observed in the 6 evaluable subjects treated at the dose of 40 mg. The NTD was determined to be 60 mg and the CC-90011 recommended phase 2 dose (RP2D) was 40 mg on Days 1 and 8 of each 21-day chemotherapy cycle.

During the Chemotherapy Treatment Period (N = 19), the most frequently reported TEAEs (in at least 20% of subjects) were anemia (78.9%), thrombocytopenia and neutropenia (68.4% each), asthenia (52.6%), nausea (42.1%), constipation (31.6%), blood alkaline phosphatase (ALP) increased (26.3%), and mucosal inflammation, pyrexia, diarrhea, decreased appetite, hyponatremia, dyspnea, and alopecia (21.1% each). Overall, 16 (84.2%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were neutropenia (63.2%), thrombocytopenia (42.1%), febrile neutropenia (15.8%), and anemia (10.5%).

As of 11 Sep 2020, a best objective response of PR was observed in the 16 of the 19 treated subjects.

The most current summary of clinical data is available in the most current version of the IB.

Potential toxicities for CC-90011 include those identified in the currently ongoing clinical studies and from nonclinical studies with CC-90011. On target, reversible and manageable thrombocytopenia has been established as a treatment emergent serious adverse event meeting the threshold or criteria for inclusion as related adverse events in the reference safety information (RSI) for CC-90011. Neutropenia has been established as a TEAE and is included as an adverse drug reaction (ADR) in the CC-90011 IB.

Bone marrow hypocellularity findings emphasize the importance of frequent blood count monitoring. Episodes of thrombocytopenia have been observed in the ongoing clinical studies and usually recover in one week's time with interruption of study drug, with recovery to Grade 1/baseline allowing continuation of study drug. Grade 1 thrombocytopenia events do not preclude the study drug administration and subjects with Grade 2 events have been safely dosed according to investigator´s judgment of the overall patient´s status. Grade 3 and 4 thrombocytopenia require dose interruption until recovery to Grade 1/baseline.

In the current proposed study, CC-90011-ST-002, subjects must have adequate laboratory values for platelet count, absolute neutrophil count (ANC), hemoglobin and white blood cells (WBC) to be included in the study (refer to protocol inclusion criteria for details). Subjects who are enrolled into the study will have ongoing safety laboratory analyses, including complete blood count (CBC) with differential and platelet count.

The protocol includes recommended dose adjustment guidelines for CC-90011 related hematological toxicities (refer to protocol section 7.4). Therapeutic use of granulocyte growth factors is allowed at any time for subjects experiencing febrile neutropenia or Grade 3/4 neutropenia. Routine prophylaxis with granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor is allowed at the Investigator's discretion after one or more occurrences of neutropenia and febrile neutropenia.

Due to potential GI toxicity, subjects with the following are excluded from participating in the study: subject has persistent diarrhea due to a malabsorptive syndrome (National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) ≥ Grade 2, despite medical management), or any other significant gastrointestinal (GI) disorder; subject with symptomatic or uncontrolled ulcers (gastric or duodenal), particularly with a history of and/or risk of perforation and GI tract hemorrhages or subject with any hemorrhage/bleeding event CTCAE > Grade 2 or haemoptysis > 1 teaspoon within 4 weeks prior to the first dose.

During study participation, subjects with ≥ Grade 1 diarrhea should promptly initiate treatment, as per recommendation of their treating physician and local guidelines. Premedication with antidiarrheal medication for subsequent doses of study treatment may be appropriate. Antiemetics will be withheld until subjects have experienced ≥ Grade 1 nausea or vomiting. Subjects may then receive prophylactic antiemetics at the discretion of the Investigator and per local guidelines.

The protocol also provides detailed guidance on dose reduction for study related hematological and non-hematological toxicities.

Nivolumab

The overall safety experience with nivolumab is based on experience in approximately 23, 507 subjects as either monotherapy or in combination with other therapeutics. Overall, the safety profile of nivolumab monotherapy is manageable. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

In general, for monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with NSCLC, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes.

The most common adverse reactions (≥20%) in patients treated by nivolumab as monotherapy were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain and vomiting.

Nivolumab is associated with immune-mediated adverse reactions including but not limited to pneumonitis, colitis, hepatitis, nephritis, endocrinopathies, skin adverse reactions (including rash, Stevens-Johnson syndrome, toxic epidermal necrolysis), encephalitis, and other immune mediated adverse reactions (myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome).

Management algorithms have been developed for the treatment of these immune-mediated adverse reactions. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management algorithms.

The proposed study includes these management algorithms to be used by the investigators. Early recognition and treatment is critical to management. Subjects should have a thorough diagnostic work-up to evaluate potential drug and non-drug related diagnoses.

Infusion reactions following administration of nivolumab are uncommon. Investigators are advised to monitor for fever, chills, shakes, headaches, itching, rash, hypertension or hypotension, or difficulty in breathing during and immediately after administration of nivolumab. Treatment recommendations are descried in the protocol (section 7.4.4), including interruption in patients with mild or moderate infusion related reactions or discontinuation of nivolumab in patients with severe or life-threatening infusion related reactions.

Overlapping toxicity

The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone.

CC-90011 has not been associated with immune mediated adverse events, but instead has mainly haematologic toxicities. In part A of the CC-90011-ST-001 study, (in 50 patients treated), the most frequently reported Grade 3 or 4 TEAEs included thrombocytopenia, neutropenia and anemia at

24.0%, 8.0% and 6.0% respectively. In part B of the CC-90011-ST-001 study, (in 17 patients treated as of 11 Sep 2020), the most frequently reported Grade 3 or 4 TEAEs included thrombocytopenia at 35.3% and neutropenia at 17.6%.

In the CC-90011-SCLC- 001 study, (as of 11 Sep 2020, in 19 patients treated with CC-90011 in combination with EP), the most frequently reported Grade 3 or 4 TEAEs included neutropenia at 63.2%, thrombocytopenia at 42.1%, and anemia at 10.5%.

Severe haematologic toxicities are not expected with nivolumab, most observed haematology laboratory abnormalities were low grade, and the immune mediated adverse events affect less than 10% of the patients treated by nivolumab alone. In patients treated with nivolumab alone (pooled dataset of 2578 patients), the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 5.2% for anaemia (all Grade 3), 1.0% for thrombocytopenia, 1.1% for neutropenia, (Opdivo summary of product characteristics [SmPC]).

The safety profile of CC-90011 is not as well-known as the safety profile for nivolumab. There is a possibility of overlapping haematologic events and patients will be monitored for this.

The emerging platelet (safety) profile of CC-90011 and nivolumab combination and decision to proceed at a reduced dose of CC-90011 40 mg, in the current study, supports assessment of benefit/risk from the perspective of population pharmacokinetics (PK) and exposure-response relationship with the safety and efficacy endpoints for the combination treatment. From available data thus far, it appears that there is some synergistic thrombocytopenia at precedented exposures of CC-90011; thus, having a composite exposure-response model for this combination will help to better characterize the overall thrombocytopenia profile. Currently, protocol amendment 1 collects nivolumab immunogenicity (IMG) samples from Cohort C at the scheduled timepoints: Cycle 1 Day 1 pre- dose, Cycle 2 Day 1 pre-dose, Cycle 3 Day 1 pre-dose, and every 4th cycle after Cycle 3 Day 1 pre-dose. In amendment number 2, both PK and IMG sample collections for nivolumab at the previously scheduled time points will be added and extended to all 3 cohorts.

Other overlapping toxicities are not known at this time and there will be careful monitoring of the combined safety profile and how it may differ from the known monotherapy safety profiles.

3 ADDITIONAL PRECAUTIONS

Steering committee

The conduct of this trial will be overseen by a Steering Committee (SC), presided over by the coordinating Principal Investigator and if possible, the representative Regional Investigators from European countries participating in this study. The SC will serve in an advisory capacity to the Sponsor. Review of AEs and SAEs and any decision to pause enrollment, or modify the dose and/or schedule of the cohorts, will be determined by the Sponsor with Steering Committee.

Initial Safety evaluation (protocol section 7.3.1)

A safety evaluation will be conducted to assess the safety of CC-90011 with nivolumab after 6 subjects have completed at least 2 Cycles. A Bayesian method will be used to monitor for the rate of thrombocytopenia Grade 4 and neutropenia Grade 3 to 4 events. The expected rate of thrombocytopenia Grade 4 is 20% and the expected rate of neutropenia Grade 3 to 4 is 12% from CC-90011 alone. No serious overlapping toxicities are expected for the combination of CC-90011 with nivolumab. No immune-related adverse events (irAEs) have been observed in the first-in-human study with CC-90011.

After the enrollment of 6 successive subjects completing 2 cycles, or sooner per protocol section 7.3.2, the following stopping criteria based on the posterior distributions of the rate of thrombocytopenia Grade 4 and neutropenia Grade 3 to 4 events with a noninformative Jeffreys prior distribution of Beta (1/2, 1/2) will be evaluated:

1. Probability (rate of thrombocytopenia Grade 4 > 0.2|data from 6 subjects) > 0.95 or
2. Probability (rate of neutropenia Grade 3 to 4 > 0.12|data from 6 subjects) > 0.95

If any of these stopping criteria are met, the starting dose of CC-90011 will be reduced to the next lower dose level 40 mg. The first criterion is equivalent to observing 3 or more thrombocytopenia events Grade 4 out of 6 and the second criterion is equivalent to observing 3 or more neutropenia events Grade 3 to 4. Enrollment will not be paused during this evaluation.

Once the starting dose is reduced to 40 mg, the same rule will be applied. If any of these stopping criteria are met for the 6 subjects treated at 40 mg, the starting dose of CC-90011 will be reduced to the next lower dose level 20 mg.

Once the initial 6 subjects at a given dose level do not trigger the dose reduction rule, subjects' safety data will be closely monitored on an ongoing basis and individual dose delays and/or reduction recommendations will be followed. In case the starting dose is reduced to a lower dose level, it will be ensured that the sample size at the selected dose meets the planned number of subjects.

Safety evaluation for CC-90011 starting dose of 40 mg (protocol section 7.3.1.1)

As of 14 Aug 2020, the Sponsor, in agreement with the Steering Committee made the decision to reduce the starting dose of CC-90011 from 60 mg to 40 mg. Implementation of this dose reduction was not considered an urgent safety measure. The same stopping criteria as specified in Sections 7.3.1 and 7.3.2 will be applied to the reduced starting dose of 40 mg.

To further evaluate if the RP2D of 60 mg that was established in the first-in-human study can be safely administered in this study and in order to maximize the potential efficacy of CC-90011 and level of target engagement, re-escalation to 60 mg may be considered after review of the overall data and AEs/SAEs by the Sponsor in agreement with the Steering Committee. Specifically, if in the first 2 cycles, there are no reports of Grade 4 thrombocytopenia or Grade 3 or 4 neutropenia, in any of the 6 subsequent subjects (without distinction of cohorts) who received 40 mg, then re-escalation of the starting dose to 60 mg for subsequent subjects may be considered.

If the stating dose is re-escalated to 60 mg, an additional 4 subjects (without distinction of cohorts) will be treated so that 6 subjects in total (including the 2 subjects in which Grade 4 thrombocytopenia [n=2] and Grade 3 neutropenia [n=1] was reported) will have received 60 mg. There will be staggered dosing, where the second subject to receive 60 mg will not be dosed until at least 15 days after the first subject has been treated and safety has been reviewed. This sentinel dosing scheme may or may not be continued for the rest of the 60 mg subjects, depending on the findings in the first subject and the overall safety profile to date.

The stopping criteria in protocol Sections 7.3.1 and 7.3.2 will be applied to these 6 subjects. Therefore, if in the first 2 cycles, there are no reports of Grade 4 thrombocytopenia and 1 or less reports of Grade 3 or 4 neutropenia, in any of the 4 subsequent subjects who received 60 mg, then 60 mg will be declared as the starting dose of CC-90011 and the dose to continue with in this study. If in the first 2 cycles, there is at least 1 report of Grade 4 thrombocytopenia or at least 2 reports of Grade 3 or 4 neutropenia, in any of the 4 subsequent subjects who received 60 mg, then 40 mg will be declared as the starting dose of CC-90011 and the dose to continue with in the study.

Definition of Stopping Criteria (protocol section 7.3.2)

If any of these stopping criteria are met for the 6 subjects treated at 20 mg, the trial will be stopped.

Events to be monitored with special interest and which may trigger the above stopping criteria include but are not limited to:

- Serious adverse events (SAEs) related to IPs of the same nature or organ system
- Clinically significant SAEs related to IPs of the same nature or organ system which would prevent further dosing of an individual subject

Review of the AEs and SAEs, and any decision to pause enrollment, or modify the dose and/or schedule of the cohorts, will be determined by the Sponsor in agreement with Steering Committee. Decisions to pause enrollment or stop cohorts or modify dose and/or schedule of the cohorts of the study will be communicated promptly to Investigators, to the Institutional Review Boards (IRBs)/Ethics Committees (ECs) (as applicable), and will be implemented in a protocol amendment which will be submitted to the appropriate regulatory authorities.

Drug-drug Interactions

CC-90011

Drug-drug interactions have not been investigated in clinical studies. In vitro studies have shown that CC-90011 is primarily metabolized by CYP3A4/5. Hence, drugs that are known strong inducers or inhibitors of this enzyme should not be co-administered with CC-90011. Should use

of these drugs become necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-90011. Examples of these drugs are described in the protocol.

In view of the potential for thrombocytopenia, nonsteroidal anti-inflammatory drugs and aspirins (aspirin dose ≤ 150 mg is allowed) should be avoided if possible and paracetamol or acetaminophen, should be administered instead.

Nivolumab

Nivolumab is a human monoclonal antibody, as such pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab.

Pregnancy, Lactation, and Fertility

Pregnant and lactating women are excluded from the proposed study.

CC-90011 has not been studied in pregnant women and the effects on the human fetus are unknown. CC-90011 should not be administered to pregnant women. No reproductive or fertility studies have been conducted with CC-90011. Therefore, prohibition of semen donation and fathering children for male subjects, and conceiving or donating ova for female subjects, is recommended for the appropriate follow-up period, as specified in the study protocol.

There are no data on the use of nivolumab in pregnant women. Studies in animals have shown embryofoetal toxicity. Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore, nivolumab has the potential to be transmitted from the mother to the developing foetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Studies to evaluate the effect of nivolumab on fertility have not been performed. Thus, the effect of nivolumab on male and female fertility is unknown.

It is not known whether CC-90011 or its metabolites are excreted in human milk. There are no data on the presence of nivolumab in human milk, the effects on the breastfed child, or the effects on milk production.

Female subjects of childbearing potential must have a negative serum or urine pregnancy test prior to Day 1 dosing with study treatment and must agree to have pregnancy tests as specified in the study protocol. Female subjects of childbearing potential must agree to use effective contraception while participating in the study and for the appropriate follow-up periods, as specified in the study protocol.

Males must practice true abstinence or agree to use barrier contraception (latex condom recommended) when engaging in sexual activity with pregnant females or females of childbearing potential from the time of signing the informed consent form and for the appropriate protocol-specified time periods, even if he has undergone a successful vasectomy.

Women should not breastfeed while receiving CC-90011 or nivolumab and for any subsequent protocol specified time periods.

Phototoxicity

Comprehensive studies to evaluate the phototoxicity potential of CC-90011 have not been conducted. As a precautionary measure, it is recommended that subjects avoid prolonged exposure to ultraviolet (UV) light, wear protective clothing and sunglasses, and use UV-blocking topical preparations while taking study treatment.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19)

At this time, the risk of COVID-19 in subjects receiving CC-90011 is unknown. Current available clinical data from the ongoing CC-90011-ST-002 study suggest an overall favorable safety profile and no specific evidence of elevated risk of infection. However, since at least a theoretical risk of increased infection rates cannot be ruled out, measures to mitigate risk associated specifically with COVID-19 will include the following:

- Continuous safety assessments will be utilized by the Investigators and Sponsor to determine whether additional safety measures are required. In addition, AEs and SAEs associated with confirmed or suspected SARS-CoV-2 infection will be collected from the date the subject signs informed consent until 100 days following discontinuation of study treatment. Adverse events will be reviewed on an ongoing basis by the Medical Monitor (or designee) and Global Pharmacovigilance and Epidemiology representatives to monitor for any safety signals or trends. The testing capability for SARS-CoV-2 to provide prompt results is not uniformly available. Due to these challenges, testing for SARS-CoV-2 will be deferred to local or regional policies. However, study subjects who test positive for SARS-CoV-2 during screening may be rescreened after meeting criteria in Section 6.1.1 of the protocol.
- Subjects with previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to screening are excluded until symptoms have completely resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the subject at a higher risk of receiving investigational treatment.
- Subjects currently in other interventional trials for COVID-19 may not participate in the study until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine prior to screening, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the Investigator and the Medical Monitor. It is also advised to avoid overlap of study treatment and vaccine administration, if possible (for example, at least 2 days, preferably 7 days apart), given that adverse events related to vaccine administration may confound potential study treatment infusion reactions.
- SARS-CoV-2 may have short- and long-term impact on the study population, which may affect the safety profile and outcome of investigational products. Thus, serologic testing will be implemented at screening, during study treatment, after a documented

or suspected SARS-CoV-2 infection, and at follow-up for potential future measurements of anti-SARS-CoV-2 serology.

- Dose delay and criteria to resume study treatment in cases when a subject develops confirmed or suspected SARS-CoV-2 is included in Section 7.4.5 of the protocol.

It is important to acknowledge the widespread impact of SARS-CoV-2 and the potential risks SARS-CoV-2 may have on this study population. However, there are limited treatment options available to individuals with advanced lung cancer who have a poor prognosis and few, if any, curative options. The absence of other available treatments supports the urgent need to develop therapeutic options for these serious diseases while not negating the implementation of mitigation measures to protect the safety of the study population.

4 CONCLUSIONS

This protocol amendment 3, is being done to modify the survival follow-up period by removing the up to 2-year duration and adding in that survival follow-up the 100-day safety follow-up visit of the last subject on study

Refer to the protocol for complete detailed changes.

The LSD-1 inhibition could prove to have a role in treating tumors resistant to current immune check-point blockade. CC-90011 has the potential to mitigate primary and acquired resistance to ICI, due to its expected reversal of the CSC phenotype and T cell exclusion in SCLC and sqNSCLC.

This multi-cohort lung cancer study will evaluate the ability of CC-90011 to increase response rates in 3 different lung cancer populations: PD-1 inhibitor naïve (Cohort A, SCLC) and a PD-1 inhibitor "experienced" (Cohort B, SCLC; and Cohort C, sqNSCLC) when given in combination with nivolumab.

Nivolumab is associated with immune-mediated adverse events. CC-90011 has mainly haematologic toxicities and has not been associated with immune mediated adverse events. During the conduct of this study we will be carefully monitoring the combined safety profile and how it may differ from the known monotherapy safety profiles.

Subject enrollment into this study will be evaluated with strict exclusion and inclusion criteria. Subjects will be monitored for possible toxicity through laboratory tests including haematology panel and chemistry panel in accordance with the schedule described in the protocol. The protocol provides detailed guidance on dose adjustments of study treatments for treatment related toxicities. Ongoing safety evaluation will be conducted and stopping criteria are defined in the protocol.

The risk-benefit assessment to support the use of the combination of CC-90011 and nivolumab in patients considers the potential adverse effects of the drug and its potential benefit to the patients. The safety profiles seen with CC-90011 and nivolumab are clinically manageable and appropriate measures to monitor and treat any expected safety events, as well as guidance to manage SARS-CoV-2/ COVID-19, have been incorporated into the protocol. Therefore, the combination of CC-90011 and nivolumab has an acceptable risk-benefit profile and supports the development in patients with advanced cancers.

5 REFERENCES

Refer to the CC-90011 IB, nivolumab IB and study protocol for the full list of references.

Opdivo ® (nivolumab) [Summary of Product Characteristics]. Ireland: Bristol-Myers Squibb Pharma EEIG; 2015. https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf. Accessed September 23, 2020

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this protocol amendment is to include a risk benefit assessment and additional language for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus-19 (COVID-19), as well as to update nivolumab guidance for male contraception and update adverse event management algorithms based on the nivolumab Investigator's Brochure (IB) version 19 addendum 01 and to extend pharmacokinetics and immunogenicity collection to all cohorts.

Significant changes included in this amendment are summarized below:

- SARS-CoV-2/COVID-19

In 2019, a new coronavirus was identified as the cause of a widespread disease outbreak. As a result, health authorities, including the European Medicines Agency (EMA) have issued guidance on the management of clinical trials during the COVID-19 pandemic. In consideration of this guidance, the safety of study subjects and risks of involvement particularly in the times of COVID-19 was assessed against the anticipated benefit of study treatment, and additional measures to mitigate the risk have been incorporated in this amendment.

- Added Section 1.3.4 Benefit/Risk Assessment Due to SARS-CoV-2/COVID-19 infection to follow EMA guidance as referenced above.
- An additional Exploratory Objective and Study Endpoint to assess the impact of SARS-CoV-2 serologic status on subjects and to support health authority requests. Exploratory Endpoints will include measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or immunoglobulin G [IgG]) and the potential association between these measurements and selected endpoints related to safety, efficacy, and/or biomarkers. To support this exploratory analysis, SARS-CoV-2 serology will be taken at screening, every 6 months during study treatment, approximately 4 weeks after a documented or suspected SARS-CoV-2 infection, and at follow-up. These collection timepoints are outlined in Table 6 and Table 10, and an additional footnote has been added to the tables for clarification.
- The Exclusion Criteria has been updated to include SARS-CoV-2/COVID-19 relevant information. Exclusion criterion 2 and 21 have been removed and condensed into Exclusion Criterion 1 to reduce redundancies and increase readability; Exclusion Criterion 22 and 23 have been added.

  1. Subject has any significant medical condition, including active or uncontrolled infection, or the presence of laboratory abnormalities, or psychiatric illness which places the subject at unacceptable risk if he/she were to participate in the study.

  22. Subject who is currently in other interventional trials, including those for COVID-19, may not participate in Bristol Myers Squibb (BMS) or Celgene Corporation clinical trials until the protocol specific washout period is achieved. If a study subject has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of

the vaccine or investigational product is stabilized, as determined by discussion between the Investigator and the Medical Monitor.

23. Previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to screening.

    a. Acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the subject at a higher risk of receiving investigational treatment.

– Sections 6.1.1 Resting During Screening Period and 7.4.5 Dose Delay and Criteria to Resume in Case of SARS-CoV-2 Infection have been added to address the criteria a subject needs to meet to continue study and/or treatment when there is a confirmed or suspected SARS-CoV-2 infection.

– Additional guidance has been added in Section 8.2 Permitted Concomitant Medications and Procedures regarding COVID-19 vaccines and administration.

– Added language in Section 5 Table of Events and 10.2.6 Outcome to reinforce the continuous monitoring and reporting of adverse events, including serious and non-serious, associated with confirmed or suspected SARS-CoV-2 infection.

Revised sections: Protocol Summary, Section 1.3.4 (added, Benefit/Risk Assessment Due to SARS-CoV-2/COVID-19 Infection), Section 2 (Study Objectives and Endpoints), Section 4.3 (Exclusion Criteria), Section 5 (Table of Events), Section 6 (Procedures), Section 6.1.1 (added, Retesting During Screening Period), Section 6.7.1 (added, Other Assessment), Table 10 (added, SARS-CoV-2 Samples Schedule), Section 7.4.5 (Dose Delay and Criteria to Resume in Case of SARS-CoV-2 Infection), Section 8.2 (Permitted Concomitant Medications and Procedures), Section 10.2.6 (Outcome).

- Nivolumab Guidance for Male Contraception and Adverse Event Management Algorithms per Nivolumab IB Version 19 Addendum 01

The nivolumab IB version 19 addendum 01 includes adverse event management algorithms based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) and the removal of male contraception language after last dose of nivolumab. The protocol has been revised to align with this updated language and guidance.

Revised sections: Section 4.2 (Inclusion Criterion Number 11), Section 7.4.3 (Criteria for Nivolumab Dose Management), Table 14 and footnotes (Recommended Treatment Modifications for Nivolumab), Appendix F (Nivolumab Management Algorithms).

- Addition of Pharmacokinetics and Immunogenicity Sample Collection for Nivolumab in all 3 Cohorts

The emerging platelet (safety) profile of CC-90011 and nivolumab combination and decision to proceed at a reduced dose of CC-90011 supports assessment of benefit/risk from the perspective of population pharmacokinetics (PK) and exposure-response relationship with the safety and efficacy endpoints for the combination treatment. From available data thus far, it appears that there is some synergistic thrombocytopenia at precedented exposures of CC-90011; thus, having a composite exposure-response model for this combination will help to better characterize the overall thrombocytopenia profile. Currently, protocol amendment 1 collects nivolumab

immunogenicity (IMG) samples from Cohort C at the scheduled timepoints: Cycle 1 Day 1 pre-dose, Cycle 2 Day 1 pre-dose, Cycle 3 Day 1 pre-dose, and Every 4th cycle after Cycle 3 Day 1 pre-dose. In this amendment, both PK and IMG sample collections for nivolumab at the previously scheduled time points will be added and extended to all 3 cohorts.

Revised sections: Protocol Summary (Exploratory Objective), Section 2 (Study Objectives and Endpoints), Section 5 (Table of Events), Section 6.2 (Treatment Period), Section 6.5.1 (Collection of Blood Samples for Nivolumab Pharmacokinetics and Immunogenicity).

The amendment also includes other clarifications and administrative changes:

- Removal of Medical Monitor address
- Update in Section 1.2.5 to align with CC-90011 IB edition 6.0.
- Update in Section 1.2.6.1 to align with current version of Nivolumab Essentials Protocol Elements
- Update in Section 7.2.1 and 8.1 to include caution of avoiding grapefruit juice during study treatment.
- Update in Table 5 footnote and Section 7.2.2 to clarify nivolumab dosing window.
- Update in Section 15.1 to clarify that monitoring can include on-site or remote visits.
- Update in Section 15.3 to align with updated Sponsor guidance on Investigational Medicinal Product Quality Complaint reporting.
- Minor formatting, editorial changes and corrections throughout.

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this protocol amendment is to address the 2 serious adverse events (SAEs) reported in the first two subjects treated in Study CC-90011-ST-002, and the resulting implementation to reduce the starting dose of CC-90011 to 40 mg. Implementation of this dose reduction was communicated to all participating sites through an administrative letter on 18 Aug 2020. This dose reduction is consistent with Protocol CC-90011-ST-002 language in Section 7.3.2 and the 2 SAEs of Grade 4 thrombocytopenia are consistent with the known safety profile of CC-90011. Therefore, the implementation of this dose reduction is not considered an urgent safety measure. The protocol is also being amended for other topics, clarifications, and administrative changes and are summarized below.

Significant changes included in this amendment are summarized below:

- **Reduction of CC-90011 Starting Dose to 40 mg**

Two SAEs of Grade 4 thrombocytopenia were reported in the first 2 subjects in this ongoing Study CC-90011-ST-002. On 14 Aug 2020, Celgene reviewed the 2 SAEs with the treating Investigator, the Steering Committee, and the Medical Monitor. On Cycle 1 Day 1 (C1D1), both subjects, who are also from the same site, received their first dose of CC-90011 60 mg and nivolumab 480 mg, and on C1D8, they received their second dose of CC-90011 60 mg. Both subjects were treated with prior chemotherapy, and followed a similar course, with normal platelet count at baseline and a decrease in platelet count (within normal protocol limits) at C1D8. On C1D15, both subjects were diagnosed with Grade 4 thrombocytopenia for which they were hospitalized and have since recovered. Both subjects received platelet transfusions and demonstrated an increase in platelet count over the course of a week. The events were assessed by the Investigator as related to CC-90011. Per protocol, study treatment was resumed upon resolution of the events with a dose reduction of CC-90011 to 40 mg. Thrombocytopenia occurred in both subjects around C1D15 and were consistent with observations from the early CC-90011 monotherapy studies.

As a result of the first 2 subjects developing Grade 4 thrombocytopenia, which both followed a similar course, Celgene in agreement with the Steering Committee concluded that new subjects enrolled in Study CC-90011-ST-002 will receive CC-90011 at a reduced starting dose of 40 mg unless otherwise determined during the ongoing safety evaluation in Section 7.3.1.1. The dose of nivolumab will remain at 480 mg.

Revised sections: Section 1.2.5.1.3 (added, Study CC-90011-ST-002), Sections 7.3.1.1 (added, Safety Evaluation for CC-90011 Starting Dose of 40 mg)

- **Safety Evaluation for CC-90011 Starting Dose of 40 mg**

The same stopping criteria as specified in Sections 7.3.1 and 7.3.2 will be applied to the reduced starting dose of 40 mg. To further evaluate if the recommended phase 2 dose of CC-90011 60 mg as established in the first-in-human study can be safely administered and in order to maximize the potential efficacy of CC-90011 and level of target engagement (see first-in-human data, Figure 2), re-escalation to 60 mg may be considered after review of the overall data and AEs/SAEs by the Sponsor in agreement with the Steering Committee. Specifically, if in the first 2 cycles, there are no reports of Grade 4 thrombocytopenia or Grade 3 or 4 neutropenia, in any of the 6 subsequent subjects (without distinction of cohorts) who received 40 mg, then re-escalation

of the starting dose to 60 mg for subsequent subjects may be considered. The decision to re-escalate the starting dose to 60 mg will be determined by the Sponsor in agreement with the Steering Committee.

If the starting dose is re-escalated to 60 mg, an additional 4 subjects (without distinction of cohorts) will be treated so that 6 subjects in total (including the 2 subjects in which Grade 4 thrombocytopenia [n=2]and Grade 3 neutropenia [n=1] was reported) will have received 60 mg. There will be staggered dosing, where the second subject to receive 60 mg will not be dosed until at least 15 days after the first subject has been treated and safety has been reviewed. This sentinel dosing scheme may or may not be continued for the rest of the 60 mg subjects, depending on the findings in the first subject and the overall safety profile to date.

The stopping criteria in Sections 7.3.1 and 7.3.2 will be applied to these 6 subjects. Therefore, if in the first 2 cycles, there are no reports of Grade 4 thrombocytopenia and 1 or less reports of Grade 3 or 4 neutropenia, in any of the 4 subsequent subjects who received 60 mg, then 60 mg will be declared as the starting dose of CC-90011 and the dose to continue with in this study. If in the first 2 cycles, there is at least 1 report of Grade 4 thrombocytopenia or at least 2 reports of Grade 3 or 4 neutropenia, in any of the 4 subsequent subjects who received 60 mg, then 40 mg will be declared as the starting dose of CC-90011 and the dose to continue with in the study.

Revised sections: Section 7.3.1 (Initial Safety Evaluation), Section 7.3.1.1 (added, Safety Evaluation for CC-90011 Starting Dose of 40 mg)

- **Addition of Blood Samples Collection for Assessment of Nivolumab Immunogenicity (only applicable to Cohort C, squamous non-small cell lung cancer)**

Blood samples will be collected to measure immunogenicity of nivolumab in squamous non-small cell lung cancer subjects (NSCLC) to assess the prevalence of anti-nivolumab antibodies (ADA) in this cohort of subjects. Samples will be collected pre-dose on the following visits: Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and Day 1 of every 4th cycle after Cycle 3. The assessment of nivolumab immunogenicity in this cohort of subjects is added as an exploratory objective. Collection of nivolumab ADA blood samples will enable exploration of nivolumab ADA incidence rate, and its potential impact on selected efficacy and safety endpoints, in the comibation with CC-90011, as mentioned in the protocol. Nivolumab ADA incidence in combination with ipilimumab is higher in NSCLC compared to nivolumab monotherapy, with ~40% versus 10%, respectively (CA209-227 Clinical Study Report; CA209-9LA Clinical Study Report). The nivolumab ADA incidence rate is unknown in combination with CC-90011. As such, these data will help to further characterize nivolumab immunogenicity in NSCLC.

Revised sections: Protocol Summary, Section 2 (Study Objectives and Endpoints), Section 5 (Table of Events), Section 6.5.1 (added, Collection of Blood Samples for Nivolumab Immunogenicity), Section 9.9.4 (Pharmacokinetic Analysis)

[redacted]

- **Removal of Preliminary Efficacy by imRECIST as an Exploratory Endpoint and Objective**

The exploratory objective to assess the preliminary efficacy of CC-90011 in combination with nivolumab based on Investigator assessed immune modified Response Evaluation Criteria in Solid Tumors (imRECIST) has been removed. This method of assessment is not yet thoroughly validated or established in the clinical setting. Furthermore, this study has a small sample size and therefore this endpoint would not provide additional value.

Revised sections: Protocol Summary, Section 2 (Study Objectives and Endpoints), Section 6.4 (Efficacy Assessment)

- **Addition of Time to Response and Time to First Subsequent Therapy as Secondary Endpoints and Objectives and Addition of Disease Control Rate at 12 weeks as an Exploratory Endpoint and Objective**

To further support the primary and secondary objectives in the original protocol, time to response and time to first subsequent therapy were added as secondary endpoints and disease control rate as an exploratory endpoint. Time to response, time to first subsequent therapy and disease control rate will provide important context to the primary endpoint, overall response rate and the secondary endpoint of overall survival across the three different cohorts. Additionally, considering the mechanism of action of CC-90011 and the proposed mechanism of CC-90011 in combination with nivolumab, time to response and disease control rate may be worthwhile to explore and will provide information that could guide future studies with this combination.

Revised sections: Protocol Summary, Section 2 (Study Objectives and Endpoints), Section 9.6 (Efficacy Analysis)

This amendment also includes other minor changes that are clarifications to existing information and/or corrections of some inadvertently inaccurate statements:

- Update of Medical Monitor email address.
- Change of Celgene Therapeutic Area Head.
- Update of Section 1.2.5 to align with CC-90011 Investigator's Brochure (IB) Edition 5.
- Update in Sections 2, 9.6.2, and 9.7 to remove physical exam from safety assessment analysis.
- Clarification of language in Protocol Summary, Sections 3.1 and 7.2.1 to reflect the CC-90011 dose that subjects will be receiving.
- Correction in Exclusion Criteria 16b to clarify that adrenal replacement steroid doses > 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease, in alignment with Section 8.1.

- [redacted]
- Addition of footnote to Table 6 to clarify nivolumab dosing window.
- Update of language in Section 6.2 to clarify that on-treatment vital signs will be source documented and collected in the electronic case report form.
- Update of language in Section 6.3.1 to clarify that adverse event evaluation for nivolumab should include assessment by the Investigator regarding whether it is considered immune-mediated.
- Addition of language in Section 6.4 to clarify that all subjects with evidence of tumor response (complete response or partial response) should have the response confirmed with repeat assessments at the next scheduled scan, but no less than 4 weeks after initial response.
- Update in Section 6.4.1 to the treatment beyond progression timepoint of a follow-up scan to 6-8 weeks of the original progression of disease in accordance to the original protocol schedule of tumor assessments.
- Clarification of language in Section 6.5 regarding the pharmacokinetic blood sample collection timepoints to be in relation to CC-90011 dose.
- Addition of footnote language to Table 8 to clarify that triplicate electrocardiogram (ECG) should be done within 2 minutes at each nominal timepoint.
- [redacted]
- Clarification in Section 7.3.2 regarding communication to regulatory authorities.
- Update in Table 10 and Section 7.4.2 to clarify permitted CC-90011 dose reductions and adjustments.
- Addition of language in Section 7.4.3 to include consultation with the Medical Monitor (or designee) regarding re-initiating nivolumab treatment in a subject with a dosing delay lasting > 10 weeks.
- Clarification in Section 7.4.3 that adverse event management of nivolumab should follow Common Terminology Criteria for Adverse Events (CTCAE) version 4 in alignment with the current nivolumab Investigator Brochure.
- Correction of language in Section 7.5 regarding subject assignment number.
- Update in Section 9.2.1 to the definition of Enrolled Population, which will consist of all subjects who signed the informed consent form and obtained a subject number.
- Minor formatting and editorial changes and corrections throughout.