DISCLOSURE

REDACTED PROTOCOL AMENDMENT 1

BGB-A317-NSCL-001

A PHASE 3, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED STUDY OF TISLELIZUMAB (BGB-A317) PLUS CHEMORADIOTHERAPY FOLLOWED BY TISLELIZUMAB MONOTHERAPY IN NEWLY DIAGNOSED, STAGE III SUBJECTS WITH LOCALLY ADVANCED, UNRESECTABLE NON-SMALL CELL LUNG CANCER

The information contained in the attached report is the property of Celgene and should not be shared or used for any purpose other than that for which it was provided.

Celgene is committed to providing information about its clinical trials to researchers and patients with the goal of furthering science and enhancing healthcare worldwide. Laws and regulations require, however, that Celgene protects patient privacy. The company may further have legal or contractual obligations not to disclose commercial or technical information provided by or related to certain partner companies or vendors.

The attached report is presented in its original format, but certain information has been redacted in order to comply with the aforementioned obligations or to protect Celgene's confidential commercial information. The redactions are based on the following principles:

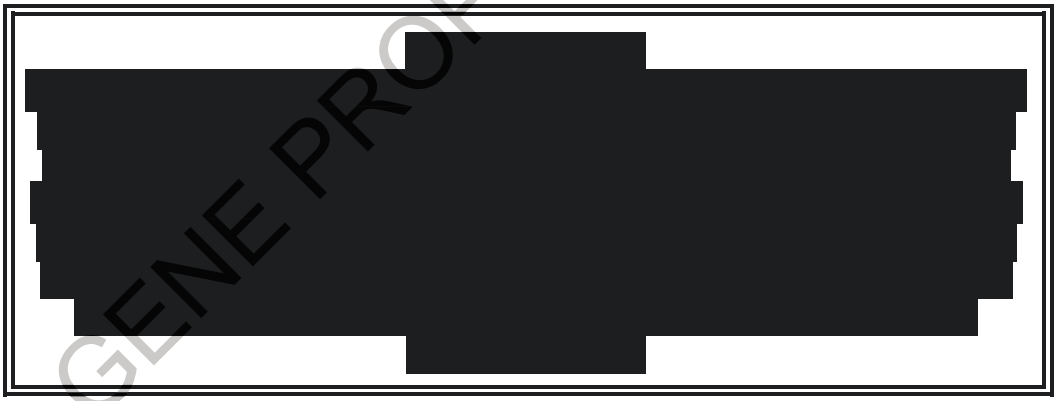
- Redacted information has been replaced by grey space, maintaining original spacing and pagination.
- Any information that might allow the identification of individuals has been redacted for anonymization.
- Attachments to this report that contain confidential information are not made available. Such attachments include those that contain identifiable patient information, such as subject listings, narratives, and profiles. They also may contain confidential commercial information such as methodologies, and hypothesis generating and exploratory analyses.
- Cross-references to these attachments (such as links to subject listings in Section 16.2) are not redacted from the body of the report. However, the hyperlinks in the electronic document are no longer functional.
- Information about Celgene vendors and their services are redacted because many contracts prohibit disclosure of that information. Further, laws and regulations prevent us from disclosing certain information about our vendors or their services because it is protected by copyright.

Information about Celgene's redaction policies and the availability of additional data from this report may be found at http://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/.

CELGENE PROPRIETARY INFORMATION

A PHASE 3, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED STUDY OF TISLELIZUMAB (BGB-A317) PLUS CHEMORADIOTHERAPY FOLLOWED BY TISLELIZUMAB MONOTHERAPY IN NEWLY DIAGNOSED, STAGE III SUBJECTS WITH LOCALLY ADVANCED, UNRESECTABLE NON-SMALL CELL LUNG CANCER

PROTOCOL NUMBER:	BGB-A317-NSCL-001
DATE FINAL:	21 May 2018
Amendment 1 FINAL:	20 Sep 2018
EudraCT NUMBER:	2018-001132-22
IND NUMBER:	138358
SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901



CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number: CCI [redacted]

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information:
Name: PPD
Title: PPD
Address: 86 Morris Avenue, Summit, NJ 07901
Phone: PPD
Email: PPD

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.

Back-up 24-hour Global Emergency Contact Call Center: PPD

CELGENE PROPRIETARY INFORMATION

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
PPD	
Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.	

CELGENE PROPRIETARY INFORMATION

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.	

CELGENE PROPRIETARY INFORMATION

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

CELGENE PROPRIETARY INFORMATION

PROTOCOL SUMMARY

Study Title

A Phase 3, randomized, blinded, placebo-controlled study of tislelizumab (BGB-A317) plus chemoradiotherapy followed by tislelizumab monotherapy in newly diagnosed, stage III subjects with locally advanced, unresectable non-small cell lung cancer.

Indication

This trial will enroll treatment-naive subjects with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC).

[redacted] The study protocols BGB-A317-NSCL-001 and BGB-A317-NSCL-001C have a total combined enrollment target of 840 subjects. The data from both study protocols will be collected into one database and the statistical analyses as described in Section 9 will be performed on the combined total number of subjects randomized into either the main protocol or the companion protocol. A single independent data monitoring committee (IDMC) and blinded independent central review will be utilized for these 2 study protocols.

Objectives

Primary Objective

The primary objective is to compare the progression free survival (PFS) of tislelizumab in combination with concurrent chemoradiotherapy (cCRT) followed by tislelizumab monotherapy (Arm 1) versus cCRT alone (Arm 3); in addition, tislelizumab given sequentially after cCRT (Arm 2) will be compared with cCRT alone (Arm 3) in newly diagnosed stage III subjects with locally advanced unresectable non-small cell lung cancer (NSCLC).

Secondary Objective(s)

The secondary objectives are to:

- Compare overall survival (OS) (key secondary objective)
- Compare OS at 24 months (key secondary objective)
- Compare centrally-assessed objective response rate (ORR) (key secondary objective)
- Compare centrally-assessed duration of response (DOR)
- Compare proportion of subjects alive and progression-free at 12 and 18 months (APF12, APF18)
- Compare time to death or distant metastasis (TTDM)
- Compare safety and tolerability of tislelizumab in combination with concurrent chemoradiotherapy (cCRT) followed by tislelizumab monotherapy versus cCRT alone, and tislelizumab given sequentially after cCRT versus cCRT alone

CELGENE PROPRIETARY INFORMATION

- Compare impact on patient-reported lung cancer symptoms (appetite loss, cough, chest pain, dyspnea, and fatigue) assessed by European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC QLQ-C30) and its lung cancer module (EORTC QLQ-LC13).
- Compare the proportion of subjects who received at least one dose of tislelizumab or placebo in the monotherapy phase before progression in Arm 1 versus Arm 2 and 3.

[redacted]

Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled multicenter global study designed to compare the efficacy and safety of tislelizumab in combination with concurrent chemoradiotherapy (cCRT) followed by tislelizumab monotherapy versus cCRT alone, and tislelizumab given sequentially after cCRT versus cCRT alone, in newly diagnosed stage III subjects with locally advanced, unresectable NSCLC.

The primary endpoint is centrally-assessed progression free survival (PFS) in the intent-to-treat (ITT) population. Newly diagnosed stage III subjects with histologically confirmed, locally advanced, unresectable NSCLC are eligible.

Approximately 840 subjects will be randomized in a 1:1:1 ratio to receive the study drug tislelizumab or placebo in the following 3 arms:

- CCI [redacted]

CELGENE PROPRIETARY INFORMATION

- CCI [redacted]

The choice of chemotherapy regimen to be used as part of study treatment will be at the Investigator's discretion, consisting of either 2 cycles of cisplatin plus etoposide or weekly carboplatin plus paclitaxel given during radiation therapy (RT) for 6 weeks. Radiation therapy should start concurrently with chemotherapy in Cycle 1 of tislelizumab or placebo. If local technical or logistical circumstances do not allow for the start of RT at the beginning of Cycle 1, a 3-day administrative window to start RT will be allowed. Tislelizumab or placebo will be given starting from Cycle 1 Day 1 (C1D1) in the cCRT phase, and continued in the monotherapy phase for a duration of 12 months following the completion of cCRT, or until disease progression, unacceptable toxicity, or treatment discontinuation for another reason.

Randomization will be stratified by age (CCI [redacted]), chemotherapy regimen (CCI [redacted]), and region (CCI [redacted]). [redacted]

Safety and efficacy will be monitored by an IDMC. CCI [redacted]

For immune therapies such as tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms, leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic progressive disease is suspected by the Investigator to reflect pseudoprogression, the subject may continue treatment until progressive disease is confirmed by repeated imaging at least 4 weeks later but not exceeding 6 to 8 weeks from the date of initial documentation of progressive disease, provided the following criteria are met:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values).
- Stable ECOG performance status (≤ 1).

CELGENE PROPRIETARY INFORMATION

- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention.

Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform subjects that this practice is not considered standard in the treatment of cancer. The decision to continue study drug(s) beyond initial Investigator-assessed progression must be discussed with the Sponsor medical monitor and documented in the study records.

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 remain blinded to the study data by arm.

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

Study Population

Adult subjects with newly diagnosed, histologically confirmed, locally advanced, unresectable stage III NSCLC for whom chemoradiotherapy is appropriate will be randomized.

Subjects with epidermal growth factor receptor (EGFR) sensitizing mutations or anaplastic lymphoma kinase (ALK) gene translocations may be randomized up to approximately 10% of the total randomized population.

Length of Study

Enrollment is expected to take approximately 28 months to complete. To reach final PFS analysis, 580 PFS events are expected across the 3 arms in approximately 35 months following randomization of the first subject.

The total study duration is estimated to be approximately 61 months from the randomization of the first subject to the final analysis, conducted when approximately 572 overall survival (OS) events have occurred across the 3 arms.

The End of Trial is defined as either the date of the last visit of the last subject to complete the posttreatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary [redacted], as prespecified in the protocol, whichever is the later date.

Study Treatments

Anti-PD-1 therapy/Placebo

Tislelizumab or placebo: CCI [redacted]

Radiation therapy

Thoracic RT will be given 5 days per week for 6 weeks, in once daily fractions, 2 Gy per fraction, to a target dose of 60 Gy in 30 fractions. Please refer to Section 7.2.2 for RT administration.

CCI [redacted]

[redacted]

CELGENE PROPRIETARY INFORMATION

[redacted]

Tislelizumab or placebo will be given starting from C1D1 in the cCRT phase, and will continue in the monotherapy phase for a duration of 12 months following the completion of cCRT, or until disease progression, unacceptable toxicity, or treatment discontinuation for another reason. The total duration of tislelizumab (Arm 1), placebo followed by tislelizumab (Arm 2), or placebo alone (Arm 3) will be approximately 14 months, including the cCRT period.

Subjects may remain on treatment until disease progression, unacceptable toxicity, initiation of a subsequent anticancer therapy, withdrawal of consent, subject refusal, lost to follow-up, physician decision, or death.

Overview of Key Efficacy Assessments

All subjects will be evaluated for tumor response and progression by Investigator assessment for therapeutic decisions according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines, at screening and every 6 weeks (± 7 days) from randomization for the first 36 weeks, and every 9 weeks (± 7 days) from Week 36 onwards until documented disease progression, start of subsequent anticancer therapy, or withdrawal of consent.

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

The primary endpoint of PFS will be based on response assessments evaluated by blinded independent central review.

In the follow-up phase, subsequent anticancer treatment administered following the last dose of investigational product (IP) and survival will be followed every 3 months (± 14 days) until death, withdrawal of consent, or lost to follow-up, whichever occurs first, or the End of Trial.

Overview of Key Safety Assessments

All subjects will be monitored for adverse events starting from the time the subject signs the informed consent form (ICF) until 30 days after the last dose of study treatment (tislelizumab/placebo, chemotherapy, or RT), as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to study treatment. Subjects will also be monitored for immune related adverse events (serious or nonserious) starting from the time the subject signs the ICF until 90 days after the last dose of tislelizumab or placebo, regardless of whether or not the subject starts a new anticancer therapy. All AEs and SAEs considered related to RT will be collected at any time after the first dose of RT, including late radiation toxicities. A thorough evaluation of medical conditions, including analysis of pulmonary function, left ventricular ejection fraction (LVEF), C-reactive protein, hepatitis B virus and hepatitis C virus (HBV and HCV), will be conducted during screening. Documented physical examination (PE), vital signs, laboratory assessments (eg, serum chemistry, hematology, coagulation, thyroid function), 12-lead electrocardiogram (ECG), ophthalmologic examination, urinalysis, HBV and HCV (if positive at screening), and Eastern Cooperative Oncology Group (ECOG) performance status will be monitored regularly. Preventative measures

CELGENE PROPRIETARY INFORMATION

will be taken to avoid pregnancy in study subjects or their partners, and females of child-bearing potential will have pregnancy testing performed at screening and then throughout the study. The full schedule of assessments is described in Table 4 and Section 6.

Statistical Methods

The primary objective of the study is to assess the efficacy of either one of the tislelizumab arms (Arm 1 or Arm 2) compared with the control arm (Arm 3) in terms of PFS. There will be one interim and one final analysis for PFS, and one interim and one final analysis for OS, respectively. CCI [redacted]

Efficacy Analyses

The primary efficacy analyses will be based on the ITT population. The primary and key secondary endpoints will also be analyzed using the per protocol population.

The primary endpoint, PFS, is defined as the time from randomization to the time of progression (based on blinded independent reviewer assessment using RECIST v1.1) or death, whichever is earlier. Subjects without progression or death will be censored according to censoring rules similar to those described by the Food and Drug Administration (FDA) in the FDA Guidance for Industry Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (FDA, 2007). The distribution of PFS will be estimated using the Kaplan-Meier method. The comparison of PFS between treatment arms (Arm 1 versus Arm 3 or Arm 2 versus Arm 3) will be conducted using a stratified log-rank test with age CCI [redacted]), chemotherapy regimen CCI [redacted]), and region (CCI [redacted] as stratification factors. The hazard ratio (between Arm 1 or Arm 2 versus Arm 3) and the corresponding 95% confidence interval will also be provided based on a stratified Cox proportional hazard model. The median PFS (with 95% confidence interval) and estimation of PFS rate (with 95% confidence intervals) for specific time points (eg, 3 months, 6 months etc.) will be provided for each treatment arm.

The first key secondary endpoint, OS, is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of analysis will be censored at the last-known-to-be-alive date. The distribution of OS will be estimated using Kaplan-Meier method. A stratified log-rank test will be used to compare treatment groups in OS. The median OS (with 95% confidence interval) and estimation of OS rate (with 95% confidence intervals) for different timepoints will be provided by treatment arm. The hazard ratio (between Arm 1 or Arm 2 versus Arm 3) and the corresponding 95% confidence interval will also be provided based on a stratified Cox regression model.

The second key secondary endpoint, OS at 24 months (OS 24), is defined as the proportion of subjects alive at 24 months. The point estimate and the corresponding 95% confidence interval for each treatment arm will be estimated using the Kaplan-Meier method. The treatment comparisons for OS 24 will be performed using an approach as described in Klein, 2007.

CELGENE PROPRIETARY INFORMATION

The third key secondary endpoint, objective response rate (ORR), is defined as the percentage of subjects who achieve a complete response (CR) or partial response (PR) based on the blinded independent reviewer assessment using RECIST v1.1 criteria. The ORR for each treatment arm will be summarized using 95% Clopper-Pearson confidence interval. The difference in ORR between treatment arms and the associated 95% Wilson score confidence interval will be provided. A Cochran-Mantel-Haenszel (CMH) test will be used to compare ORR between treatment arms.

Safety Analyses

Safety analyses will be performed based on the safety population. Safety and tolerability will be monitored through continuous reporting of AEs and SAEs, laboratory abnormalities, and incidence of subjects experiencing dose modifications, dose interruptions, and/or premature discontinuation of IP. Descriptive statistics will be provided for summaries of adverse events, clinical laboratory data, and other safety assessments. Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs), defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study treatment up to 30 days following study treatment discontinuation or initiation of new anticancer therapy, whichever occurs first. Treatment-emergent AEs also include all immune-related AEs (irAEs) recorded up to 90 days after the last dose of tislelizumab or placebo, regardless of whether or not the subject starts a new anticancer therapy. All events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized per treatment arms by MedDRA system organ class and preferred terms. Grade 3 or higher TEAEs, SAEs, TEAEs leading to dose reduction and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized per treatment arms by MedDRA system organ class and preferred terms. Additionally, adverse events of special interest for tislelizumab will be summarized in the same manner.

CCI [redacted].

Power and Sample Size

There are 2 primary hypotheses to test in this study:

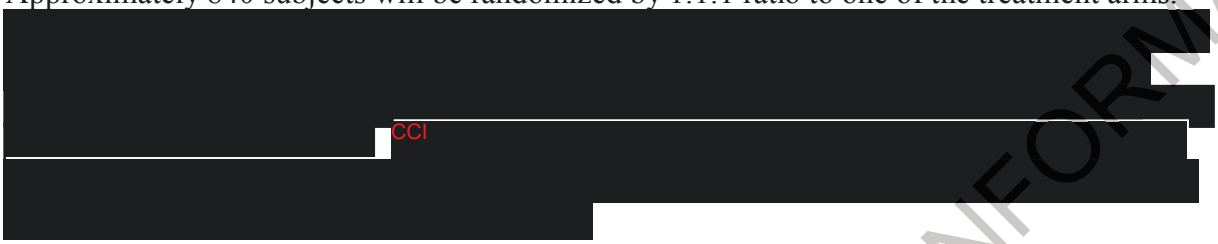
- H_1: Arm 1 ≤ Arm 3 in PFS versus Arm 1 > Arm 3 in PFS
- : Arm 2 ≤ Arm 3 in PFS versus Arm 2 > Arm 3 in PFS

CCI [redacted]

CELGENE PROPRIETARY INFORMATION

A group sequential boundary based on Lan-Demets spending function that approximates the O'Brien-Fleming boundary is calculated for the comparison associated with each of the 2 primary hypotheses for the PFS endpoint. The key secondary endpoint of OS will be tested only if the hypothesis for the primary endpoint PFS is rejected at the interim or the final PFS analysis, in each pairwise comparison of treatment groups (Arm 1 versus Arm 3 or Arm 2 versus Arm 3). In addition, the other 2 key secondary endpoints, OS 24 and ORR, will also be tested if both the PFS and OS hypotheses in the same pairwise comparison of treatment groups are rejected. The overall type one error rate will be controlled using a graphic approach as described by Maurer and Bretz (Maurer, 2013).

Approximately 840 subjects will be randomized by 1:1:1 ratio to one of the treatment arms.



CELGENE PROPRIETARY INFORMATION

TABLE OF CONTENTS

CELGENE PROPRIETARY INFORMATION

CELGENE PROPRIETARY INFORMATION

CELGENE PROPRIETARY INFORMATION

CELGENE PROPRIETARY INFORMATION

CELGENE PROPRIETARY INFORMATION

CELGENE PROPRIETARY INFORMATION

LIST OF TABLES

CELGENE PROPRIETARY INFORMATION

LIST OF FIGURES

[redacted]

CELGENE PROPRIETARY INFORMATION

1. INTRODUCTION

1.1. Disease Background

1.1.1. Non-small Cell Lung Cancer

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 (Globocan, 2012). Globally, across all cancer types, lung cancer is more common in men (16.8%) compared to women (8.8%). As lung cancer can be asymptomatic at early stages, most lung cancers are diagnosed at an advanced stage which is not curable by surgery (American Joint Committee on Cancer [AJCC] Cancer Staging Manual, 2017), resulting in a poor prognosis. Non-small cell lung cancer (NSCLC) is the most common histological type of lung cancer, accounting for 80% to 85% of all lung cancers, and originates from the epithelial cells of the lung with the following major histological subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (National Cancer Institute, 2018).

About one third of subjects with NSCLC present with locally advanced stage III disease, which includes subjects with involvement of locoregional mediastinal lymph nodes or mediastinal organs, with 5-year survival rates of 36% for stage IIIA, 26% for stage IIIB, and 13% for stage IIIC (American Cancer Society, 2018). Some patients with stage IIIA disease can undergo resection, and have improved survival compared to those that are unresectable.

1.1.2. First-line Concurrent Chemotherapy/ Radiation Therapy for Locally Advanced NSCLC

Concurrent chemoradiotherapy (cCRT) has become the standard of care for subjects with locally advanced, unresectable stage III NSCLC (National Comprehensive Cancer Network [NCCN], 2018) (European Society for Medical Oncology [ESMO] guidelines [Postmus, 2017]). Combined modality treatment with chemotherapy and radiation was shown to be superior to radiation therapy alone (Rolland, 2007). The positive outcomes for cCRT have been shown in multiple studies. A meta-analysis from the mid-1990s using updated data on individual subjects from 52 randomized clinical trials (NSCLC Collaborative Group, 1995) and a subsequent meta-analysis of platinum-based chemotherapies from 1764 subjects (Aupérin, 2006) demonstrated that adding sequential or concurrent chemotherapy to radiotherapy improved survival in locally advanced NSCLC. When concurrent versus sequential chemoradiotherapy was compared directly in data for 1205 subjects from 6 clinical trials, there was a significant benefit of cCRT on overall survival (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.74 to 0.95; P = 0.004), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years. For progression-free survival, the HR was 0.90 (95% CI, 0.79 to 1.01; P = 0.07). Concurrent treatment decreased locoregional progression (HR, 0.77; 95% CI, 0.62 to 0.95; P = 0.01), although concurrent treatment was not different from sequential treatment on distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; P = 0.69). Concurrent chemoradiotherapy increased acute esophageal toxicity, but there was no significant difference regarding acute pulmonary toxicity (Aupérin, 2010).

In order to improve outcomes for subjects with unresectable stage III NSCLC, induction and consolidation chemotherapy have also been studied. There was more neutropenia observed with

CELGENE PROPRIETARY INFORMATION

induction chemotherapy with no improvement in overall survival (Vokes, 2007). Consolidation chemotherapy has also not been shown to have any impact on overall survival compared to cCRT alone (Tsujino, 2013). Therefore, cCRT is considered the standard of care for patients with locally advanced, unresectable stage III NSCLC. Of note, the standard of care for patients with stage III NSCLC remains cCRT regardless of epidermal growth factor receptor (EGFR) sensitizing mutations or anaplastic lymphoma kinase (ALK) gene translocations (NCCN, 2018; Postmus, 2017). Epidermal growth factor receptor and ALK targeted agents are not utilized as upfront therapy and are still being investigated in trials such as the Radiation Thoracic Oncology Group (RTOG) 1306 study (Berman, 2016).

Multiple chemotherapy backbone regimens have also been found to be acceptable combination regimens in stage III NSCLC as part of the standard of care for cCRT. Most regimens are combinations of cisplatin with either pemetrexed, etoposide, vinblastine, or vinorelbine. Few studies have been conducted comparing these chemotherapy regimens, and no chemotherapy regimen has been clearly demonstrated to be better than others. Of the chemotherapy doublets that have comparative evidence, cisplatin in combination with either pemetrexed or etoposide has been studied in this stage III NSCLC treatment population. The PROCLAIM multinational trial (Senan, 2016) endeavored to establish whether cisplatin/pemetrexed is superior to cisplatin/etoposide when given concurrently with standard radiation therapy (RT) at 60-66 Gray (Gy), followed by a consolidation phase. Cisplatin/pemetrexed was not found to be superior in OS to cisplatin/etoposide (median overall survival [OS] 26.8 months versus 25.0 months; P = 0.831). Both arms had low incidences of Grades 3 or 4 pneumonitis (< 3%), with no significant differences between arms in treatment discontinuations due to drug-related adverse events (AEs) or drug-related deaths. The PROCLAIM study therefore establishes that outcomes with cisplatin with either pemetrexed or etoposide when used in cCRT with conventional radiation therapy are similar.

Carboplatin with paclitaxel given weekly during radiation is another acceptable cCRT option as recommended by the NCCN guidelines, with the 2 cycles of carboplatin and paclitaxel consolidation considered as optional (NCCN, 2018). This regimen has been evaluated in several studies (Belani, 2005; Vokes, 2007; Yamamoto, 2010; Bradley, 2015) and is commonly used as a first-line treatment for locally advanced, unresectable stage III NSCLC in the US and other countries globally. Weekly carboplatin/paclitaxel was used as part of the chemotherapy regimen backbone in the RTOG 0617 study that evaluated standard versus high doses of radiation to be given concurrently with chemotherapy (Bradley, 2015). A Phase 3 trial of concurrent thoracic radiation in unresectable stage III NSCLC found that weekly carboplatin/paclitaxel was superior to second-generation chemotherapy regimens such as mitomycin/vindesine, weekly irinotecan/carboplatin, or cisplatin or carboplatin as a single agent with radiation therapy (Yamamoto, 2010). Of note, in the Phase 3 PACIFIC study, which evaluated the anti-programmed cell death protein-ligand 1 (PD-L1) inhibitor durvalumab compared to placebo after cCRT, carboplatin with paclitaxel was the most common chemotherapy regimen chosen by investigators, administered to 33.9% of subjects in the intent-to-treat (ITT) population; consolidation chemotherapy after radiation was not permitted in this study (Antonia, 2017).

In an attempt to improve outcomes, higher doses of radiation have been studied in combination with chemotherapy. Approximately 60 Gy in 1.8 to 2 Gy fractions has been previously established as the standard conventional radiation dose in stage III NSCLC in the RTOG 7301 study (Bradley, 2015). Subsequently the RTOG 0617 study has shown that 74 Gy was not better

CELGENE PROPRIETARY INFORMATION

than 60 Gy (Bradley, 2015). In fact, the median OS was 28.7 months for those subjects who received 60 Gy versus 20 months for those who received 74 Gy. Local relapse rates were also lower in the 60 Gy cohort. Thus, the accepted standard of care is approximately 60 Gy in 2 Gy fractions (NCCN, 2018) (ESMO 2017 guidelines [Postmus, 2017]).

1.1.3. Anti-PD-1/PD-L1 Therapy for Locally Advanced or Metastatic Lung Cancers

Anti-programmed cell death protein-1 (PD-1) therapy has emerged as an effective treatment for those expressing varying degrees of (PD-L1) (Hanna, 2017). Anti-PD-1 and anti-PD-L1 therapies target the programmed death receptor pathway of T lymphocytes, and this checkpoint has been found to be activated in cancer allowing tumors to evade the host immune system. In the US and other regions, multiple anti-PD-1 (eg, nivolumab and pembrolizumab) and anti-PD-L1 (eg atezolizumab) therapies have been approved in lung cancer in the second line setting (Table 1). In the first line setting, pembrolizumab has been approved by the US Food and Drug Administration (FDA) as monotherapy in subjects with metastatic NSCLC whose tumors express a high level of PD-L1 (Tumor Prognostic Score ≥ 50%). Pembrolizumab has also been granted accelerated approval by the FDA in the first-line setting in combination with pemetrexed and carboplatin in metastatic nonsquamous NSCLC (Table 1).

In the locally advanced, first-line NSCLC setting, the potential benefits of checkpoint blockade when given sequentially following completion of cCRT have been demonstrated by the PACIFIC trial (Antonia, 2017). This is a global Phase 3 trial of the anti-PD-L1 therapy, durvalumab, compared to placebo as consolidation therapy following 2 or more cycles of platinum-based chemotherapy administered concurrently with RT without progression in subjects with unresectable stage III NSCLC. Subjects who were able to complete chemoradiotherapy, and who remained progression free at that time, were randomized within 1 to 42 days after completing at least 2 cycles of platinum-based chemotherapy (containing etoposide, vinblastine, vinorelbine, a taxane, or pemetrexed) administered concurrently with definitive radiation therapy of 54 to 66 Gy. The trial demonstrated that median progression free survival (PFS) was significantly longer with durvalumab compared to placebo (median PFS 16.8 months versus 5.6 months, stratified HR for disease progression or death = 0.52), with a similar safety profile in the 2 groups. Notably, enrollment was not restricted to any thresholds for the level of PD-L1 expression, and results showed that the PFS benefit was irrespective of baseline PD-L1 expression (HR 0.59 [95% CI, 0.43 to 0.82] for a PD-L1 expression level of < 25% and 0.41 [95% CI, 0.26 to 0.65] for a PD-L1 expression level of ≥ 25%). In February 2018, based on the results of the PACIFIC study, durvalumab was approved by the US FDA for the treatment of subjects with unresectable stage III NSCLC whose cancer had not progressed after chemoradiation (FDA News Release, 2018). This immunotherapy thus becomes the first treatment approved to reduce the risk of NSCLC progression in this setting, and may lead to a change in first line treatment for stage III subjects, with the potential recommendation that anti-PD-L1 consolidation therapy be offered after concurrent chemoradiation therapy (NCCN, 2018). However, there are still some caveats to the PACIFIC study. There is some uncertainty as to whether all subjects enrolled in this study underwent appropriate evaluations for optimal staging, and whether this trial included subjects with occult stage IV disease (Copur, 2018). In addition, almost 30% of subjects enrolled did not proceed to randomization in the study, with the exact reasons for dropout not further specified beyond the majority of subjects not meeting eligibility criteria (Antonia, 2017). It not clear whether these subjects were able to complete the cCRT

CELGENE PROPRIETARY INFORMATION

prior to randomization or the status of these subjects during the cCRT period. Furthermore, OS data is not yet available. If an OS benefit is eventually shown, cCRT followed by anti-PD-L1 therapy with durvalumab is anticipated to become an emerging standard of care for subjects with stage III NSCLC.

There are multiple ongoing studies evaluating anti-PD-1 or PD-L1 therapies in combination with radiation or chemoradiotherapy. Based on the mechanism of action and biology of PD-1/PD-L1, it is not anticipated that the antibody will act as a direct radiation sensitizer for normal or malignant cells. Emerging retrospective and prospective data suggests that anti-PD-1 therapy (at the established monotherapy dosing) in combination with radiation has similar toxicity to that anticipated with either treatment alone (Nomura, 2018; Fiorica, 2018). This and other emerging data support that anti-PD-1 therapies can be safely added to standard of care chemotherapy regimens in NSCLC, with the potential for improved efficacy compared to chemotherapy alone. For example, the Phase 2 NICOLAS trial is evaluating the anti-PD-1 therapy, nivolumab, with cCRT in stage III NSCLC (Jabbour, 2017), and several ongoing trials are testing concurrent anti-PD-1 or anti-PD-L1 therapies with cCRT in other solid tumor malignancies.

In the metastatic NSCLC setting, prior to the advent of immune checkpoint inhibitors (ICIs), the mainstay of treatment was chemotherapy involving platinum-containing doublets. The 5-year survival rate for these subjects was low, ranging from 10% for stage IVA to less than 1% for stage IVB (American Cancer Society, 2018). Additional treatment for some patients is based on tumor mutation status such as EGFR, ALK or proto-oncogene tyrosine-protein kinase ROS (ROS-1) mutations, where tyrosine kinase inhibitors are primary treatment options. In 2017, pembrolizumab in combination with pemetrexed and carboplatin was granted accelerated approval in the US in the first-line setting for all nonsquamous stage IV subjects based on the results of the Keynote-021 Phase 2 randomized study (Langer, 2016). Pembrolizumab is also approved for and recommended by the NCCN as a single-agent, first-line therapy in patients with advanced NSCLC who have PD-L1 expression levels of $\geq$ 50% and EGFR mutation and ALK and ROS rearrangements negative or unknown based on the Keynote-024 study (Reck, 2016) (Table 1). Most recently, the KEYNOTE-189 Phase 3 study showed that in subjects with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard chemotherapy (pemetrexed with a platinum-based drug) resulted in a significantly longer rate of OS at 12 months (69.2% versus 49.4% [HR 0.49; 95% CI, 0.38 to 0.64; $P < 0.001$]) and median PFS (8.8 months versus 4.9 months [HR 0.52; 95% CI, 0.43 to 0.64; $P < 0.001$]) than chemotherapy alone (Gandhi, 2018). In addition, the median PFS was significantly prolonged among subjects with stage IV or recurrent NSCLC who had high tumor mutational burden and were treated with nivolumab plus ipilimumab in the first-line setting compared to chemotherapy alone (7.2 months versus 5.5 months [HR 0.58; 97.5% CI, 0.41 to 0.81; $P < 0.001$]) (Hellmann, 2018).

Targeted therapy is recommended for subjects with metastatic NSCLC with ALK or ROS1 rearrangements or EGFR mutations, and subsequent targeted therapy can be used in subjects with EGFR mutations or ALK translocations upon progression (NCCN, 2018). For those subjects who do not have these genetic alterations, the NCCN recommends ICIs as preferred subsequent therapy based on improved OS, longer duration of response, and fewer AEs when compared to cytotoxic therapy. Nivolumab has been FDA approved as subsequent therapy for patients with metastatic nonsquamous NSCLC (Checkmate-057) (Borghaei, 2015) and metastatic squamous NSCLC (Checkmate-017) (Brahmer, 2015) who have progressed on or after first-line

CELGENE PROPRIETARY INFORMATION

chemotherapy based on the Phase 3 randomized trial data. Based on data from Keynote-010 (Herbst, 2016) and Keynote-001(Garon, 2015) and FDA accelerated approval, the NCCN also recommends pembrolizumab as subsequent therapy for patients with metastatic NSCLC and PD-L1 expression. Atezolizumab has also been FDA approved for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. A summary of approved anti-PD-1 and anti-PD-L1 inhibitors for the treatment of advanced or metastatic NSCLC (not including durvalumab which was approved in Feb 2018 by US FDA for treatment of patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy) can be found in Table 1.

CELGENE PROPRIETARY INFORMATION

Table 1: Approved Anti-PD-1 or Anti-PD-L1 Inhibitors for the Treatment of Advanced or Metastatic NSCLC

	Second-line treatment for advanced or metastatic lung cancer									First-line treatment for advanced NSCLC			
Study	**KEYNOTE10[a] (Herbst, 2016)**			**CHECKMATE 057 (Borghaei, 2015)**		**CHECKMATE 017 (Brahmer, 2015)**		**OAK (Rittmeyer, 2017)**		**KEYNOTE24[b] (Reck, 2016)**		**KEYNOTE021 Cohort G (Langer, 2016; Borghaei, 2017)**	
Subjects	N = 1034			N = 582		N = 272		N = 1225		N = 305		N = 123	
Treatment	Pembro-lizumab 2 mg/kg (n = 345)	Pembro-lizumab 10 mg/kg (n = 346)	Doce-taxel (n = 343)	Nivo-lumab (n = 287)	Doce-taxel (n = 268)	Nivo-lumab (n = 131)	Doce-taxel (n = 129)	Atezo-lizumab (n = 425)	Doce-taxel (n = 425)	Pembro-lizumab mono-therapy (n = 154)	Platinum-based-chemo-therapy (n = 151)	Pembrolizumab plus pemetrexed/ carboplatin (n = 60)	Chemo-therapy only (n = 63)
OS (months)	10.4 (9.4 - 11.9)	12.7 (10.0 - 17.3)	8.5 (7.5 - 9.8)	12.2	9.4	9.2	6	13.8 (11.8 - 15.7)	9.6 (8.6 - 11.2)	80.2	72.4	NR (22.8 - NR)	20.9 (14.9 - NR)
HR (95% CI)	0.71, (0.58 - 0.88; p = 0.0008)	0.61, (0.49 - 0.75; p < 0.0001)	NA	0.73, (0.59 - 0.89; p = 0.002)		0.59, (0.44 - 0.79; p < 0.001)		0.74, (0.58 - 0.93; p = 0.0102)		0.60 (0.41-0.89; p = 0.005)		0.59, (0.34-1.05; p = 0.03)	
mPFS (months)	3.9 (3.1 - 4.1)	4.0 (2.7 - 4.3)	4.0 (3.1 - 4.2)	2.3	4.2	3.5	2.8	2.8 (2.6 - 3.0)	4.0 (3.3 - 4.2)	10.3	6	19.0 (8. 5 - NR)	8.9 (6.2 - 11.8)
HR (95% CI)	0.88, (0.74 - 1.05; p = 0.068)	0.79, (0.66-0.94; p = 0.004)	NA	0.92, (0.77-11; p = 0.39)		0.62, (0.47 - 0.81; p < 0.001		0.95, (0.82-1.10)		0.50, (0.37 - 0.68; p < 0.001)		0.54, (0.33 - 0.88; p = 0.0067)	
ORR (%)	18 (14 - 23)	18 (15 - 23)	9 (7 - 13)	19	12	20,	9	14	13	44.8	27.8	55% (95% CI = 42 – 68)	29% (95% CI = 18 – 41)
p-value	p < 0.001	p < 0.001	NA	p = 0.021	NA	p = 0.008	NA	NA	NA	NA	NA	NA	NA
TEAE ≥ Grade 3 (%)	13	16	35	10	54	7	55	15	43	26.6	53.3	40	26

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

[b] FDA approval was granted for pembrolizumab as a single-agent, first-line therapy in patients with advanced NSCLC who have PD-L1 expression levels of ≥ 50% and EGFR mutation and ALK and ROS rearrangements negative or unknown

CELGENE PROPRIETARY INFORMATION

Abbreviations: CI = confidence interval; HR = hazard ratio; mPFS = median progression-free survival duration in months; NA = not available; NSCLC = non-small cell lung cancer; NR = not reported; ORR = overall response rate; OS = overall survival; PD-1 = programmed cell death protein-1; PD-L1 = program cell death protein ligand-1; TEAE = treatment emergent adverse event

CELGENE PROPRIETARY INFORMATION

1.2. Compound Background

1.2.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1 under clinical development for the treatment of several human malignancies.

Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity (K_D = 0.15 nM). It competitively blocks the binding of both PD-L1 and programmed cell death ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T cells and preactivated, primary peripheral blood mononuclear cells. In addition, tislelizumab has demonstrated antitumor activity in several human cancer allogeneic xenograft models, in which peripheral blood mononuclear cells were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice. Robust antitumor activity of tislelizumab was also observed in human PD-1 transgenic mice transplanted with B16/F10 mouse melanoma cells overexpressing antimurine granulocyte-macrophage colony-stimulation factor.

The IgG4 variant antibody has very low binding affinity to FcγRIIIA and complement 1q, a subunit of complement 1, by in vitro assays, suggesting low or no antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effects in humans (Labrijn, 2009). Unlike native IgG4 antibody, tislelizumab has no observable fragment antigen-binding-arm exchange activity in an in vitro assay, predicting the antibody would be stable in vivo and unlikely to form bispecific antibodies.

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

CELGENE PROPRIETARY INFORMATION

CELGENE PROPRIETARY INFORMATION

CELGENE PROPRIETARY INFORMATION

[redacted]

CCI

[redacted]

CELGENE PROPRIETARY INFORMATION

[redacted]

1.3. Rationale

1.3.1. Study Rationale and Purpose

While cCRT has become the standard of care for the treatment of locally advanced, unresectable stage III NSCLC, as shown by the RTOG 9410 study which reported a significant improvement in overall survival with concurrent cisplatin-based chemoradiotherapy compared to sequential chemoradiotherapy (Curran, 2011), there has not been substantial improvement subsequently with cCRT alone despite exploration of different treatment options such as dose escalation of radiation, induction chemotherapy, and various regimens of consolidative chemotherapy following cCRT (Postmus, 2017).

There is strong evidence that not only can there be synergy of ICIs with chemotherapy, this can occur with concurrent chemoradiotherapy as well. It is now known that both chemotherapy and RT can up-regulate the expression of PD-L1 (Zhang, 2008; Deng, 2014) due to the release of cytokines and other inflammatory molecules, which could make such tumors sensitive to a PD-1/PD-L1 directed therapy. In this setting, chemotherapy and RT act as priming agents for immunotherapy; elimination of cancer cells by chemotherapy and/or RT triggers release of

CELGENE PROPRIETARY INFORMATION

antigens, which can turn poorly immunogenic or immunosuppressive tumors into an immunogenic environment (Vanneman, 2012). In addition, RT has an impact on the immune system by engaging both the innate and the adaptive arms, eliciting tumor-specific T-cells and establishing an immune memory against the tumor. This prolongs the effect of radiation, improving locoregional control, decreasing metastatic spread, and increasing overall survival (Formenti, 2013). It is also anticipated that while chemotherapy has been shown to sensitize tumors to radiation therapy, immunotherapy with PD-1/PD-L1 therapies may be less directly interacting, and emerging data suggests that PD-1/PD-L1 antibodies can be given at full doses with RT as they can be with chemotherapy (Fiorica, 2018).

As described earlier, the PD-L1 inhibitor, durvalumab, has demonstrated a PFS improvement in locally advanced, unresectable stage III NSCLC patients who were fully recovered and had not progressed following a full course of combined modality therapy. A limitation of the PACIFIC study is that there was no requirement for fluorodeoxyglucose-positron emission tomography (FDG-PET) scans and/or brain imaging to rule out stage IV disease; this may have confounded the efficacy results in favor of the durvalumab arm and depressed the efficacy observed with combined modality alone in the control arm. This study will require all subjects to be staged with FDG-PET and brain imaging to better establish that all randomized subjects are stage III. As only approximately 70% of subjects in the PACIFIC study who were enrolled were randomized, this trial will seek to determine if improved efficacy can be achieved to allow a higher proportion of subjects to complete the cCRT phase and enter the monotherapy phase. In consideration of the limitations of the PACIFIC trial, this protocol will evaluate whether the addition of an anti-PD-1 therapy added to combined modality therapy can benefit subjects with definitive stage III unresectable NSCLC. In addition, the PACIFIC study subgroup analysis of PFS showed that subjects who started durvalumab closer to the last radiation therapy (last radiation to randomization < 14 days versus ≥ 14 days) seemed to trend towards greater PFS benefit with durvalumab. Thus, the earlier introduction of tislelizumab given simultaneously with cCRT (Arm 1) may lead to further enhancement of immune mediated antitumor efficacy.

1.3.2. Rationale for the Study Design

All randomized subjects on this trial will receive standard of care combined modality cCRT. In order to minimize the heterogeneity of different chemotherapy backbones, this study will allow Investigators the option of cisplatin-etoposide as established by the PROCLAIM study. This study will also allow weekly paclitaxel and carboplatin to give Investigators more than one chemotherapy option, as supported by the NCCN guidelines and the literature (NCCN, 2018; Yamamoto, 2010). Radiotherapy will be given concurrently with chemotherapy for 5 days per week for 6 weeks, in once daily fractions, 2 Gy per fraction, to a target dose of 60 Gy in 30 fractions. As a pooled analysis of 41 Phase 2/3 trials did not show any evidence that consolidation after cCRT improves survival for stage III NSCLC and current guidelines continue to recommend cCRT alone (Bayman, 2014; Postmus, 2017), no consolidation chemotherapy will be given.

Induction chemotherapy will not be allowed. All treatment will be initiated after randomization, and the study will be stratified according to the chemotherapy regimen chosen.

This study will employ a 3-arm design to evaluate the anti-PD-1 antibody, tislelizumab, in locally advanced unresectable stage III NSCLC. Subjects will be randomized 1:1:1 to receive

CELGENE PROPRIETARY INFORMATION

tislelizumab together with cCRT followed by tislelizumab monotherapy, or placebo together with cCRT followed by tislelizumab monotherapy, or placebo together with cCRT followed by placebo monotherapy. Subjects will be required to have EGFR mutation and ALK gene translocation results available prior to randomization; EGFR/ALK positive subjects will be allowed up to a maximum of 10% of the total number of subjects randomized. The standard of care for patients with stage III NSCLC regardless of EGFR mutation or ALK gene translocation remains cCRT (NCCN, 2018; Postmus, 2017). Targeted therapy is not utilized as upfront therapy for patients with EGFR mutations or ALK gene translocations and is still being investigated in trials such as RTOG 1306 (Berman, 2016). A recent meta-analysis of 5 trials involving 3025 subjects with advanced second-line or later NSCLC randomized to receive a checkpoint inhibitor or docetaxel showed that there was prolonged survival in those who were EGFR wild type but not in those who were EGFR mutant (Lee, 2018), suggesting that there is no clear benefit from checkpoint inhibitor monotherapy for patients with EGFR mutations. In contrast, in the PACIFIC study, subjects with EGFR mutation comprised 6% of the study population and the results in the subgroup analyses were consistent with the ITT population with a demonstrated PFS benefit from durvalumab, though a significant number of subjects (26%) did have unknown EGFR mutation status (Antonia, 2017). In the study IMpower150, where EGFR/ALK subjects represented 14% of the enrolled population, benefits have been observed (Reck, 2017). Thus, this study will include a limited number of subjects with EGFR mutation or ALK gene translocation, as this population warrants further investigation of anti-PD-1 therapy with cCRT in the first-line setting for stage III unresectable NSCLC. By requiring testing at screening, this study will better address the effect of anti-PD-1 therapy in patients with tumors expressing these gene alterations. In addition, this study will require all subjects be staged with FDG-PET CT and brain imaging to better establish that all randomized subjects are stage III.

Prior studies of PD-1/PD-L1 therapy given concurrently with chemotherapy or with or in close proximity to radiation suggests a manageable safety profile (Samstein, 2017). Furthermore, the PACIFIC study did not show any new safety signals when durvalumab was given after cCRT, with the safety profile consistent with other immunotherapies and monotherapy, with pneumonitis mostly low grade, and clinically important Grade 3 or 4 toxicities were balanced between the 2 groups. However, the safety and tolerability of checkpoint inhibitors given concurrently with cCRT is still being evaluated. Preliminary data suggest that combining anti-PD1 therapy and RT is safe (Liniker, 2016). Most recently, the early interim safety analysis of the NICOLAS study, a Phase 2 trial evaluating the addition of the anti-PD-1 therapy nivolumab to first-line cCRT in locally advanced, unresectable stage III NSCLC showed that this approach was safe and tolerable in that study, with no unexpected AEs or increased safety risks identified. At the time of this early interim safety analysis, 49 subjects had been recruited with a median follow-up of 6.6 months. The most frequently observed AEs were fatigue and anemia. For the first 21 patients, no pneumonitis grade ≥ 3 was observed by the end of the 3-month post-RT follow-up period (Peters, 2018). To address any potential toxicities of administering anti-PD-1 treatment, particularly when given simultaneously with cCRT, a rigorous safety assessment will be implemented, with independent data monitoring committee (IDMC) safety reviews to assess for early safety signals. CCI [redacted]

CELGENE PROPRIETARY INFORMATION

CCI [redacted] Enrollment may continue during these IDMC safety reviews.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

1.3.3.1. Rationale for Selection of Tislelizumab Dose

The PK, safety, and efficacy data obtained from first in human study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for pivotal studies of tislelizumab. The flat dose of CCI [redacted] was selected for further evaluation. Rates of treatment-related AEs and serious adverse events (SAEs) observed in patients receiving CCI [redacted] were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed overall response rates (ORR) in subjects treated with tislelizumab CCI [redacted] ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at CCI [redacted]. According to PK data from BGB-A317_Study_001, Phase 1a, the clearance of tislelizumab was found to be independent of body weight, ethnicity, and gender, and the observed serum exposure of a CCI [redacted] fell between serum exposure observed after CCI [redacted] doses (dose range with comparable safety and efficacy rates).

Additionally, no unexpected treatment related AEs occurred in the CCI [redacted] cohort (BGB-A317_Study_001, Phase 1a, Part 3) when compared to body-weight-based cohorts. Of the evaluable subjects treated (n = 13), 3 patients (23%) had a best overall response of PR, 4 subjects (31%) had a best overall response of stable disease, and 6 subjects (46%) had a best overall response of progressive disease (PD). Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in subjects receiving tislelizumab CCI [redacted].

CCI [redacted]

1.3.3.2. Rationale for Selection of Chemotherapies

Multiple chemotherapy backbone regimens, including combinations of cisplatin with either pemetrexed, etoposide, vinblastine, or vinorelbine, have been studied in stage III NSCLC and are acceptable combination regimens that can be utilized as standard of care in cCRT. Few studies have been conducted comparing these chemotherapy regimens, and no chemotherapy regimen has been clearly demonstrated to be better than others. Of these chemotherapy doublets that have comparative evidence, cisplatin in combination with either pemetrexed or etoposide has been studied in this treatment population. The PROCLAIM multinational trial endeavored to establish whether cisplatin-pemetrexed is superior to cisplatin-etoposide when given concurrently with standard radiotherapy at 60 to 66 Gy, followed by a consolidation phase; cisplatin-pemetrexed was not found to be superior in OS to cisplatin-etoposide (median OS 26.8 versus 25.0 months; P = 0.831). Both arms had low incidences of Grades 3 or 4 pneumonitis (< 3%) and there were no significant differences between arms in treatment discontinuations due to drug-related AEs or

CELGENE PROPRIETARY INFORMATION

drug-related deaths (Senan, 2016). Carboplatin with paclitaxel given weekly during radiation is another acceptable cCRT option as recommended by the NCCN guidelines, with the 2 cycles of carboplatin and paclitaxel consolidation considered as optional (NCCN, 2018). Weekly carboplatin/paclitaxel with RT has been evaluated in several studies (Belani, 2005; Vokes, 2007; Yamamoto, 2010; Bradley, 2015) and is often used as a first-line treatment for locally advanced, unresectable stage III NSCLC in the US and other countries globally. Weekly carboplatin/paclitaxel was used as part of the chemotherapy regimen backbone in the RTOG 0617 study that evaluated standard versus high doses of radiation to be given concurrently with chemotherapy (Bradley, 2015). A Phase 3 trial of concurrent thoracic radiation in unresectable stage III NSCLC found that weekly carboplatin/paclitaxel was superior to second-generation chemotherapy regimens such as mitomycin/vindesine, weekly irinotecan/carboplatin, or cisplatin or carboplatin as a single agent with radiation therapy (Yamamoto, 2010).

For the chemotherapy backbone, this study will allow Investigators the choice of cisplatin/etoposide, given concurrently with RT based on the PROCLAIM study, or carboplatin/paclitaxel given weekly with RT; neither regimen will allow chemotherapy consolidation.

1.3.3.3. Rationale for Selection of Radiotherapy Dose

The total dose of RT will be 60 Gy in 30 once-daily fractions of 2 Gy according to the standard dose recommended by the American Society of Radiation Oncology (Rodrigues, 2015), based on the dose for locally advanced, unresectable stage III NSLC established in the RTOG 0617 study (Bradley, 2015). The dose of 60 Gy is endorsed by ASCO (Bezjak, 2015), and is a dose supported by the NCCN and ESMO guidelines for cCRT (NCCN, 2018; Postmus, 2017). Dose escalation beyond 60 Gy in the context of combined modality concurrent chemoradiation has not been found to be associated with any clinical benefits (Rodrigues, 2015).

Although other recent Phase 3 studies such as PROCLAIM had used a dose of 66 Gy (2 Gy per fraction), PROCLAIM was designed before the results of the RTOG 0617 study became available (Senan, 2016). As the present trial will involve administration of a PD-1 inhibitor with cCRT, it is critical for the radiation dosing to be standardized across the entire study globally, with the target dose of 60 Gy chosen as it is appropriate to eradicate the primary tumor and the involved lymph nodes, while minimizing toxicities such as acute radiation esophagitis and pneumonitis as much as possible.

CCI [redacted]

CELGENE PROPRIETARY INFORMATION

CCI

[redacted]

1.3.5. Rationale for Patient-Reported Outcomes and Quality of Life or Health Economics

It will be important to assess treatment effectiveness both in terms of objective outcomes (eg, PFS or OS) and subjective, patient reported outcomes (PROs) to ensure that the addition of tislelizumab to cCRT followed by tislelizumab monotherapy in newly-diagnosed, unresectable locally advanced NSCLC subjects, does not result in a detrimental impact on subjects' health-related quality of life (HRQoL) when compared to cCRT alone. This detailed information can help both clinicians and subjects to make informed and comprehensive decisions regarding the best available treatments. Patient reported outcomes are any information self-reported by the subject regarding their functioning or symptoms in relation to their health condition or therapy. Patient-reported HRQoL falls under the umbrella of PROs and covers physical symptoms and functioning domains, and usually provides an overall subject evaluation of their health and quality of life.

CELGENE PROPRIETARY INFORMATION

2. STUDY OBJECTIVES AND ENDPOINTS

Table 2: Study Objectives

Primary Objective
The primary objective is to compare the progression free survival (PFS) of tislelizumab in combination with concurrent chemoradiotherapy (cCRT) followed by tislelizumab monotherapy (Arm 1) versus cCRT alone (Arm 3); in addition, tislelizumab given sequentially after cCRT (Arm 2) will be compared with cCRT alone (Arm 3) in newly diagnosed stage III subjects with locally advanced unresectable non-small cell lung cancer (NSCLC).
Secondary Objective(s)
The secondary objectives are to: • Compare overall survival (OS) (key secondary objective) • Compare OS at 24 months (key secondary objective) • Compare centrally assessed objective response rate (ORR) (key secondary objective) • Compare centrally assessed duration of response (DOR) • Compare proportion of subjects alive and progression-free at 12 and 18 months (APF12, APF18) • Compare time to death or distant metastasis (TTDM) • Compare safety and tolerability of tislelizumab in combination cCRT followed by tislelizumab monotherapy versus cCRT alone, and tislelizumab given sequentially after cCRT versus cCRT alone • Compare impact on patient-reported lung cancer symptoms (appetite loss, cough, chest pain, dyspnea, and fatigue) assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and its lung cancer module (EORTC QLQ-LC13) • Compare the proportion of subjects who received at least one dose of tislelizumab or placebo in the monotherapy phase before progression in Arm 1 versus Arm 2 and 3.
CCI [redacted]
[redacted]

CELGENE PROPRIETARY INFORMATION

Table 3: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Progression free survival (PFS)	The time from the date of randomization to the date of the first objectively documented tumor progression as assessed by blinded independent central review per RECIST v1.1 or death from any cause, whichever occurs first	Every 6 weeks post C1D1 for the first 36 weeks and then every 9 weeks until disease progression, new disease therapy, death or withdrawal of consent
Key Secondary	Overall survival (OS)	The time from the date of randomization to the date of death due to any cause	Randomization to death
	OS at 24 months	The proportion of subjects alive at 24 months after randomization	Randomization to 24 months
	Objective response rate (ORR)	The proportion of subjects in the ITT population who had complete response (CR) or partial response (PR) as assessed by blinded independent central review per RECIST v1.1	Every 6 weeks post C1D1 for the first 36 weeks and then every 9 weeks until disease progression, new disease therapy, death or withdrawal of consent
Secondary	Duration of response (DoR)	The time from the first occurrence of a documented objective response to the time of relapse, as determined by blinded independent central review per RECIST v1.1, or death from any cause, whichever comes first	Every 6 weeks post C1D1 for the first 36 weeks and then every 9 weeks until disease progression, new disease therapy, death or withdrawal of consent
	Proportion of subjects alive and progression-free at 12 months (APF12)	The proportion of subjects alive and progression free at 12 months (APF12) will be defined as the Kaplan-Meier estimate of PFS at 12 months.	Every 6 weeks post C1D1 for the first 36 weeks and then every 9 weeks until, disease progression, new disease therapy, death or withdrawal of consent
	Proportion of subjects alive and progression-free at 18 months (APF18)	The proportion of subjects alive and progression free at 18 months (APF18)	Every 6 weeks post C1D1 for the first 36 weeks and then every 9 weeks until disease progression, new disease therapy, death or withdrawal of consent

CELGENE PROPRIETARY INFORMATION

Table 3: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Time to distant metastasis (TTDM)	TTDM will be defined as the time from the date of randomization until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST v1.1 or proven by biopsy.	Every 6 weeks post C1D1 for the first 36 weeks and then every 9 weeks until disease progression, new disease therapy, death or withdrawal of consent or death
	Safety and tolerability	Safety and tolerability will be assessed from adverse events (using NCI CTCAE v5.0), laboratory tests, vital signs, ECOG performance status, physical exams, concomitant medications, and dose modifications.	Signature of informed consent through 90 days after the last dose of study treatment
	Impact on the selected patient-reported lung cancer symptoms (appetite loss, cough, chest pain, dyspnea, and fatigue) assessed by the corresponding domains in EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13).	Differences between study arms, tests for within-group changes over time and tests for both deterioration and improvement will be performed on the selected lung cancer symptoms (appetite – item 13 of EORTC QLQ-C30, cough – items 31 to 32 of EORTC QLQ-LC13, chest pain – item 40 of EORTC QLQ-LC13, dyspnea – items 33 to 35 of EORTC QLQ-LC13, and fatigue – items 10, 12, 18 of EORTC QLQ-C30)	Based on tislelizumab/placebo 21-day cycle: Screening, Day 1 of every cycle during study treatment, at discontinuation of the study treatment, and 30 days after the last dose of tislelizumab/placebo
	Proportion of subjects who continue to monotherapy phase	Proportion of subjects who receive at least one dose of tislelizumab or placebo in the monotherapy phase before progression as determined by blinded independent central review per RECIST v1.1	Randomization to the first dose in the monotherapy phase
CCI [redacted]	[redacted]	[redacted]	[redacted]

CELGENE PROPRIETARY INFORMATION

Table 3: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	CCI		

CELGENE PROPRIETARY INFORMATION

Table 3: Study Endpoints (Continued)

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

Abbreviations: AEs = adverse events; C1D1 = Cycle 1 Day 1; CCI [redacted]; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire lung cancer module; IHC = immunohistochemistry; ITT = intent-to-treat; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; CCI [redacted] QoL = quality of life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; CCI [redacted].

CELGENE PROPRIETARY INFORMATION

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled multicenter global study designed to compare the efficacy and safety of tislelizumab in combination with cCRT followed by tislelizumab monotherapy versus cCRT alone, and tislelizumab given sequentially after cCRT versus cCRT alone, in newly diagnosed stage III subjects with locally advanced, unresectable NSCLC.

The primary endpoint is centrally-assessed PFS in the intent-to-treat (ITT) population. Newly diagnosed stage III subjects with histologically confirmed, locally advanced, unresectable NSCLC are eligible.

Approximately 840 subjects will be randomized in a 1:1:1 ratio to receive tislelizumab or placebo in the following 3 arms:

- CCI [redacted]

The choice of chemotherapy regimen to be used as part of study treatment will be at the Investigator's discretion, consisting of 2 cycles of cisplatin plus etoposide or weekly carboplatin plus paclitaxel given during RT for 6 weeks. Radiation therapy should start concurrently with chemotherapy in Cycle 1 of tislelizumab or placebo. If local technical or logistical circumstances do not allow for the start of RT at the beginning of Cycle 1, a 3-day administrative window to start RT will be allowed. Tislelizumab or placebo will be given starting from Cycle 1 Day 1 (C1D1) in the cCRT phase, and continued in the monotherapy phase for a duration of 12 months following the completion of cCRT, or until disease progression, unacceptable toxicity, or treatment discontinuation for another reason.

Subjects with EGFR sensitizing mutations or ALK gene translocations may be randomized up to approximately 10% of the total randomized population.

Randomization will be stratified by age [CCI redacted]), chemotherapy regimen [CCI redacted]), and region ([CCI redacted]). [CCI redacted]

[CCI redacted]

CELGENE PROPRIETARY INFORMATION

[CCI redacted]

CCI [redacted]

For immune therapies such as tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic progressive disease is suspected by the Investigator to reflect pseudoprogression, the subject may continue study treatment until progressive disease is confirmed by repeated imaging at least 4 weeks later but not exceeding 6 to 8 weeks from the date of initial documentation of progressive disease, provided the following criteria are met:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values).
- Stable ECOG performance status (≤ 1).
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention.

Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform subjects that this practice is not considered standard in the treatment of cancer. The decision to continue study drug(s) beyond initial Investigator-assessed progression must be discussed with the Sponsor medical monitor and documented in the study records.

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.

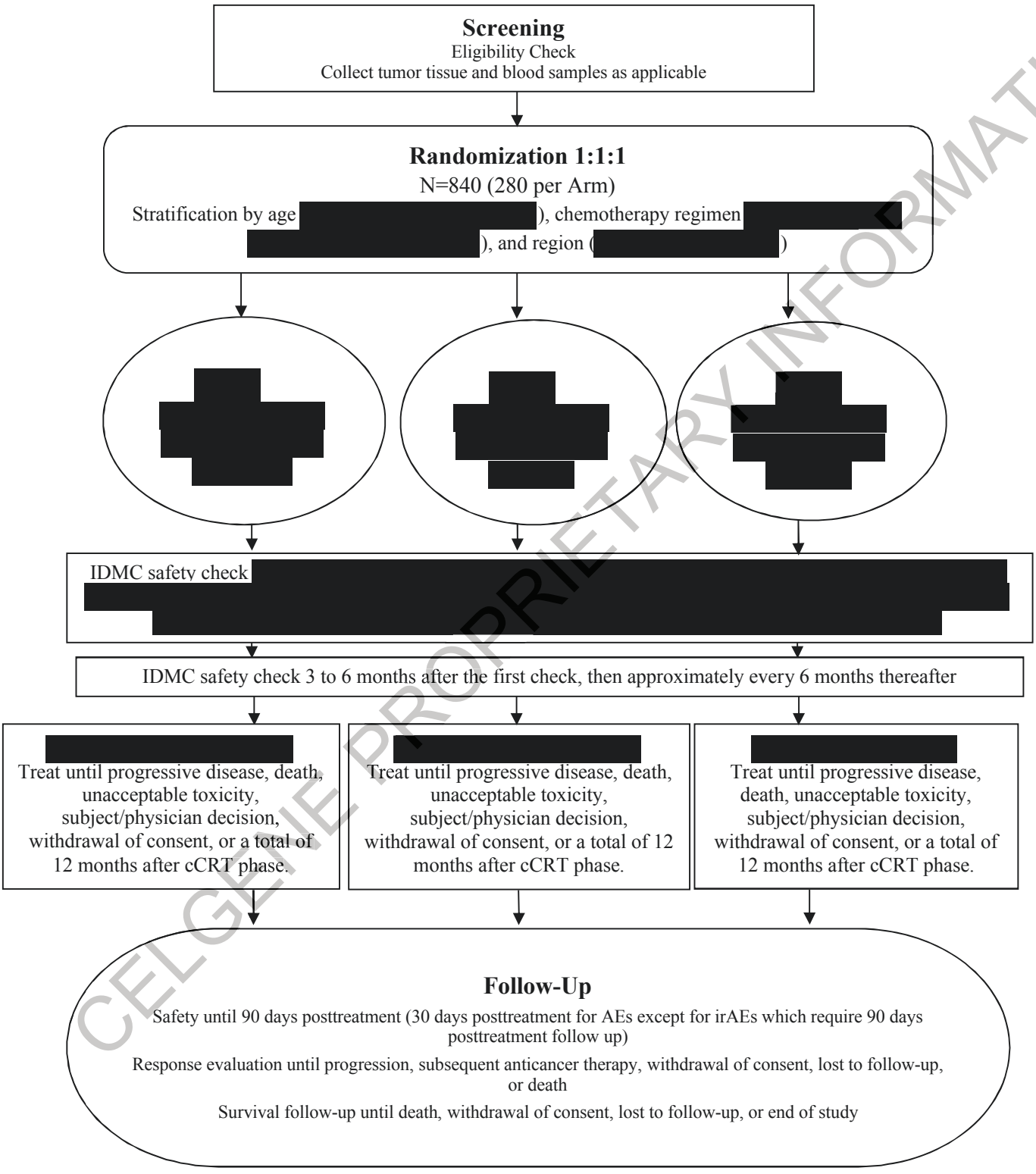
CCI [redacted]

The blind should be maintained for persons responsible for the ongoing conduct of the study through database lock and statistical analyses. Blinded persons may include but are not limited to: Clinical Research Physician, Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, Clinical Research Associates. 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 remain blinded to the study data by arm.

CELGENE PROPRIETARY INFORMATION

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

Figure 1: Overall Study Design



CELGENE PROPRIETARY INFORMATION

Abbreviations: C1D1 = Cycle 1 Day 1; CCI ; IDMC = independent data monitoring committee; CCI

3.2. Study Duration for Subjects

Subjects may begin screening up to 28 days before randomization. Treatment must begin within 3 days of randomization. Subjects will be treated for a maximum of approximately up to 6 weeks by cCRT plus either tislelizumab or placebo, followed by tislelizumab or placebo monotherapy for a total of 12 months after completion of cCRT. Subjects will be followed in survival follow-up until death, withdrawal of consent, lost to follow-up, or end of study. The total duration of tislelizumab (Arm 1), placebo followed by tislelizumab (Arm 2), or placebo alone (Arm 3) will be approximately 14 months, including the cCRT period.

Enrollment is expected to take approximately 28 months to complete. The total study duration is estimated to be approximately 61 months from the randomization of the first subject to the final analysis, conducted when approximately 572 OS events have occurred across the 3 arms.

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 posttreatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary CCI analysis, as prespecified in the protocol, whichever is the later date.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 840 subjects with newly-diagnosed, locally advanced, stage III unresectable NSCLC will be randomized worldwide.

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 must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject has newly diagnosed, histologically confirmed, locally advanced, stage III unresectable NSCLC.
    a. Staging will be confirmed at screening by PET/CT and brain imaging by magnetic resonance imaging (MRI) or computed tomography (CT) with contrast.
    b. FDG-PET/CT will be performed whole body, or sufficient to rule out distant metastases (eg, from skull base to knees), to exclude distant disease and confirm that subjects are in stage III. If the CT scan portion is with contrast and is of sufficiently high quality, a separate CT scan at screening can be skipped.
    c. While centers are encouraged to obtain tissue confirmation of lymph node metastases in N2 or N3 disease, the tumor board/multidisciplinary team in individual cases may dispense with this procedure (AJCC Cancer Staging Manual, 2017).
4. Subject must have EGFR mutation and ALK gene translocation status available (testing using tumor tissue only) prior to randomization:
    a. If EGFR mutation and ALK gene translocation results are not available, subjects will be tested for EGFR sensitizing mutation or ALK translocation (using tumor tissue only). The test results verifying the presence or absence of both EGFR mutation and ALK gene translocation must be made available to the Sponsor for assessment before randomization.
    b. Subjects with EGFR mutation or ALK gene translocation will represent approximately 10% of the total randomized population. After this number is reached, subjects with EGFR mutation or ALK gene translocation will be excluded.
5. Subjects must be able to provide fresh or archival tumor tissues (formalin-fixed paraffin embedded [FFPE] blocks or at least 15 to 20 freshly cut unstained FFPE slides) with an associated pathological report (squamous or nonsquamous). In the absence of archival tumor tissues, a fresh biopsy (a minimum of 2 to 3 cores) of a tumor lesion at baseline is mandatory. Subjects may be permitted to be enrolled on a case-by-case basis after discussion with the Sponsor medical monitor if fewer than 15 unstained slides can be provided.
6. Subject has Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.

CELGENE PROPRIETARY INFORMATION

7. Subject has adequate hematologic and end-organ function, as defined by the following laboratory results (obtained ≤ 2 weeks prior to randomization):
   a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   b. Platelet count ≥ 100 x 10^9/L
   c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L (≥ 28 days after growth factor support or transfusion)
   d. Calculated creatinine clearance (CrCl) ≥ 60 mL/min (Cockcroft-Gault formula) for subjects receiving cisplatin/etoposide, and ≥ 45 mL/min (Cockcroft-Gault formula) for subjects receiving carboplatin/paclitaxel.
   e. Total serum bilirubin ≤ 1.5 x upper limit of normal (ULN) (≤ 3 x ULN, if Gilbert's syndrome or if indirect bilirubin concentrations are suggestive of extrahepatic source of the elevation)
   f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN
8. 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 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 therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.
   b. Agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study treatment; 2) while taking study treatment; 3) during dose interruptions; and 4) for at least 120 days after the subject's last dose of tislelizumab or placebo and 180 days after the subject's last dose of chemotherapy. The 2 methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
  - Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, intrauterine, or implantable)
  - Tubal ligation
  - Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of surgical success.

CELGENE PROPRIETARY INFORMATION

- Examples of additional effective methods:
  - Male condom or female condom with or without spermicide
  - Diaphragm
  - Cervical cap, diaphragm, or sponge with spermicide
  - Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action

9. Male subjects must:
   a. Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 120 days after the subject's last dose of tislelizumab or placebo and 180 days after the subject's last dose of chemotherapy, or longer if required by local regulations, even if he has undergone a successful vasectomy.
   b. Agree to not donate sperm
10. 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 received prior therapies targeting PD-1 or PD-L1.
2. Subject has received chemotherapy, radiation, targeted therapy, biologic therapy, immunotherapy or investigational agent used to control NSCLC.
3. Subject has a history of severe hypersensitivity reactions to other monoclonal antibodies.
4. Subject has a history of interstitial lung disease or documented ongoing interstitial lung disease or history of pneumonitis that has required oral or intravenous steroids.
5. Subject's radiation treatment plans are likely to encompass a volume of whole lung receiving ≥ 20 Gy in total (V20) of more than 38% of lung volume.
6. Subject has clinically significant pericardial effusion.
7. Subject has clinically uncontrolled pleural effusion or ascites that requires pleurocentesis or paracentesis for drainage within 2 weeks prior to randomization.
8. Subject has had a major surgical procedure, open biopsy, or significant traumatic injury ≤ 14 days prior to randomization, or anticipation of need for major surgical procedure during the course of the study. Note: Eligible patients for this study must have locally advanced, stage III NSCLC that is considered to be unresectable. Any patient for whom the institutional practice would consider surgery to be a treatment option if disease

CELGENE PROPRIETARY INFORMATION

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

downstaging is observed after completion of the chemoradiotherapy should be considered ineligible.

a. Placement of vascular access device is not considered major surgery.

9. Subject has any active malignancy ≤ 2 years before randomization, with the exception of NSCLC and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).
10. Subject has severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection.
11. Subject has known Human Immunodeficiency Virus (HIV) infection.
12. Subject has untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers with HBV deoxyribonucleic acid (DNA) > 500 IU/mL (2500 copies/mL), or active hepatitis C.
    a. Subjects with inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL), and cured hepatitis C can be enrolled.
13. 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.
14. Subject has medical conditions requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of randomization.
    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.
15. Subject has any of the following cardiovascular criteria:
    a. Evidence of acute or ongoing cardiac ischemia
    b. Current symptomatic pulmonary embolism
    c. Acute myocardial infarction ≤ 6 months prior to randomization
    d. Heart failure of New York Heart Association Classification III or IV ≤ 6 months prior to randomization
    e. Grade ≥ 2 ventricular arrhythmia ≤ 6 months prior to randomization
    f. Cerebral vascular accident or transient ischemic attack ≤ 6 months prior to randomization
16. Subject has had prior allogeneic stem cell transplantation or organ transplantation.

CELGENE PROPRIETARY INFORMATION

17. Subject has used any live vaccines against infectious diseases (eg, varicella, zoster, etc.) within 4 weeks (28 days) of randomization. Seasonal influenza vaccines that do not contain live virus are permitted.
18. Subject has used any herbal or patent medicines to control cancer or boost immunity within 14 days of the first study treatment administration.
19. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
20. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
21. Subject has any condition that confounds the ability to interpret data from the study.
22. Subject has a contraindication to the planned chemotherapy regimen to be administered on the study.

CELGENE PROPRIETARY INFORMATION

5. TABLE OF EVENTS

Table 4: Table of Events

Events	Screening[a]	Treatment Period During cCRT						Treatment Period After cCRT Up to 12 Months of Treatment					Follow-up Period		
	Day -28 to -1	D1[b]	D8	D15	D22	D29	D36	D43	D50	D57	Day 1 of each 21-Day Cycle (starting D64)	EOT[c]	30-Day FU	90-Day FU[c]	PD/ Survival
Window (days)	-	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	±7	±14
STUDY ENTRY AND GENERAL ASSESSMENTS															
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	X	X	-	-	X	-	-	X	-	-	X	X	-	-	-
Complete medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Disease history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior/concomitant medication evaluation	Continuous from ≤ 28 days prior to randomization until 30 days post last dose of study treatment													-	-
Prior/concomitant procedures evaluation	Continuous from ≤ 28 days prior to randomization until 30 days post last dose of study treatment													-	-
EGFR/ALK testing on tumor tissue (if status not available)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-

CELGENE PROPRIETARY INFORMATION

Table 4: Table of Events (Continued)

Events	Screening[a]	Treatment Period During cCRT						Treatment Period After cCRT Up to 12 Months of Treatment					Follow-up Period		
	Day -28 to -1	D1[b]	D8	D15	D22	D29	D36	D43	D50	D57	Day 1 of each 21-Day Cycle (starting D64)	EOT[c]	30-Day FU	90-Day FU[d]	PD/ Survival
Window (days)	-	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	±7	±14
Confirmation of mediastinal nodal involvement, if applicable (Section 4.2)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient Reported Outcomes: EORTC QLQ-C30, LC13	X	X	-	-	X	-	-	X	-	-	X	X	X	-	-
SAFETY ASSESSMENTS															
Adverse event evaluation[e]	Continuous from informed consent until 30 days post last dose of study treatment for AEs; 90 days post last dose of tislelizumab/placebo for irAEs														-
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Vital signs/weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Performance status ECOG	X	X	-	-	X	-	-	X	-	-	X	X	X	-	-
Height	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Body surface area calculation	-	X	X	X	X	X	X	-	-	-	-	-	-	-	-
Pulmonary function test	X	Only if clinically indicated										-	-	-	-
12-lead electrocardiogram	X	X	Only if clinically indicated									X	X	-	-

CELGENE PROPRIETARY INFORMATION

Table 4: Table of Events (Continued)

Events	Screening[a]	Treatment Period During cCRT						Treatment Period After cCRT Up to 12 Months of Treatment					Follow-up Period		
	Day -28 to -1	D1[b]	D8	D15	D22	D29	D36	D43	D50	D57	Day 1 of each 21-Day Cycle (starting D64)	EOT[c]	30-Day FU	90-Day FU[d]	PD/ Survival
Window (days)	-	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	±7	±14
Left ventricular ejection fraction	X	Only if clinically indicated												-	-
OCT (or equivalent diagnostic test) and visual acuity tests[g]	X	Approximately every 15 weeks (± 7 days) during study treatment										X[g]			
Hematology laboratory[fh]	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Chemistry laboratory[fh]	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Coagulation laboratory (PT, PTT, INR)[h]	X	X	-	-	X	-	-	X	-	-	X	X	X	-	-
Thyroid function[h]	X	X	-	-	X	-	-	X	-	-	X	X	X	-	-
C-reactive protein	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HBV/ HCV test[i]	X	If clinically indicated. For subjects who have detectable HBV DNA or HCV RNA at screening or upon repeat testing, respective viral load test every 4 cycles (ie, Day 1 of Cycles 5, 9, 13, etc.).												-	-
Urinalysis	X	If clinically indicated												-	-
Serum β-hCG pregnancy test	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urine β-hCG pregnancy test[j]	X	X	-	-	X	-	-	X	-	-	X	X	X	-	-

CELGENE PROPRIETARY INFORMATION

Table 4: Table of Events (Continued)

Events	Screening[a]	Treatment Period During cCRT						Treatment Period After cCRT Up to 12 Months of Treatment					Follow-up Period		
	Day -28 to -1	D1[b]	D8	D15	D22	D29	D36	D43	D50	D57	Day 1 of each 21-Day Cycle (starting D64)	EOT[c]	30-Day FU	90-Day FU[d]	PD/ Survival
Window (days)	-	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	±7	±14
EFFICACY ASSESSMENTS															
Tumor assessment CT/MRI	X	Every 6 weeks after randomization for the first 36 weeks (± 7 Days), and every 9 weeks from Week 36 (± 7 Days) onward until disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study													
FDG-PET/CT	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CT scan, with contrast, of the head or brain MRI with contrast	X	Only if clinically indicated													
CCI [redacted]															
[redacted]															
[redacted]															
[redacted]															
[redacted]															
[redacted]															

CELGENE PROPRIETARY INFORMATION

Table 4: Table of Events (Continued)

Events	Screening[a]	Treatment Period During cCRT						Treatment Period After cCRT Up to 12 Months of Treatment					Follow-up Period		
	Day -28 to -1	D1[b]	D8	D15	D22	D29	D36	D43	D50	D57	Day 1 of each 21-Day Cycle (starting D64)	EOT[c]	30-Day FU	90-Day FU[d]	PD/ Survival
Window (days)	-	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	±7	±14
CCI															
TREATMENT															
CCI															
Administer IP: tislelizumab/placebo	-	X	-	-	X	-	-	X[n]	-	-	X	-	-	-	-
Administer radiotherapy[o]	-	60 Gy in 30 fractions (2 Gy per day/5 days per week)						-	-	-	-	-	-	-	-
Accountability tislelizumab/placebo	-	X	-	-	X	-	-	X	-	-	X	-	-	-	-
Accountability etoposide/cisplatin	-	X	X			X	X	-	-	-	-	-	-	-	-
CCI															
Administer IP: tislelizumab/placebo	-	X			X			X[n]			X				

CELGENE PROPRIETARY INFORMATION

Table 4: Table of Events (Continued)

Events	Screening[a]	Treatment Period During cCRT						Treatment Period After cCRT Up to 12 Months of Treatment					Follow-up Period		
	Day -28 to -1	D1[d]	D8	D15	D22	D29	D36	D43	D50	D57	Day 1 of each 21-Day Cycle (starting D64)	EOT[c]	30-Day FU	90-Day FU[d]	PD/ Survival
Window (days)	-	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	±7	±14
Administer appropriate chemotherapy premedications	-	X	X	X	X	X	X	-	-	-	-	-	-	-	-
CCI [redacted]															
Administer radiotherapy[o]	-	60 Gy in 30 fractions (2 Gy per day/5 days per week)						-	-	-	-	-	-	-	-
Accountability tislelizumab/placebo	-	X	-	-	X		-	X	-	-	X	-	-	-	-
CCI [redacted]															
FOLLOW-UP															
Survival follow-up	-	-	-	-	-	-	-	-	-	-	-	-	X	X	Every 3 months (± 14 days) until death
Disease therapy since IP discontinuation	-	-	-	-	-	-	-	-	-	-	-	-	X	X	At every survival follow-up visit

CELGENE PROPRIETARY INFORMATION

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; β-hCG = beta human chorionic gonadotropin; CBC = complete blood count; cCRT = concurrent chemoradiotherapy; CK = creatine kinase; CK-MB = creatine kinase – cardiac muscle isoenzyme; CT = computed tomography; D = day; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOT = end of treatment; CCI [redacted] FDG-PET = fluorodeoxyglucose - positron emission tomography; FU = follow-up; Gy = gray; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus HCV = hepatitis C virus; IP = investigational product; IRT = integrated response technology; MRI = magnetic resonance imaging; LC13 = Lung Cancer Module of EORTC QLQ-C30; OCT = optical coherence tomography; PD = progressive disease; CCI [redacted] RNA = ribonucleic acid; RT = radiation therapy; SAE = serious adverse event; SOC = standard of care; CCI [redacted]

[a] Screening evaluations must be completed within 28 days of randomization.

[D1b] Subjects should have Cycle 1 Day 1 (C1D1) dosing initiated within 3 days of randomization.

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

[c] The 90-Day Follow up Visit could be completed at the site or by telephone.

[e] All AEs and SAEs, regardless of relationship to study treatment, will be reported until 30 days after last dose of study treatment. Immune-related AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab or placebo, regardless of whether or not the subject starts a new anticancer therapy. All AEs and SAEs considered related to RT will be collected at any time after the first dose of RT, including late radiation toxicities. After a subject has been discontinued from the study treatment, Investigators are not obligated to actively seek AEs or SAEs in former subjects. However, if the Investigator learns of any AE related to radiation or any SAE, and he/she considers the SAE related to the study drug, the Investigator will notify the sponsor as described in Section 10.

[f] Vitals, weight, hematology and chemistry will be collected weekly during Cycles 1, 2, and 3.

[g] Eye exam, visual acuity test, and optical coherence tomography (OCT) (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used rather than repeating tests. Eye exam, visual acuity test, and OCT (or equivalent diagnostic test) will be assessed at screening and then approximately every 15 weeks (± 7 days) during study treatment. The ophthalmologic assessments including eye exam, visual acuity test, and OCT (or equivalent diagnostic test) should only be performed once at either the EOT or during safety follow up, within 30 days of study treatment end.

[h] Hematology, serum chemistry, coagulation and thyroid function laboratory tests will be performed centrally. Local laboratory tests can be used for enrollment and dosing day. If screening laboratory tests are performed within 3 days of C1D1, these tests do not need to be repeated on C1D1. Before any administration of study treatment on each cycle, the results of CBC and serum chemistry should be available and reviewed by the Investigator. Of note, creatine kinase (CK) and creatine kinase – cardiac muscle isoenzyme (CK-MB) will be assessed as part of the serum chemistry panel (as per Section 6). In case CK-MB fractionation is not available, please assess troponin (troponin I and/or T) instead.

[i] Testing will be performed by a central laboratory and/or the local laboratory at screening and will include at screening HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). After screening, HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA) may be performed if clinically indicated; for subjects who have detectable HBV DNA or HCV RNA at screening or upon repeat testing, respective viral load testing will be performed every 4 cycles (ie, Day 1 of Cycles 5, 9, 13, etc).

[j] Urine pregnancy tests will be performed at each visit prior to dosing. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[redacted]

CELGENE PROPRIETARY INFORMATION

[redacted]

[c] Cycle 3 Day 1 dosing may be delayed up to 7 days in order to ensure that cCRT is completed prior to the start of monotherapy with tislelizumab or placebo.

[b] The schedule of radiotherapy and chemotherapy administrations is detailed in Table 5. Once commenced, radiotherapy should be given for 5 consecutive days weekly. Radiotherapy commences on Day 1 of chemotherapy, with a ± 3 days administrative window allowed for Day 1 of each cycle only.

CELGENE PROPRIETARY INFORMATION

6. PROCEDURES

[redacted]

6.1. Screening Period

Screening evaluations including laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary. These evaluations must be completed within 28 days of randomization unless noted otherwise below.

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 following will be performed at screening as specified in the Table of Events:

- 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 randomization may be used for screening assessments rather than repeating such tests.
- Inclusion/exclusion criteria assessment
- Interactive response technology (IRT) for subject number
- Complete medical history (all relevant medical conditions diagnosed/occurring prior to screening should also be included)
- Demographics (year of birth, sex, race, and ethnicity, if allowed by local regulations)
- Disease history (including but not limited to specific information regarding diagnosis, staging, and histology)

CELGENE PROPRIETARY INFORMATION

- Prior and concomitant medication evaluation (including those taken ≤ 28 days before randomization)
- Prior and concomitant procedures (including all procedures occurring ≤ 28 days before randomization)
- EGFR sensitizing mutation and ALK gene translocation testing. If EGFR mutation and ALK gene translocation results are not available, subjects will be tested for EGFR sensitizing mutation and ALK gene translocation.
- Cytological or histological confirmation of mediastinal nodal involvement (N2 and N3) if available
- Pulmonary function tests: All subjects will undergo pulmonary function testing, which may include but is not limited to spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability for the study.
- Adverse event assessment begins when the subject signs the informed consent form.
- Physical examination (can be source documented only), height and weight
- Vital signs: to include temperature and measurements of pulse rate, respiratory rate, and blood pressure
- ECOG performance status
- 12-lead electrocardiogram (ECG)
- Left ventricular ejection fraction (LVEF) assessment by echocardiogram or other medically appropriate method (eg, multiple-gated acquisition scan [MUGA])
- Eye exam, visual acuity test, and optical coherence tomography (OCT) (or equivalent diagnostic test) will be assessed by an appropriate specialist at screening. Eye exam, visual acuity test, and OCT (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used for the screening evaluation.
- Hematology panel including complete blood count (CBC), differential, absolute neutrophil count and platelet count. The results confirming study eligibility must be obtained ≤ 2 weeks prior to randomization.
- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), alkaline phosphatase, AST/SGOT, ALT/SGPT, serum albumin, total bilirubin, creatinine, CK and CK-MB, and if needed, troponin I and/or T). The results confirming study eligibility must be obtained ≤ 2 weeks prior to randomization.
- Coagulation studies including prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR). Local lab results allowed to confirm subject eligibility.
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)

CELGENE PROPRIETARY INFORMATION

- C-reactive protein
- HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA) will be performed by the central laboratory and/or the local laboratory at screening and will include HBV/HCV serology (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).
- Urinalysis (including, but not limited to, specific gravity, pH, glucose, protein, ketones, blood)
- Serum β-subunit of human chorionic gonadotropin (β-hCG) pregnancy test is required at screening for all female subjects of childbearing potential, including premenopausal women who have had a tubal ligation. A second confirmatory pregnancy test, either serum or urine, must be performed within 72 hours prior to the first administration of study treatment, if the initial serum pregnancy test did not already occur with 72 hours of dosing (negative results required for study treatment administration). Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted.
- Efficacy assessment/tumor evaluation (see Section 6.4).
- Fluorodeoxyglucose - positron emission tomography (FDG-PET)/CT scan to be performed whole body, or sufficient to rule out distant metastases (eg, from skull base to knees). If the CT scan portion on the chest/abdomen/pelvis areas is with contrast and is of sufficient diagnostic quality, a separate repeat tumor CT scan at screening can be skipped. Subsequent tumor assessments will be done using CT scans (or MRI if CT scan cannot be done).
  - Local assessment will be used for eligibility assessment
  - Central reader will perform a retrospective assessment
- Brain imaging by MRI with contrast or CT with contrast
  - Local assessment will be used for eligibility assessment
  - Central reader will perform a retrospective assessment
- Patient Reported Outcomes: European Organization for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC QLQ-C30), Lung Cancer Module of EORTC QLQ-C30 (LC13), [redacted]
- Collect archival tumor tissues (formalin-fixed paraffin embedded [FFPE] blocks or slides) with an associated pathological report (squamous or nonsquamous). In the absence of archival tumor tissues, a fresh biopsy (2 or 3 cores) of a tumor lesion at baseline is mandatory.

CELGENE PROPRIETARY INFORMATION

- CCI [redacted]

6.2. Treatment Period

The subject may be randomized once all inclusion/exclusion criteria are verified and subject is deemed to be eligible; this must occur within 28 days of the subject signing the ICF.

For all tislelizumab/placebo dosing visits starting with Cycle 2, an administrative window of ±3 days is permitted.

If screening assessments are performed within 72 hours of C1D1, safety laboratory and physical examinations need not be repeated at C1D1.

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

Duration of treatment cycles and schedule of study treatments administration are described in Section 7.2.

The following evaluations will be performed at the frequency specified in the Table of Events; see Table 4. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- IRT registration for subject randomization and IP assignment
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Adverse event evaluation (continuously)
- Physical examination (source documented only)
- Vital signs (temperature, systolic and diastolic blood pressure, and pulse): on-treatment vital sign measurements will be source documented only. However, if an abnormal (out of range) value is reported at any given visit, that parameter should be collected in the electronic case report form (eCRF) at every subsequent scheduled visit until it returns to normal, and as an AE if appropriate.
- Weight
- ECOG Performance status
- Left ventricular ejection fraction (LVEF) assessment by echocardiogram or other medically appropriate method (eg, MUGA), if clinically indicated
- Body surface area to be calculated and collected at chemotherapy dosing visits
- 12-lead ECG at Cycle 1 Day 1 and then as clinically indicated
- Eye exam, visual acuity test, and OCT (or equivalent diagnostic test) assessed by an appropriate specialist approximately every 15 weeks (± 7 days) during study treatment and at a final assessment less than 30 days after the last dose of study treatment. In addition, Investigators should solicit subjects regarding changes in

CELGENE PROPRIETARY INFORMATION

vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

- Hematology panel including complete blood count, differential, absolute neutrophil count and platelet count
- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, BUN, alkaline phosphatase, AST/SGOT, ALT/SGPT, serum albumin, total bilirubin, creatinine, CK and CK-MB, and if needed, troponin I and/or T)
- Coagulation panel (PT, PTT, INR)
- Thyroid function testing (TSH, free T3, free T4)
- HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA) if clinically indicated; for subjects who have detectable HBV DNA or HCV RNA at screening or upon repeat testing, respective viral load test every 4 cycles (ie, Day 1 of Cycles 5, 9, 13, etc).
- Urinalysis (including, but not limited to, specific gravity, pH, glucose, protein, ketones, blood), if clinically indicated
- Urine (or serum) β-hCG pregnancy test prior to dosing on Day 1 of each cycle for females of childbearing potential
- Efficacy assessment/tumor evaluation (see Section 6.4)
- Brain imaging by MRI with contrast or CT with contrast, only if clinically indicated
- Patient Reported Outcomes: EORTC QLQ-C30, LC13, CCI , CCI and CCI (see Section 6.7) on Day 1 of every cycle
- Anti-tislelizumab antibodies assays: serum samples will be tested for the presence of anti-drug antibodies (ADAs) to BGB-A317 using a validated immunoassay
- Blood (serum) for pharmacokinetics
- CCI
- Tislelizumab or placebo administration (see Section 7.2.1)
- Tislelizumab or placebo accountability
- Chemotherapy administration (see Section 7.2.1)
- Chemotherapy accountability
- Radiotherapy administration (see Section 7.2.2)

6.2.1. End of Treatment

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

CELGENE PROPRIETARY INFORMATION

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

- IRT registration for subject treatment discontinuation
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Adverse event evaluation (continuously)
- Physical examination (source documented only)
- Weight
- Vital signs (temperature, systolic and diastolic blood pressure, and pulse)
- ECOG performance status
- 12-lead ECG
- Left ventricular ejection fraction (LVEF) assessment by echocardiogram or other medically appropriate method (eg, MUGA), if clinically indicated
- Eye exam, visual acuity test, and OCT (or equivalent diagnostic test) assessed by an appropriate specialist should only be performed once at either the EOT or during safety follow up, within 30 days after the last dose of study treatment.
- Hematology panel including complete blood count, differential, absolute neutrophil count and platelet count
- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, BUN, alkaline phosphatase, AST/SGOT, ALT/SGPT, serum albumin, total bilirubin, creatinine, CK and CK-MB, and if needed, troponin I and/or T)
- Coagulation panel (PT, PTT, INR)
- Thyroid function testing (TSH, free T3, free T4)
- HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA) if clinically indicated; for subjects who have detectable HBV DNA or HCV RNA at screening or upon repeat testing, respective viral load test.
- Urinalysis (including, but not limited to, specific gravity, pH, glucose, protein, ketones, blood), if clinically indicated
- Urine β-hCG pregnancy test 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)
- Patient Reported Outcomes: EORTC QLQ-C30, LC13, CCI [redacted] CCI [redacted] CCI [redacted] (see Section 6.7)
- CCI [redacted]

CELGENE PROPRIETARY INFORMATION

- CCI [redacted]

6.3. Follow-up Period

6.3.1. Safety Follow-up

Subjects who discontinue tislelizumab/placebo treatment for any reason will be asked to return to the clinic for a Safety Follow-up Visit within 30 days (± 7 days) after the last study treatment or before the initiation of a new anticancer treatment, whichever comes first.

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

- Concomitant medications evaluation
- Concomitant procedures evaluation
- Adverse event evaluation (continuously until 90 days after last dose of study treatment)
- Physical examination (source documented only)
- Weight
- Vital signs (temperature, systolic and diastolic blood pressure, and pulse)
- ECOG performance status
- 12-lead electrocardiogram
- Left ventricular ejection fraction (LVEF) assessment by echocardiogram or other medically appropriate method (eg, MUGA), if clinically indicated
- Eye exam, visual acuity test, and OCT (or equivalent diagnostic test) assessed by an appropriate specialist should only be performed once at either the EOT or during safety follow up, within 30 days after the last dose of study treatment.
- Hematology panel including complete blood count, differential, absolute neutrophil count and platelet count
- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, BUN, alkaline phosphatase, AST/SGOT, ALT/SGPT, serum albumin, total bilirubin, creatinine, CK and CK-MB, and if needed, troponin I and/or T)
- Coagulation panel (PT, PTT, INR)
- Thyroid function testing (TSH, free T3, free T4)
- HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA) if clinically indicated; for subjects who have detectable HBV DNA or HCV RNA at screening or upon repeat testing, respective viral load test.
- Urinalysis (including, but not limited to, specific gravity, pH, glucose, protein, ketones, blood), if clinically indicated

CELGENE PROPRIETARY INFORMATION

- Urine β-hCG pregnancy test for females of childbearing potential
- Patient Reported Outcomes: EORTC QLQ-C30, LC13, CCI CCI and CCI (see Section 6.7) at 30 days after the last study treatment.
- CCI
- [redacted]
- Blood for pharmacokinetics
- CCI
- Survival data
- Disease therapy since IP discontinuation

All subjects will be monitored for adverse events starting from the time the subject signs the ICF until 30 days after the last dose of study treatment (tislelizumab/placebo, chemotherapy, or RT), as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to study treatment, as described in Section 10.1. Subjects will also be monitored for immune related adverse events (serious or nonserious) starting from the time the subject signs the ICF until 90 days after the last dose of tislelizumab or placebo, regardless of whether or not the subject starts a new anticancer therapy. All AEs and SAEs considered related to RT will be collected at any time after the first dose of RT, including late radiation toxicities. The 90-Day Follow-up Visit could be conducted at site or by telephone, and will also include collection of survival data and disease therapy since IP discontinuation.

6.3.2. Efficacy Follow-up

All subjects who discontinue treatment for reasons other than disease progression, start of a subsequent anticancer therapy, or withdrawal of consent from the entire study, will be followed for efficacy response assessments by CT scan or MRI 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 3 months (± 14 days) for survival until withdrawal of consent, death, or lost to follow-up, whichever occurs first, or until the End of Trial. Subsequent anticancer therapies should be collected at the same time schedule. Subsequent 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 cancer.

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

6.4. Efficacy Assessment

Tumor assessments by CT scan or MRI of the chest and abdomen/pelvis should be performed at screening within 28 days before randomization, and every 6 weeks (± 7 days) from randomization for the first 36 weeks, then every 9 weeks (± 7 days) thereafter until disease

CELGENE PROPRIETARY INFORMATION

progression, start of subsequent anticancer therapy, or withdrawal of consent from the entire study. The first 6-week tumor assessment after randomization should take place prior to initiation of monotherapy treatment (Cycle 3 Day 1). 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 with historical tumor scans evaluable per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 performed ≤ 28 days before randomization need not repeat scans for the purposes of screening, as use of historical tumor scans done within the 28-day screening window is permitted. Evaluation of response for therapeutic decisions should be performed using RECIST v1.1 guidelines (Appendix I) by Investigator assessment.

Central imaging reviewers blinded to treatment will provide independent review for disease progression and responses for all subjects enrolled into the study. Prospective collection of all on-study scans for all subjects enrolled in the study will be included as part of the review.

Films or electronic copies should be collected by the site and sent to the central imaging reviewer(s) and a copy of the file will be kept on site. Complete details regarding image handling and submission can be found in the Imaging Manual.

For immune therapies such as tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic progressive disease is suspected by the Investigator to reflect pseudoprogression, the subject may continue treatment with tislelizumab until progressive disease is confirmed by repeated imaging at least 4 weeks later but not exceeding 6 to 8 weeks from the date of initial documentation of progressive disease, provided the following criteria are met:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values).
- Stable ECOG performance status (≤ 1).
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention.

Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform subjects that this practice is not considered standard in the treatment of cancer. The decision to continue study drug(s) beyond initial Investigator-assessed progression must be discussed with the Sponsor medical monitor and documented in the study records.

CCI [redacted]

CELGENE PROPRIETARY INFORMATION

CCI

[redacted]

CELGENE PROPRIETARY INFORMATION

6.7. Patient Reported Outcomes

The predominant patient-reported lung cancer symptoms (appetite loss, cough, chest pain, dyspnea, and fatigue) assessed by the EORTC QLQ-C30 and its lung cancer module LC13 will be a predefined secondary endpoint; CCI

[redacted]

CCI [redacted]

It will be important to assess treatment effectiveness both in terms of objective outcomes (eg, PFS or OS) and subjective, patient reported outcomes (PROs) to ensure that the addition of tislelizumab to cCRT followed by tislelizumab monotherapy in newly-diagnosed, unresectable locally advanced NSCLC subjects, does not result in a detrimental impact on subjects' health-related quality of life (HRQoL) when compared to cCRT alone. This detailed information can help both clinicians and subjects to make informed and comprehensive decisions regarding the best available treatments. Patient reported outcomes are any information self-reported by the subject regarding their functioning or symptoms in relation to their health condition or therapy. Patient-reported HRQoL falls under the umbrella of PROs and covers physical symptoms and functioning domains, and usually provides an overall subject evaluation of their health and quality of life.

Patient reported outcomes will be assessed in all randomized subjects using 2 European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life instruments—the EORTC QLQ-C30 version 3 (Aaronson, 1993) and the lung cancer specific module (EORTC QLQ-LC13) (Bergman, 1994); CCI [redacted]

The EORTC QLQ-C30 and its lung cancer-specific module EORTC QLQ-LC13 are the most frequently used instruments in lung cancer subjects (Bouazza, 2017). The International Consortium for Health Outcomes Measurement (ICHOM) also recommends these instruments as PRO measures for monitoring lung cancer (Mak, 2016).

Patient-reported outcomes assessment will be performed electronically using a tablet at screening, on Day 1 of each treatment cycle, at the EOT visit and 30 days after EOT.

6.7.1. EORTC QLQ-C30

The EORTC QLQ-C30, is a 30-item, psychometrically robust, cross-culturally accepted and internationally validated questionnaire designed to be applicable to a broad spectrum of cancer subjects as a core questionnaire, assessing QoL, psychosocial burden and physical symptoms. It is classified into 15 domains including 5 functional subscales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning); 3 multi-item symptom subscales (fatigue, nausea/vomiting, and pain); a global QoL subscale; and 6 single items addressing various symptoms and perceived financial impact. All EORTC QLQ-C30 items use a 4-point Likert scale (ie, "not at all," "a little," "quite a bit," and "very much"), except the 2 items assessing global QOL (item 29 and item 30), which use a 7-point scale. The EORTC QLQ-C30 uses a recall period of one week (Aaronson, 1993; Hjermstad, 1995; King, 1996; Osoba, 1997; Osoba, 1998). Each item from the EORTC QLQ-C30 questionnaires is measured on a 4-point response scale; (not at all, a little, quite a bit, very much), with the exception of the 2 items measuring global health and QoL, which are measured on a 7-point response scale. The scale scores are linearly transformed to 0 to 100 scores (Aaronson, 1993). Scores vary from 0 (worst) to 100 (best) for the functional dimensions and GHS, and from 0 (best) to 100 (worst) for the

CELGENE PROPRIETARY INFORMATION

symptom dimensions; higher scores indicate better QoL, better functioning, or more severe symptoms, respectively. A copy of the questionnaire is presented in Appendix B.

6.7.2. EORTC QLQ-LC13

Subjects' disease-related symptoms will be assessed using the EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13; referred to here as the LC13) which is a lung-cancer specific PRO and the first module to be used in conjunction with the EORTC QLQ-C30 (Aaronson, 1993; Bergman, 1994). The LC13 covers 13 typical symptoms of lung cancer subjects, such as coughing, pain, dyspnea, sore mouth, peripheral neuropathy, and hair loss. Extensive field testing was conducted for validity, reliability, responsiveness (Bergman, 1994) as well as field studies to prove the validity of these instruments (Koller, 2015). In 2 international field studies, respectively, 883 and 735 lung cancer subjects (from Europe, North America, Australia, and Japan) completed the questionnaire pre- and on-treatment to assess the psychometric properties. The results demonstrated good reliability of the multi-item dyspnea scale. Validity was evaluated with an analysis of variance by disease stage and by performance status (Bergman, 1994). Overall, the EORTC QLQ-LC13 has undergone extensive testing and demonstrated good psychometric properties. A copy of the questionnaire is presented in Appendix C.

CCI [redacted]

CCI [redacted]

CELGENE PROPRIETARY INFORMATION

CCI

[redacted]

CELGENE PROPRIETARY INFORMATION

CCI

[redacted]

.

CELGENE PROPRIETARY INFORMATION

7. DESCRIPTION OF STUDY TREATMENTS

Tislelizumab and placebo will be supplied by the Sponsor and labeled appropriately as investigational product for this study.

Cisplatin, etoposide, carboplatin, and paclitaxel will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines. Please refer to local cisplatin, etoposide, carboplatin, and paclitaxel prescribing information for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of cisplatin, etoposide, carboplatin, and paclitaxel. The dosing schedules and dose adjustments to be followed for this study are described in Section 7.2.1, Section 7.2.2, and Section 7.2.5.

Additional information may be included on the label as needed or applicable. Label(s) for investigational product (IP, also referred to as investigational medicinal product [IMP]) will contain information as required per local health authority.

7.1. Description of Investigational Product(s)

7.1.1. Tislelizumab (BGB-A317)

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial containing a total of 100 mg antibody in 10 mL of isotonic solution.

The study drug must be kept at the temperature condition as specified on the label. Tislelizumab must be stored at temperatures between 2ºC and 8ºC (36 to 46ºF) and protected from light.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the Investigator's Brochure for other details regarding tislelizumab.

7.1.2. Placebo

At the start of the study, placebo may not be available for distribution. Until placebo becomes available, sites that randomize subjects will be required to have an unblinded pharmacist (or designated site personnel) prepare a placebo IV bag until the Sponsor supplied placebo becomes available (please refer to Section 7.2.9 for further details). The Sponsor supplied placebo is a sterile, preservative-free solution for infusion.

7.1.3. Chemotherapy

Chemotherapy dosing durations are specified in Table 5. All other aspects of management (ie, handling, storage, administration, and disposal) of cisplatin, etoposide, carboplatin and paclitaxel will be in accordance with the relevant local guidelines, package inserts and summaries of product characteristics (SmPC). For sites where the Sponsor is required to provide all study drugs including standard of care drugs, cisplatin, etoposide, carboplatin, and paclitaxel will either be supplied or reimbursed by the Sponsor or designee.

For the carboplatin/paclitaxel regimen supportive treatments are listed in Section 7.2.3.

For further details, refer to the Pharmacy Manual for the respective chemotherapies.

CELGENE PROPRIETARY INFORMATION

7.2. Treatment Administration and Schedule

7.2.1. Dosage, Administration, and Compliance

Dosing schedules for tislelizumab or placebo and chemotherapy with RT are provided in Table 5.

The dosing schedule for tislelizumab or placebo after completion of cCRT is provided in Table 6.

All subjects will be monitored continuously for AEs. Treatment modifications (eg, dose delay, reduction, interruption or discontinuation) will be based on specific laboratory and adverse event criteria, as described in Section 7.2.5.

CELGENE PROPRIETARY INFORMATION

Table 5: Timing of Dose Administration of Tislelizumab or Placebo in Combination with Chemotherapy During cCRT

Order of administration on Day 1	Drug	Dose	Route	Days	Notes
CCI					
1	Tislelizumab/Placebo	CCI		Concurrent with RT on Days 1 CCI	Day 1: infuse over 60 minutes (wait 1 hour before chemotherapy). If well tolerated, then can decrease infusion time as follows: CCI infuse over 30 minutes[a] (wait 1 hour before chemotherapy)
CCI					
CCI					
1	Tislelizumab/Placebo	CCI		Concurrent with RT on Days 1 CCI	Day 1: infuse over 60 minutes (wait 1 hour before chemotherapy) If well tolerated, then can decrease infusion time as follows: CCI: infuse over 30 minutes[a] (wait 1 hour before chemotherapy)
CCI					

CELGENE PROPRIETARY INFORMATION

Table 5: Timing of Dose Administration of Tislelizumab or Placebo in Combination with Chemotherapy During cCRT (Continued)

Order of administration on Day 1	Drug	Dose	Route	Days	Notes
	Dexamethasone[bc]	20 mg	PO or IV	Prior to paclitaxel on Days 1, 8, 15, 22, 29, and 36	For oral administration: approximately 12 and 6 hours, or for IV administration: 30 to 60 min prior to paclitaxel
	Diphenhydramine[bd]	50 mg	IV	Prior to paclitaxel on Days 1, 8, 15, 22, 29, and 36	30 to 60 minutes prior to paclitaxel
	Cimetidine or ranitidine[be]	300 mg 50 mg	IV	Prior to paclitaxel on Days 1, 8, 15, 22, 29, and 36	30 to 60 minutes prior to paclitaxel

AUC = area under the curve; BID = twice daily; cCRT = concurrent chemotherapy and radiotherapy; IM = intramuscular; IV = intravenous; PO = per oral; RT = radiation therapy.

[a] Reduction of tislelizumab or placebo infusion time from 60 minutes to 30 minutes is based on the 60-minute infusion being well tolerated. See Section 7.2.1.1.

[b] These products may be obtained by the investigational sites as local commercial products in certain countries if allowed by local regulations. These products should be prepared/stored/administered in accordance with the package inserts or summaries of product characteristics (SmPCs).

[c] Due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. In addition, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as front-line treatment whenever is clinically feasible.

[d] Or equivalent antihistamine (eg, chlorpheniramine).

[e] Or equivalent histamine H2 receptor antagonist (eg, famotidine).

CELGENE PROPRIETARY INFORMATION

[redacted]

In the event that RT is interrupted to allow recovery from toxicities, the monotherapy administration of tislelizumab or placebo (starting with Cycle 3 Day 1) will not begin until completion of the full course of RT. In this case Cycle 3 Day 1 may be delayed up to 7 days. If a subject is unable to start Cycle 3 dosing within 7 days, then Cycle 3 will be considered "missed", and dosing will resume at the scheduled Cycle 4 Day 1.

As monotherapy, tislelizumab or placebo will be administered for a duration of 12 months from the first dose of tislelizumab or placebo after completion of the cCRT period, or until disease progression, intolerable toxicity, or treatment discontinuation for another reason.

The total duration of tislelizumab (Arm 1), placebo and tislelizumab (Arm 2), and placebo (Arm 3) will be approximately 14 months, including the cCRT period.

Table 6: Timing of Dose Administration of Tislelizumab or Placebo Monotherapy After Completion of cCRT

Drug	Dose	Route	Days	Notes
Tislelizumab/Placebo	[redacted]	IV	[redacted]	Infuse over 30 minutes (with 30 minutes monitoring)

cCRT = concurrent chemoradiotherapy; IV = intravenous

7.2.1.1. Tislelizumab or Placebo

Tislelizumab or placebo will be administered on Day 1 [redacted].

Tislelizumab or placebo will be administered, before chemotherapy, by IV infusion through an IV line containing a sterile, nonpyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, after infusion of tislelizumab or placebo on Day 1 of Cycle 1 and Cycle 2, subjects must be monitored for at least 1 hour (before chemotherapy administration) in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion (C1D1) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab or placebo must not be concurrently administered with any other drug (refer to Table 5).

Details of tislelizumab or placebo and chemotherapy dose administration are summarized in Table 5.

As monotherapy, tislelizumab or placebo will be administered for a duration of 12 months from the first dose of tislelizumab or placebo after completion of the cCRT period, or until disease

CELGENE PROPRIETARY INFORMATION

progression, intolerable toxicity, or treatment discontinuation for another reason. Details of tislelizumab or placebo dose administration in monotherapy are summarized in Table 6.

Guidelines for dose delay, treatment interruption, or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Section 7.2.5, Section 8.3, and Appendix H.

Refer to the Pharmacy Manual for detailed instructions on IP preparation, storage, and administration.

7.2.1.2. Chemotherapy

Chemotherapy regimens are administered after administration of tislelizumab or placebo.

CCI [redacted]. In addition, all subjects should receive the appropriate premedications as per the local approved label. Additional premedications should be administered as per standard practice. Due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. In addition, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as front-line treatment whenever is clinically feasible.

Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin injection should not be used for the preparation and administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

Dosing of carboplatin will be based on the Calvert formula:

carboplatin dose (mg) = (Target AUC) x (GFR + 25).

For the purposes of this protocol, the glomerular filtration rate (GFR) is considered to be equivalent to the creatinine clearance (calculated by the method of Cockcroft, 1976); see Appendix G. Carboplatin dose should be calculated prior to each dose using actual weight if the subject's body weight changes by more than 10% from baseline (or the newly referred body weight) and current serum creatinine level according to local prescribing information and local practice.

Each drug in the regimen should be administered sequentially. Details of tislelizumab or placebo and chemotherapy dose administration, including order of dosing and times between doses, are summarized in Table 5.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 7.2.5.3. For commercially available drugs, please refer to the appropriate SmPC as a resource for guidelines.

CELGENE PROPRIETARY INFORMATION

Subjects will be monitored continuously for AEs and will be instructed to notify their physician immediately of any AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of each therapy.

7.2.2. Radiation Therapy

The chemotherapy should generally be delivered prior to the radiation therapy on the day of treatment. Chemotherapy doses that are missed during a weekly schedule concurrent with RT are not to be made up, but these should be documented. Every effort should be made to continue the RT during the concurrent phase in an uninterrupted manner. Should a subject develop severe esophagitis necessitating interruption of chemotherapy, the RT may continue, provided the Investigator believes supportive care will enable the subject to complete this part of the therapy without excess risk.

Prior to inclusion of any subject on this study, the radiation oncologist will evaluate the thoracic CT scan or MRI to ensure that the treatment volumes are unlikely to significantly exceed the specified normal tissue constraints. A subject will be excluded if the subject's radiation treatment plans are likely to encompass a volume of whole lung receiving ≥ 20 Gy in total (V20) of more than 38% of lung volume.

All patients will receive RT using either a standardized 3-dimentional conformal radiotherapy (3DCRT) technique, or an intensity modulated radiotherapy (IMRT) on a linear accelerator delivering a beam energy of ≥ 6 MV. The total dose of RT will be 60 Gy in 30 once-daily fractions of 2 Gy (Bradley, 2015), prescribed at the International Commission on Radiation Units and Measurements (ICRU) 50 reference point, and given according to the recommendations for radiotherapy delivery of the European Organization for Research and Treatment of Cancer (EORTC)-Radiotherapy Group (De Ruysscher, 2017) and the International Commission on Radiation Units & Measurements Report 50 (ICRU Report 50, 1993).

Weekly clinical assessments are required during the cCRT treatment. While 60 Gy in 30 fractions is the target dose of radiation, concern about patient tolerance discovered during treatment planning or delivery, for example, a V20 exceeding that recommended in the protocol, may dictate that a lower dose be administered. Definitive radiation therapy will be considered as receiving a minimum of 56 Gy to the PTV.

7.2.2.1. Radiation Dose Specifications

Subjects will receive treatment 5 days per week, in once daily fractions, 2 Gy per fraction, to a target dose of 60 Gy in 30 fractions. Normalization of the treatment plan will cover 95% of the planning target volume (PTV) with the prescription dose. The minimum PTV dose should ideally not fall below 93% of the prescription dose. All radiation doses will be calculated with inhomogeneity corrections that take into account the density differences within the irradiated volume (that is, air in the lung and bone). The maximum and minimum point doses (within the PTV) will be reported. No field reductions will be permitted and the entire PTV must be treated daily. Radiation therapy commences on Day 1 of chemotherapy, with a ± 3 days administrative window allowed. When both chemotherapy and RT are administered at the same center/location, it is recommended that RT should follow within 30 to 60 minutes of the completion of chemotherapy or post-cisplatin hydration.

CELGENE PROPRIETARY INFORMATION

When the RT is delivered at a separate location, logistic considerations may result in RT being delivered prior to the administration of chemotherapy or post-cisplatin hydration. On days where RT and/or chemotherapy are delayed for administrative reasons within the allowed protocol window of 3 days, this will not be considered a protocol violation, provided the full planned dose of RT is administered**.**

7.2.2.2. Variations of Dose Prescription

The variations in dose prescription are described here, and summarized in Table 7 below.

No deviation: ≥ 99% of the PTV receives at least 93% of the prescribed dose, and no volume > 1 cm^3 within the PTV receives > 110% of the prescribed dose, and no more than a contiguous volume of 1 cm^3 outside the PTV receives a maximum of 110% of the prescribed dose, and the volume of both lungs (%) receiving a dose of 5Gy or higher (V5) is ≤ 65%.

Minor deviation: Deviations of this magnitude are not desirable, but are acceptable. Between < 99% but > 95% of the PTV receives at least 93% of the prescribed dose, or a contiguous volume of > 1 cm^3 within the PTV receives > 110% but < 115% of the prescribed dose, or a contiguous volume of >1cm^3 outside the PTV receives > 110% but < 115% of the prescribed dose, or V5 is > 65% but ≤ 80%.

Major deviation: Doses in this region are not acceptable. Less than 95% of the PTV is covered by 93% of the prescribed dose, or a contiguous volume of >1 cm^3 within the PTV receives > 115% of the prescribed dose, or a contiguous volume of >1 cm^3 outside the PTV receives > 115% of the prescribed dose, or V5 > 80%.

Table 7: Summary of Dose Prescription Variations

	No Deviation	**Minor Deviation**	**Major Deviation**
PTV volume coverage	≥ 99% of PTV receives at least 93% of prescribed dose	> 95% but <99% of PTV receives at least 93% of prescribed dose	< 95% of PTV receives 93% of prescribed dose
Excessive dose within PTV	No contiguous volume > 1 cm^3 within the PTV receives > 110% of prescribed dose	> 1 cm^3 contiguous volume within PTV receives > 110% but < 115% of prescribed dose	> 1 cm^3 contiguous volume within PTV receives
Excessive dose outside PTV	No contiguous volume > 1 cm^3 outside PTV receives > 110% of prescribed dose	> 1 cm^3 contiguous volume outside PTV receives > 110% but < 115% of prescribed dose	> 1 cm^3 contiguous volume outside PTV receives > 115% of prescribed dose
Excessive V5 dose	V5 ≤ 65%	V5 > 65% but ≤ 80%	V5 > 80%

Abbreviations: PTV = planning target volume; V = volume.

CELGENE PROPRIETARY INFORMATION

7.2.2.3. Localization, Simulation, and Immobilization

Each subject will be positioned in an institutional specific immobilization device in the treatment position on a flat table. All planning CT scans should be performed in the treatment position using the same immobilization device for setup as is used at the linear accelerator. Optimal immobilization is critical for this protocol in order to ensure reproducibility of the daily setup. Either a conventional (non-4D CT) treatment planning CT study or a 4-dimensional computed tomography (4DCT) will be performed. Conventional CT scans will be performed during quiet, uncoached respiration while the subject undertakes a normal respiration, using at least 5-mm slices through the entire target volume. The whole thorax (cricoid to L2) should be covered using < 1 cm slices in order to generate dose-volume histograms to be calculated of the lungs, spinal cord, heart, and esophagus. A treatment planning FDG-PET/CT scan (or FDG-PET alone) with the subject in the treatment position can be used for treatment planning. Where a PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan.

The gross tumor volume (GTV), Internal Target Volume (ITV) and PTV will be defined on all appropriate slices (see definitions in Section 7.2.2.4). Intravenous contrast during the planning CT is optional, provided that a recent diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, intravenous contrast can be administered during the planning CT, if this is considered necessary in the view of the radiation oncologist. If contrast is used, the densities can be overridden or the contrast scan could be registered to a noncontrast scan for planning purposes. Acceptable methods of accounting for tumor motion include design of the PTV to cover the excursion of the lung primary cancer and nodes during breathing such as an ITV approach, breath-holds (eg, Eleckta ABC device), or respiratory gating (for example, Varian RPM system).

7.2.2.4. Radiation Treatment Planning

Three-Dimensional Conformal Radiotherapy (3DCRT)

The PTV is to be treated with any combination of coplanar or noncoplanar 3D conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. The treatment plan used for each subject will be based on an analysis of the volumetric dose, including dose-volume histogram analyses of the PTV and critical normal structures. Each field is to be treated daily.

Intensity Modulated Radiation Therapy

The use of intensity modulated radiation therapy (IMRT) is permitted, provided that the institution has been using this technique for treating lung cancer for at least 6 months prior to study activations. As IMRT results in a greater proportion of out of target lung receiving radiation outside the PTV, it is recommended to maintain the total lung V5 level at 65% or less.

7.2.2.5. Radiation Treatment Documentation

Centers participating in this study will perform heterogeneity corrections for all study treatment planning. It is recognized that differences between calculation algorithms in the different treatment planning systems may result in dose variations for individual subjects. However, the clinical impact of this variation is likely to be limited when compared with other potential

CELGENE PROPRIETARY INFORMATION

sources of variation that may arise in a multicenter trial, including interinstitutional and interclinician variations in contouring the GTV.

On the first day of therapy, and periodically thereafter in accordance with standard department protocols, one of the following verification procedures will be performed: a cone-beam CT scan, portal image of each field of 3DCRT or orthogonal images that localize the isocenter placement. These images should be compared to localization films and discrepancies corrected. These images will not be submitted for central review.

Dose volume histograms will be generated for PTV, both lungs, lungs minus PTV, spinal cord, esophagus, and heart. The following dose values should be recorded:

- Prescription point dose
- Minimum, maximum, and mean dose in PTV
- Maximum dose to spinal cord
- V20 and V5

7.2.2.6. Organs at Risk

Contouring of normal tissues and organs for radiotherapy planning will be in accordance with published guidelines (Kong, 2011). Normal tissue constraints shall be prioritized in the following order for treatment planning:

1 = spinal cord, 2 = lungs, 3 = heart, 4 = esophagus, and 5 = brachial plexus

Spinal cord: The spinal canal will be contoured and taken to represent the spinal cord. The maximum cord dose will be limited to 46 Gy, but subjects who receive up to 48 Gy in order to ensure adequate tumor dose will be considered to have as a minor deviation. Subjects who receive more than 48 Gy to the cord will be counted as a major deviation.

Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with spinal cord dose constraints. The volume of both lungs (total lung volume minus PTV) that receive more than 20 Gy (V20) should not exceed 35%. All V20s up to 38% will be permitted and viewed as a minor deviation, provided the treating radiation oncologist believes this level of exposure is within subject tolerance.

Heart: The heart will be contoured on all slices and detailed guidance for contouring is Feng, 2011. The cranial border will include the infundibulum of the right ventricle and the apex of both atria, and exclude the great vessels as much as possible. The caudal border is defined as the lowest part of the left ventricle that is distinguishable from the liver. The recommended dose limits are 60 Gy < 1/3; 45 Gy < 2/3; and 40 Gy < 100% of the heart.

Esophagus: Esophagitis is an expected side effect of concurrent therapy and has a relationship to higher doses of radiation encompassing the entire esophageal circumference. The outer wall of the esophagus will be contoured completely throughout the length of esophagus that is encompassed by a dose of radiation ≥ 46 Gy.

Brachial Plexus: For tumors in close proximity to the brachial plexus, the plexus should be contoured to ensure that the maximal point dose to this structure is kept under 64 Gy.

CELGENE PROPRIETARY INFORMATION

Radiation toxicities will be assessed according to NCI CTCAE v5.0 criteria and reported per Section 10.1. Note, radiation toxicities can arise more than 90 days after the completion of radiation therapy.

7.2.2.7. Quality Assurance and Compliance with Protocol-defined Radiation Prescription (Quality Control)

A formal radiotherapy quality assurance (QA) program will be a mandatory component of this study. Eligible radiotherapy facilities will complete a facility questionnaire in order to ensure that they are equipped to deliver radiation to the required quality. Prior to randomization of the first subject, sites will need to have undergone a "benchmarking" process where a 3-dimensional CT scan of an anonymized clinical case with stage III NSCLC will be electronically transmitted to participating sites by the QA program, and the local radiation oncologists from the sites will be required to contour target volumes and organs-at-risk volumes, in accordance with the quality assurance criteria specified for thoracic radiation therapy as defined in the approved RT QA program. This process will serve to ensure protocol-compliant contouring and radiotherapy planning. The radiotherapy plans will be reviewed by physicists and a radiation oncologist at the QA program, who will provide appropriate feedback to sites participating in this benchmarking.

Early-treatment Subject Dosimetry Review:

An early-treatment subject dosimetry review of the treatment plan will be conducted for at least one case per center. The treatment plan feedback should be provided to the center by the time 5 fractions (10 Gy) have been delivered to the first study subject. The objective of the review is to gain additional assurance that subjects treated at the site will conform to the protocol radiation requirements. Additional QA dosimetry reviews may be done subsequently in a sample of cases during the course of the study. Subjects may have their radiation field altered based on information obtained from these QA reviews. This should be sufficient to ensure adherence to the radiation prescription defined in the protocol.

Post-treatment Subject Dosimetry Review:

All subjects treated by radiation in the study will have a retrospective radiation dosimetry review by the QA program, either during the course of the study or at the completion of the study, to correlate the degree of local control and toxicity with adherence to the protocol radiation prescription. This will be a confirmation of the treatment delivered, and an overall assessment of compliance with protocol stipulations regarding radiation treatment.

7.2.2.8. Radiation Adverse Events and Interruption

Investigators will be advised to suspend the use of chemotherapy given with radiation if they believe that continuing chemotherapy administration will compromise delivery of full-dose radiation in an uninterrupted manner.

Reversible or permanent alopecia, bone marrow toxicity, esophagitis and skin pigmentation are expected side effects of radiation therapy. Radiation-induced myocarditis and spinal cord injury rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation-induced changes and subsequent fibrosis of the lung may occur within lung volumes receiving ≥ 20 Gy. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

CELGENE PROPRIETARY INFORMATION

- In case of interruptions due to machine breakdown or public holidays or any interruptions of radiation therapy up to 7 days, radiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported.
- During cCRT, esophagitis is managed according to Table 13 and Table 17 for the cisplatin/etoposide and carboplatin/paclitaxel regimens, respectively, and Table 9 and Table 10 in regard to RT. During this cCRT period, in case of Grade 3 esophagitis related to chemotherapies or tislelizumab or placebo, chemotherapies or tislelizumab or placebo should be held if the Investigator believes continued use will jeopardize the delivery of full-dose RT, and radiation is to be continued. Retreatment with chemotherapies and/or tislelizumab or placebo is permitted if there is resolution of the esophagitis to ≤ Grade 2.

  If Grade 4 esophagitis related to RT, chemotherapies or tislelizumab or placebo occurs, RT, chemotherapies, and/or tislelizumab or placebo should be held until resolution of the esophagitis to ≤ Grade 2.
- During cCRT, in case of Grade 3 or Grade 4 radiation pneumonitis/lung infiltrates related to RT, the recommendation is to hold RT, chemotherapies and tislelizumab or placebo. Retreatment with RT, chemotherapies and tislelizumab or placebo is acceptable if symptoms resolve to ≤ Grade 1 or are controlled on prednisolone ≤ 10 mg/day (or equivalent corticosteroids). Discontinue study treatment if symptoms persist with corticosteroid treatment.

Radiation toxicities will be assessed according to NCI CTCAE v5.0 criteria and reported per Section 10.1. Note, radiation toxicities can arise more than 90 days after the completion of radiation therapy.

Esophagitis

The first symptoms of acute esophagitis usually start in the second or third week of RT, commonly at the dose of 18.0 to 21.0 Gy of standard fractionated RT (Wei, 2006), and include a sensation of difficult swallowing (dysphagia). This may progress to painful swallowing of food and saliva (odynophagia) and later to constant pain not necessarily related to swallowing. In severe cases, subjects may not be able to swallow at all and may require intravenous hydration, feeding through a gastric tube and, in rare cases, parenteral nutrition.

Symptomatic esophagitis is common with combined modality therapy (Werner-Wasik, 2005) and it does not constitute a reason to interrupt or delay radiotherapy or chemotherapy, provided oral intake is sufficient to maintain hydration. Symptoms of acute esophagitis may persist for 1 to 3 weeks after completion of RT. If CTCAE Grade 4 esophagitis occurs and treatment is interrupted, every effort should be made to limit the interruption to 3 treatment days or less. Subjects requiring hospitalization, placement of a feeding tube in the stomach, or intravenous feedings because of esophagitis may have their treatment interrupted in order to allow for healing of the esophageal mucosa.

Table 13 and Table 17 summarize the dose modifications of the chemotherapy regimens in cases of esophagitis Grade 3 or 4.

Table 8 lists esophagitis grading and clinical states according to the CTCAE v5.0.

CELGENE PROPRIETARY INFORMATION

Table 8: CTCAE Scale: Acute Esophagitis Related to Radiation

Grade	Clinical State
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; altered eating/swallowing; oral supplements indicated
3	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated
4	Life-threatening consequences; urgent operative intervention indicated
5	Death

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; TPN = total parenteral nutrition.

Acute esophageal toxicity should be managed with diet and medications, alone or in various combinations (Table 9 and Table 10), or comparable regimen, and intervention should be initiated at the first signs or symptoms of esophageal toxicity.

Table 9: Dietary and Nutritional Support Recommendations for Acute Radiation Esophagitis

Supportive Measure	Recommendation
Dietary modification	• Consider dietician referral • Avoid potentially irritant foods (tobacco, alcohol, coffee, and spicy foods) • Soft, bland diet • Small, frequent meals
Nutritional support	• Liquid meal replacements/supplements • Intravenous hydration • Electrolyte correction • For prolonged symptoms, enteral feeding or total parenteral nutrition may be required, although former is preferred • Antiemetics may be beneficial

Modified from Baker, 2016

Table 10: Recommendations for Medication Management of Radiation Esophagitis

Treatment Option	Management of Esophagitis
1	Ketoconazole 200 mg PO QD
2	Fluconazole 100 mg PO QD until the completion of radiation
3	Mixture of: viscous lidocaine 60 mL + Mylanta (or generic equivalent antacid) 30 mL + sucralfate (1 gm/mL) 10 mL. Take 15 to 30 mL PO q3 to 4h PRN

CELGENE PROPRIETARY INFORMATION

Table 10: Recommendations for Medication Management of Radiation Esophagitis (Continued)

Treatment Option	Management of Esophagitis
4	Ranitidine 150 mg PO BID (or other histamine-2 [H2] receptor blocker or a proton pump inhibitor such as omeprazole) until completion of radiation
5	Grade 4 esophagitis: hold CRT until Grade 2 or less

Abbreviations: BID = twice daily; CRT = chemoradiotherapy; h = hour; PO = oral; PRN = when necessary; q = every; QD = every day.

7.2.3. Supportive Care

Subjects should receive full supportive care, including epoetin and other hematopoietic growth factors (eg, colony-stimulating factors [CSFs]), transfusions of blood and blood products, antibiotics, antiemetics, other applicable medications, as needed according to local standard of care guidelines or practices.

Subjects on the carboplatin/paclitaxel regimen should receive supportive care including dexamethasone, antihistamines and histamine H2 antagonists according to SmPCs, local standard of care guidelines, or practices; refer to Table 5.

7.2.4. Overdose or Incorrect Administration

Any overdose (defined as ≥ 600 mg of tislelizumab or placebo in a 24-hour period, greater than 10% of the calculated chemotherapy dose, or any dose over the protocol specified RT dose) or incorrect administration of study drug should be noted in the subject's chart and on the appropriate eCRF. Adverse events associated with an overdose or incorrect administration of study drug will be recorded on the adverse event eCRF. If an overdose or incorrect administration of study treatment takes place and adverse events with significant safety influence are observed, the Sponsor or designee must be notified within 24 hours of awareness via the SAE reporting process as described in Section 10.5. Supportive care measures should be administered as appropriate.

7.2.5. Dose Delay and Modification

Every effort should be made to administer the study drugs according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines provided below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the subject's chart and recorded in the eCRF.

7.2.5.1. General Guidance Regarding Dose Modifications

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the subject's chart and recorded in the eCRF. The severity of adverse events will be graded according to the NCI CTCAE v5.0 grading system.

CELGENE PROPRIETARY INFORMATION

Chemotherapy-related toxicities should be managed according to the prescribing information of the approved product combined with institutional standard practices. The details in this section are for reference:

- Baseline body weight is used to calculate the required chemotherapy doses. Dose modifications are required if the subject's body weight changes by more than 10% from baseline (or the newly referred body weight). Chemotherapy doses should not be modified for any body weight change of less than 10%, unless there is an ongoing toxicity requiring dose modification. When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If any component of chemotherapy is temporarily interrupted, both chemotherapeutic agents will be delayed until doublet chemotherapy can be given as planned.
- In case of chemotherapy related toxicity, chemotherapy will be delayed until it has resolved to baseline or ≤ Grade 1 prior to administering the next dose of chemotherapy, with the exception of toxicities of alopecia, Grade 2 fatigue, or other AEs which, in the opinion of the Investigator, would not affect the safety evaluation of tislelizumab or placebo, in which case chemotherapy should continue as scheduled. Chemotherapy treatment may be delayed from a planned administration date up to 2 weeks for either chemotherapy regimen.
- In case of tislelizumab or placebo related toxicity, tislelizumab or placebo will be delayed until it has resolved to baseline or ≤ Grade 1 prior to administering the next dose of tislelizumab or placebo, with the exception of alopecia, Grade 2 fatigue, or other AEs which, in the opinion of the Investigator, would not affect the safety evaluation of the study drugs. Chemotherapy should continue as scheduled. If the AE is resolved within 10 days, tislelizumab or placebo will be administered on the first available day. If the AE is not resolved within 10 days, tislelizumab or placebo will be omitted. If the AE is resolved within 21 days, tislelizumab or placebo and chemotherapy will be administered on Day 1 of the next planned cycle.
- The tumor assessment schedule will not be altered if chemotherapy and/or tislelizumab or placebo are delayed or discontinued.
- Every effort should be made to continue treatments in combination when the subject's condition allows, also taking into consideration the subject's convenience for the treatment schedule.
- Following either completion of or discontinuation from chemotherapy, tislelizumab or placebo should be continued as scheduled, if clinically appropriate.
- If one component of chemotherapy is discontinued permanently during a cycle of treatment for reasons other than PD, the other component of chemotherapy could be continued per the study protocol or local practice.
- If tislelizumab or placebo is discontinued permanently during a cycle of chemotherapy concurrent with RT, the subject may continue the cCRT per the study protocol or local practice.

CELGENE PROPRIETARY INFORMATION

7.2.5.2. Dose Modification for Tislelizumab or Placebo

There will be no dose reduction for tislelizumab or placebo in this study.

Dose delays or interruptions of tislelizumab or placebo of less than 12 weeks will be permitted. Investigators should make every effort to maintain dose intensity in subjects.

Subjects may temporarily suspend study drug (tislelizumab or placebo) if they experience toxicity that is considered related to tislelizumab or placebo and requires a dose to be withheld. If a dose of tislelizumab or placebo is delayed for ≤ 10 days for a planned dosing cycle (eg, Cycle 3 Day 1), tislelizumab or placebo should be administered and all assessments should be conducted on the first available day according to the original cycle (ie, Cycle 3). If the delay is more than 10 days, the subject should skip the tislelizumab or placebo dose, and tislelizumab or placebo will be administered on Day 1 of the next planned cycle (ie, Cycle 4 Day 1, 42 days after the last dose given on Cycle 2 Day 1).

The subjects should resume tislelizumab or placebo treatment as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) within 12 weeks after last dose of tislelizumab or placebo. If the subject is unable to resume tislelizumab or placebo within 12 weeks after the last dose of tislelizumab or placebo, then the subject should be discontinued from study treatment, unless approval to continue treatment is obtained from the Sponsor medical monitor.

If a scheduled dose coincides with a holiday that precludes dosing, dosing should commence on the nearest following date (≤ 3 days after scheduled dosing) and subsequent dosing can continue on a new 21-day schedule based on the infusion date.

Subjects who discontinue treatment due to tislelizumab (or placebo) and/or chemotherapy toxicity in the absence of disease progression should continue with tumor assessments until disease progression.

Guidelines for dose modification, treatment interruption, or discontinuation, and for the management of irAEs and infusion-related reactions, are provided in detail in Section 7.2.5.2, Section 8.3, and Appendix H.

7.2.5.3. Dose Modifications of Chemotherapy

Toxicities related to chemotherapy must be resolved to baseline or ≤ Grade 1 prior to administering the next dose of chemotherapy, with the exception of alopecia, Grade 2 fatigue, or other AEs which, in the opinion of the Investigator, would not affect the safety evaluation of the study drugs. A maximum of 2 dose reductions are permitted for cisplatin and etoposide. If additional reductions are required, that chemotherapeutic agent must be discontinued. Dose reductions of one chemotherapeutic agent do not require the same dose reductions of the other chemotherapeutic agent within the combination, unless the toxicities can reasonably be attributed to both agents. Once the dose has been decreased, it should remain reduced for all subsequent administrations, or further reduced if necessary. There will be no dose escalations in this study. Chemotherapy treatment may be delayed from a planned administration date up to 2 weeks for either chemotherapy regimen.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or

CELGENE PROPRIETARY INFORMATION

holidays). Subjects should be placed back on study therapy within 2 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

Dose modification guidelines for chemotherapy, depending on the severity of toxicity and an assessment of the risk versus benefit for the subject, with the goal of maximizing subject compliance and access to supportive care, are described in Section 7.2.5.3 and Section 8.3.

For toxicities not listed, dose modifications are permitted per local standards.

During the cCRT period, it is possible that abnormal liver function tests may arise as a result of radiation to the liver, as could occur with malignancies involving the lower part of the right lung. If the Investigator believes abnormal bilirubin or transaminase elevations are due to radiation and not due to drug effects and that no dose modifications are necessary, continued full-dose chemotherapy may proceed after agreement with Sponsor.

7.2.5.3.1. Cisplatin and Etoposide

7.2.5.3.1.1. Hematologic Toxicity

Dose adjustments at the start of a subsequent cycle of study treatment will be based on platelet and neutrophil nadir (lowest value) counts from the preceding cycle. Prior to treatment, the ANC must be ≥ 1.5 x 10^9/L and platelets must be ≥ 100 x 10^9/L (Table 11).

Table 11: Lab parameters to Initiate Cisplatin and Etoposide Regimen

Laboratory Parameter	Value
ANC	≥ 1.5 X 10^9 cells/L
Platelets	≥ 100 X 10^9 cells/L

Abbreviations: ANC = absolute neutrophil count

Treatment may be delayed up to 2 weeks to allow sufficient time for recovery. Upon recovery, treatment should be administered according to the guidelines in Table 12.

Table 12: Dose Modifications for Cisplatin and Etoposide Based on Hematologic Nadir Values Prior to the Next Dose

ANC (x10^9L)		Platelet (x10^9L)	Dose for etoposide (mg/m^2)	Dose for Cisplatin (mg/m^2)
≥ 0.5	and	≥ 50	100% of previous dose	100% of previous dose
< 0.5	and	≥ 50	75% of previous dose	75% of previous dose
< 1.0 + fever of ≥ 38.3°C[a]	and	≥ 50	75% of previous dose	75% of previous dose
Any	and	< 50	75% of previous dose	50% of previous dose
Any	and	≤ 25	50% of previous dose	50% of previous dose

CELGENE PROPRIETARY INFORMATION

Table 12: Dose Modifications for Cisplatin and Etoposide Based on Hematologic Nadir Values Prior to the Next Dose (Continued)

ANC ($x10^9$L)		Platelet ($x10^9$L)	Dose for etoposide (mg/m^2)	Dose for Cisplatin (mg/m^2)
Any	and	< 50 with bleeding[b]	50% of previous dose	50% of previous dose
Recurrence of Grade 3 or 4 after 2 dose reductions (with either neutropenia or thrombocytopenia)			Discontinue subject from study treatment	

Abbreviations: ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events.
[a] These criteria meet the CTCAE v5.0 definition of ≥ Grade 3 febrile neutropenia (NCI 2006).
[b] This criterion meets the CTCAE v5.0 definition of ≥ Grade 3 bleeding (NCI 2006).

7.2.5.3.1.2. Nonhematologic Toxicity

In general, for nonhematologic toxicities greater than or equal to Grade 3, treatment should be delayed until resolution to less than or equal to the subject's baseline value before resuming treatment at a reduced dose. However, exceptions may be made for Grade 3 neurotoxicity or esophagitis. In the case of neurotoxicity, the Investigator and subject may decide to continue treatment at a reduced dose, with no delay required, as neurotoxicity may not resolve to baseline values. Adjustments for esophagitis should follow dose modifications as described in Table 13, which lists the relevant dose adjustments of etoposide and cisplatin for nonhematologic toxicities.

Table 13: Dose Modifications for Cisplatin and Etoposide Based on Nonhematologic Toxicity

Event[a]	Dose for Etoposide (mg/m^2)	Dose for Cisplatin (mg/m^2)
Other toxicity Grade 0 to 2	100% of previous dose	100% of previous dose
Diarrhea Grade 0 to 2 requiring hospitalization	100% of previous dose	100% of previous dose
Mucositis Grade 3 or 4	75% of previous dose	100% of previous dose
Esophagitis Grade 3[b]	Hold at the Investigator's discretion	Hold at the Investigator's discretion
Esophagitis Grade 4[c]	Hold etoposide	Hold cisplatin

CELGENE PROPRIETARY INFORMATION

Table 13: Dose Modifications for Cisplatin and Etoposide Based on Nonhematologic Toxicity (Continued)

Event[a]	Dose for Etoposide (mg/m^2)	Dose for Cisplatin (mg/m^2)
Hepatic toxicity (transaminase elevation) Grade 3 or 4	75% of previous dose	75% of previous dose
Neurotoxicity Grade 2	100% of previous dose	50% of previous dose
Neurotoxicity Grade 3[d, e]	75% of previous dose	discontinue cisplatin
Neurotoxicity Grade 4	Discontinue etoposide	Discontinue cisplatin
Any Grade 3 or 4 not specified above	75% of previous dose	75% of previous dose
Recurrence of any Grade 3 or 4 toxicity after 2 dose reductions	Discontinue etoposide	Discontinue cisplatin

[a] Except nausea and/or vomiting.
[b] Grade 3 esophagitis will occur in a significant number of subjects toward the end of radiation therapy. For subjects who experience this event earlier in the course of their treatment than anticipated, the advice would be to hold chemotherapy and assess at weekly intervals. If symptoms do not progress at the time of assessment, chemotherapy can be resumed at 75% of previous dose for both drugs.
[c] Grade 4 esophagitis results in holding chemotherapy until toxicity resolves to ≤ Grade 2, and then chemotherapy may be resumed at 75% of previous dose for both drugs.
[d] Delay until resolution of toxicity to baseline value is not required for Grade 3 neurotoxicity.
[e] At the discretion of the attending physician, subjects experiencing Grade 3 neurologic toxicity as a transient ischemic attack that has completely resolved may not require dose reduction or discontinuation.

Table 14 lists dose modification for cisplatin based on renal toxicity.

Table 14: Dose Modifications for Cisplatin Based on Renal Toxicity

Day	Calculated CrCl (mL/min)	Cisplatin dose (mg/m^2)
On Days 1 and 8 of the subsequent cycle	≥ 60	100% of previous dose
On Days 1 and 8 of the subsequent cycle	< 60	Omit cisplatin dose, delay 1 week
If, after 1-week delay	≥ 60	75% of previous dose and increase pre- and post- cisplatin hydration

CELGENE PROPRIETARY INFORMATION

Table 14: Dose Modifications for Cisplatin Based on Renal Toxicity (Continued)

Day	Calculated CrCl (mL/min)	Cisplatin dose (mg/m^2)
If, after 1-week delay	< 60	Notify Sponsor to determine if further chemotherapy is possible

Abbreviations: CrCl = creatinine clearance

7.2.5.3.2. Carboplatin and Paclitaxel

Before starting a new cycle of treatment, the creatinine clearance of the subject must be ≥ 45 mL/minute.

During the concurrent treatment, carboplatin (AUC = 2) and paclitaxel (40 to 50 mg/m^2) are administered intravenously on Day 1 of a weekly cycle (Days 1, 8, 15, 22, 29, and 36, during cCRT period). Prior to treatment, ANC must be ≥ 1.5 X 10^9 cells/L, and platelets must be ≥ 100 X 10^9 cells/L (Table 15). Chemotherapy treatment may be delayed up to 2 weeks from a planned administration date; if toxicities have not resolved to acceptable levels at that time notify the Sponsor's medical monitor to determine if further chemotherapy is possible. Doses that are missed during the weekly schedule concurrent with radiation will not be made up but will be documented.

7.2.5.3.2.1. Hematologic Toxicity

Table 15: Parameters to Initiate Carboplatin and Paclitaxel Regimen

Laboratory Parameter	Value
Creatinine clearance	≥ 45 mL/minute
ANC	≥ 1.5 X 10^9 cells/L
Platelets	≥ 100 X 10^9 cells/L

Abbreviations: ANC = absolute neutrophil count

Treatment may be delayed to allow sufficient time for recovery. Upon recovery, treatment should be administered according to the guidelines in Table 16 and Table 17 for hematologic toxicities and nonhematologic toxicities, respectively.

Table 16: Dose Modifications for Carboplatin and Paclitaxel Based on Hematologic Toxicities

Adverse Event		Treatment
Febrile neutropenia; documented infection		Chemotherapy delay until recovered to ≤ Grade 1 (ANC ≥ 1.5 x 10^9/L)
Neutropenia	Grade 3 or 4	Chemotherapy delay until ≤ Grade 1 (ANC ≥ 1.5 x 10^9/L)
Thrombocytopenia	≥ Grade 2 to 4	Chemotherapy delay until ≤ Grade 1 (platelets < LLN - 75,000/mm^3)

CELGENE PROPRIETARY INFORMATION

Table 16: Dose Modifications for Carboplatin and Paclitaxel Based on Hematologic Toxicities (Continued)

Adverse Event		Treatment
Thrombocytopenia	≥ Grade 3 associated with clinically significant bleeding	Discontinue chemotherapy

Abbreviations: ANC = absolute neutrophil count; LLN = Lower limit of normal

7.2.5.3.2.2. Nonhematologic Toxicity

For toxicities not listed in Table 17, dose modifications are permitted per local standards.

Table 17: Dose Modifications for Carboplatin and Paclitaxel Based on Nonhematologic Toxicity

Event	Dose for Carboplatin (AUC)	Dose for Paclitaxel (mg/m^2)
Ototoxicity Grade 3 to 4	Hold chemotherapy until ≤ Grade 2	
Neuropathy Grade 2	Continue carboplatin	Hold paclitaxel until ≤ Grade 1
Neuropathy Grade 3	Continue carboplatin	Discontinue paclitaxel
Neuropathy Grade 4	Discontinue chemotherapy	
Esophagitis Grade 3[a] or 4[b]	Hold chemotherapy until ≤ Grade 2	
Oral mucositis or stomatitis Grade 4	Discontinue chemotherapy	
Diarrhea Grade 4	Discontinue chemotherapy	
Other non-hematologic toxicity Grade 3 to 4	Hold chemotherapy until ≤ Grade 1 or baseline[c]	
Any toxicity which recurs after 2 prior dose delays for the same drug-related AE	Discontinue chemotherapy	

Abbreviations: AE = adverse event; AUC = are under the curve.

[a] Grade 3 esophagitis will occur in a significant number of subjects toward the end of radiation therapy. For subjects who experience this event earlier in the course of their treatment than anticipated, the advice would be to hold chemotherapy and assess at weekly intervals. If symptoms do not progress at the time of assessment, chemotherapy can be resumed.

[b] Grade 4 esophagitis results in holding chemotherapy until toxicity resolves to ≤ Grade 2, and then chemotherapy may be resumed.

[c] Skin reactions, paronychia, alopecia, fatigue, nausea/vomiting or other AEs which, in the opinion of the Investigator, would not affect the safety evaluation of tislelizumab or placebo, may resolve to Grade 2 or baseline.

7.2.6. Specific Considerations

Treatment may be delayed allowing a subject sufficient time to recover from treatment-related toxicity.

Any subject who has had 2 dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from chemotherapy treatment.

CELGENE PROPRIETARY INFORMATION

7.2.7. Clinically Significant Effusions

If a subject develops clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) and the Investigator determines that the effusion represents disease progression, it is recommended that the effusion be drained for cytologic evaluation for disease progression if clinically feasible. If the effusion represents disease progression, the subject should be discontinued from study treatment and tumor assessment by imaging must be performed prior to initiation of subsequent anti-cancer therapy. This imaging needs to be submitted for central review as for any other imaging for tumor assessment.

7.2.8. Creatinine Clearance

Enrollment and dosing decisions should be based on calculated CrCl using the standard Cockcroft and Gault formula (Cockcroft, 1976; see Appendix G).

Local laboratory values used for serum creatinine may be used to calculate CrCl for enrollment or dosing decisions; however, if local laboratories are used to calculate CrCl, the same local laboratory must be used throughout the study. In addition, a separate serum specimen must be collected before the initiation of treatment and whenever subsequent samples are collected for dosing decisions. These additional samples will be sent to a central laboratory and used for subsequent safety analyses.

For subjects receiving cisplatin/etoposide, the CrCl should be ≥ 60 mL/min prior to the start of any cycle; if a subject's CrCl has not returned to ≥ 60 mL/min within 42 days after the last study therapy administration, the subject must be discontinued from the study treatment unless continuation is approved by the Sponsor. For subjects receiving carboplatin/paclitaxel, the CrCl should be ≥ 45 mL/min prior to the start of any cycle; if a subject's CrCl has not returned to ≥ 45 mL/min within 42 days after the last study therapy administration, the subject must be discontinued from the study treatment unless continuation is approved by the Sponsor.

7.2.9. Blinding

This is a randomized, double-blind, Phase 3 study. Subjects will be randomized to receive tislelizumab or placebo in a double-blind fashion.

At the start of the study, placebo may not be available for distribution. Until placebo becomes available, sites that randomize subjects will be required to have an unblinded pharmacist (or designated site personnel) prepare a placebo IV bag for subjects randomized to placebo identical in appearance to those provided to the infusion team for subjects randomized to tislelizumab. Once placebo becomes available, sites will use the Sponsor supplied placebo. All subjects, study site staff and Sponsor representatives, with the exception of designated individuals, will remain blinded to the subject's randomized treatment arm.

For sites that receive tislelizumab and placebo exclusively from the Sponsor (meaning, the site does not use institution-supplied placebo at any point in the trial), the subject, all study site staff and Sponsor representatives, with the exception of designated unblinded individuals, will be blinded to the subject's randomized treatment arm.

- Emergency unblinding

Emergency unblinding for AEs may be performed through the study IRT.

CELGENE PROPRIETARY INFORMATION

In case of an emergency, the Investigator or designated site personnel, as documented in the delegation of authority log, has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor medical monitor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, the Sponsor must be notified immediately.

- Inadvertent unblinding

Every effort will be made to blind both the subject and the Investigator to the identity of tislelizumab or placebo, but the inadvertent unblinding of a subject may occur. If an Investigator, site personnel performing assessments, or subject is unblinded, the unblinding will not be sufficient cause (in and of itself) for that subject to be discontinued from study therapy or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the subject remain on tislelizumab or placebo. For subjects to continue on tislelizumab or placebo in the event of unblinding, the Investigator must obtain specific approval from the Sponsor's medical monitor.

7.3. Method of Treatment Assignment

Subjects who enter screening will be assigned the next available subject number. All eligible subjects will be randomized by IRT via 1:1:1 ratio to either one of the following treatment groups:

[redacted]

The permuted block randomization method will be used to generate the randomization codes and the randomization will be performed by IRT to ensure a 1:1:1 treatment assignment ratio. The randomization schedule will be generated by the Sponsor or its designee. The randomization will be stratified by age ([redacted]), chemotherapy regimen ([redacted]), and region ([redacted]).

If one of the tislelizumab arms (Arm 1 or Arm 2) is discontinued at study interim due to safety findings, and the Sponsor decides to continue the study with the remaining tislelizumab arm and the control arm (Arm 3), the newly recruited subjects will be randomized to the remaining 2 arms using a 1:1 randomization ratio, until the originally planned sample size of 560 in the remaining 2 arms is reached.

CELGENE PROPRIETARY INFORMATION

7.4. Packaging and Labeling

The label(s) for IP will include the 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.

7.5. Investigational Product Accountability and Disposal

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

Accountability for study drug that is administrated 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 study drug received, to whom it was administered (subject-by-subject accounting), and accounts of any tislelizumab or placebo accidentally or deliberately destroyed or returned. Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF and source documents. Unless otherwise notified, all vials of study drug, 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 vials of study drug to the Sponsor at the end of the study, or the study drug 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 vials.

7.6. Investigational Product Compliance

Accurate recording of all IPs administered will be made in the appropriate section of the subject's eCRF and source documents. The Investigator or designee is accountable for the compliance of all study-specific IPs either administered or in their custody during the course of the study.

CELGENE PROPRIETARY INFORMATION

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 study treatments or disease progression. Supportive care, including but not limited to antiemetic medications, may be administered at the discretion of the Investigator.

[redacted]

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

8.1. Permitted Concomitant Medications and Procedures

Most concomitant medications and therapies deemed necessary for supportive care (eg, antiemetics, antidiarrheal) and in a subject's interest are allowed. All treatments that the Investigator considers necessary for a subject's health and safety purpose may be administered at the discretion of the Investigator in keeping with the local standards of medical care. All concomitant medication including all prescription, over-the-counter, herbal supplements, and IV medications and fluids will be recorded on the eCRF. If changes (dose, stop, or start) in concomitant medication occur during the study, documentation of drug dosage, frequency, route, date, and reason for use will be recorded on the eCRF.

All concomitant medications received within 28 days before randomization and 30 days after the last infusion or dose of study treatment should be recorded.

Systemic corticosteroids required for the control of irAEs must be tapered over at least 1 month and be at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab or placebo administration. The short-term use of steroids as prophylactic treatments (eg, subjects with contrast allergies to diagnostic imaging contrast dyes) is also permitted.

Subject may continue to receive hormone replacement therapy or supportive care if initiated prior to enrollment.

Premedications and postmedications per the chemotherapy labels and per local guidelines are permitted.

The use of bisphosphonates during the trial for a nonmalignant indication is permitted.

Hematopoietic growth factors such as growth-colony stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) may be used according to institutional or other specific guidelines (eg, country, regional, or oncology organizations, such as American Society of Clinical Oncology [ASCO], etc.) to treat febrile neutropenia and Grade 3 to 4 neutropenia, but should not be used as primary or secondary prophylaxis. The use of any growth factor support must be documented in the subject's record and eCRF. Growth factors must be discontinued at least 48 hours prior to initiation of the next cycle of study drug.

According to the NCCN 2018 guidelines (NCCN, 2018), erythropoiesis-stimulating agents (ESAs) may be considered for the treatment of cancer-related anemia in subjects undergoing

CELGENE PROPRIETARY INFORMATION

palliative treatment. Erythropoietic therapy may be considered for treatment of study drug-induced anemia in cases where hemoglobin is < 11 g/dL or a decrease of ≥ 2 g/dL from baseline, but only after the subject has been counseled about the risks and benefits of ESA use.

8.2. Prohibited Concomitant Medications and Procedures

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

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent) within 14 days before randomization and during the study, except to treat or control a drug-related AE or for short-term use as prophylactic treatment (eg, antiemetic therapy for specific chemotherapy).
- Any concurrent antineoplastic therapy (ie, chemotherapy, targeted therapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer).
- Extensive radiation therapy during monotherapy (except for local, palliative radiotherapy provided that it does not compromise tumor assessments of target lesions).
- Live vaccines within 28 days before randomization and 60 days following the last dose of study drugs. (NOTE: seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.)
- During cisplatin and carboplatin use, concurrent therapy with drugs having a potential ototoxic or nephrotoxic effect (eg, aminoglycosides, cefalotine, furosemide, amphotericin B) should be avoided or adequately monitored since this may lead to increased or exacerbated toxicity due to platin-induced changes in renal clearance of these substances.
- The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a PK drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (eg ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (eg, rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.
- Refer to the approved product labeling for complete information regarding drug-drug interactions.
- The following are also excluded during the study:
  - Herbal remedies with immunostimulating properties (ie, mistletoe extract) or known to potentially interfere with major organ function (ie, hypericin)

CELGENE PROPRIETARY INFORMATION

– Subject should not abuse alcohol or other drugs during the study.

The following guideline should be also followed during the study:

- With the exception of diagnostic biopsy of tumor tissue or placement of a venous access device, the Investigator should discuss with the medical monitor any individual subject requiring surgery during the study.
- Eligible subjects for this study must have locally advanced, stage III NSCLC that is considered to be unresectable. Any subject for whom the institutional practice would consider surgery to be a treatment option if disease downstaging is observed after completion of the chemoradiotherapy should have been considered ineligible for participation in the study. Thus, surgical resection of NSCLC due to subsequent downstaging of the stage III NSCLC after chemoradiotherapy prior to progression is prohibited during the course of the study.

8.3. Required Concomitant Medications and Procedures

8.3.1. Management of Immune-related Adverse Events

Immune-related AEs are of special interest in this study. If the events listed below or similar events occur, the Investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, disease progression or other neoplastic causes) with appropriate diagnostic tests, which may include but are not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out and the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune mediated mechanism of action, the irAE indicator in the eCRF AE page should be checked.

A list of potential irAEs is shown below in Table 18. All conditions similar to those listed should be evaluated in subjects receiving tislelizumab or placebo to determine whether they are immune-related.

Recommendations for diagnostic evaluation and management of irAEs (see Appendix H) are based on a recent ESMO guideline (Haanen, 2017). For any adverse events not included in Appendix H, please refer to the recent ESMO guideline for further guidance on diagnostic evaluation and management of immune-related toxicities.

Table 18: Immune-Related Adverse Events

Body System Affected	Events
Skin (mild-common)	Pruritus or maculopapular rash; vitiligo
Skin (moderate)	Follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet's syndrome
Skin (severe-rare)	Full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	Colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation

CELGENE PROPRIETARY INFORMATION

Table 18: Immune-Related Adverse Events (Continued)

Body System Affected	Events
Endocrine	Thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	Pneumonitis/diffuse alveolitis
Eye	Episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	Arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	Anemia; leukopenia; thrombocytopenia
Renal	Interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	Pericarditis; myocarditis; heart failure

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase

The management of irAEs is detailed in Appendix H.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, tislelizumab or placebo should be discontinued after consultation with the Sponsor. Subjects who experience a recurrence of any event at the same or higher severity grade with rechallenge should permanently discontinue treatment.

8.3.2. Management of Infusion Reactions

The symptoms of infusion-related reactions include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Subjects should be closely monitored for such reactions. Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 19.

CELGENE PROPRIETARY INFORMATION

Table 19: Management of Infusion Reactions

NCI CTCAE Grade – severity	Guideline for Modification of Tislelizumab or Placebo Treatment
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease tislelizumab or placebo infusion rate by 50% and closely monitor any worsening. Manage medically as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions have resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe 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.	Immediately discontinue the tislelizumab or placebo infusion. Proper medical management should be instituted as described below. The subject should be withdrawn from tislelizumab or placebo treatment.
Grade 4 – life threatening Life threatening consequences; urgent intervention indicated.	Immediately and permanently discontinue tislelizumab or placebo treatment. Proper medical management should be instituted as described below.

Abbreviations: IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug.
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.
For further information, please refer to CTCAE v5.0.

Once the tislelizumab or placebo infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions with premedication. If the subject has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued, and the subject should be withdrawn from tislelizumab or placebo treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, subjects should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

CELGENE PROPRIETARY INFORMATION

NCI-CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.3.3. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (Soar, 2008). Subjects should be instructed to report any delayed reactions to the Investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction (typically manifested within minutes following administration of the drug/antigen and characterized by: respiratory distress; laryngeal edema; and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea), the infusion must be immediately stopped and the subject discontinued from the study.

The subjects will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed and then the subject should be placed on monitor immediately and ICU should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drugs(s) infusion. Alternative treatments for fever (ie, paracetamol) may be given to subjects at the discretion of the Investigator.

8.3.4. Treatment of Hepatitis B and Hepatitis C

Patients with active hepatitis B defined as either detectable HBsAg or HBV DNA at baseline must initiate treatment 2 weeks prior to randomization or first dose, and continue until 6 months after the last dose. Patients should continue effective antiviral treatment during the study to decrease potential viral re-activation risk. Peg-IFN, tenofovir, and entecavir are recommended in the American Association for the Study of Liver Disease guideline because they lack resistance with long-term use (Terrault, 2016). The Investigator might use other antiviral agents, if appropriate, following local guidelines. Management of antiviral therapy is at the discretion of the Investigator.

Patients with active hepatitis C should undergo treatment with antiviral therapy following the American Association for the Study of Liver Diseases guideline or the local guidelines as appropriate. However, interferon-based therapy for either HBV or HCV is not permitted on study.

CELGENE PROPRIETARY INFORMATION

9. STATISTICAL CONSIDERATIONS

9.1. Overview

[redacted] The study protocols BGB-A317-NSCL-001 and BGB-A317-NSCL-001C have a total combined enrollment target of 840 subjects. [redacted] The data from both study protocols will be collected into one database and the statistical analyses as described in Section 9 will be performed on the combined total of subjects randomized into either the main protocol or the companion protocol. A single IDMC and blinded independent central review will be utilized for these 2 study protocols.

This is a Phase 3, randomized, double-blind, placebo-controlled study designed to compare efficacy and safety in either tislelizumab concurrent with chemoradiotherapy followed by tislelizumab monotherapy (Arm 1), or placebo concurrent with chemoradiotherapy followed by tislelizumab (Arm 2), versus placebo concurrent with chemoradiotherapy followed by placebo (Arm 3), in subjects with locally advanced, unresectable non-small cell lung cancer. The primary treatment comparisons are the pairwise comparisons of either one of the tislelizumab arms (Arm 1 or Arm 2) versus the control Arm (Arm 3).

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 Definition

9.2.1. Intent-to-treat Population

The intent-to-treat (ITT) population will consist of all randomized subjects regardless of whether the subjects receive any IP or have any efficacy assessment conducted.

9.2.2. Safety Population

The safety population will include any subjects who receive at least one dose of tislelizumab or placebo. In safety analyses, subjects will be included in treatment groups according to the actual treatment they receive, if the treatment received is different from the randomized treatment group.

9.2.3. Per Protocol Population

The per protocol population will include all subjects in the safety population who have met all the eligibility criteria and have no major protocol violation.

CELGENE PROPRIETARY INFORMATION

9.3. Power and Sample Size Consideration

9.3.1. Multiplicity Control Strategy

There are 2 primary hypotheses in this study:

- H_1: PFS in Arm 1 ≤ Arm 3 versus PFS in Arm 1 > Arm 3
- : PFS in Arm 2 ≤ Arm 3 versus PFS in Arm 2 > Arm 3

CCI [redacted]

There will be one interim and one final analysis for PFS, and one interim and one final analysis for OS, respectively. The interim OS analysis will occur at the same as the final PFS analysis. Therefore, there will be 3 data cutoff time points in this study:

[redacted]

Although PFS is the primary endpoint of this study and the final PFS analysis will be completed at the second data cutoff time point, the study may continue to follow up for overall survival until a prespecified total number of OS events accumulates, if either of the PFS hypotheses are rejected at the interim or the final PFS analysis.

A group sequential design is implemented based on Lan-Demets spending function that approximates the O'Brien-Fleming boundary for each of the primary hypotheses for the PFS endpoint. The hypotheses associated with the key secondary endpoint OS

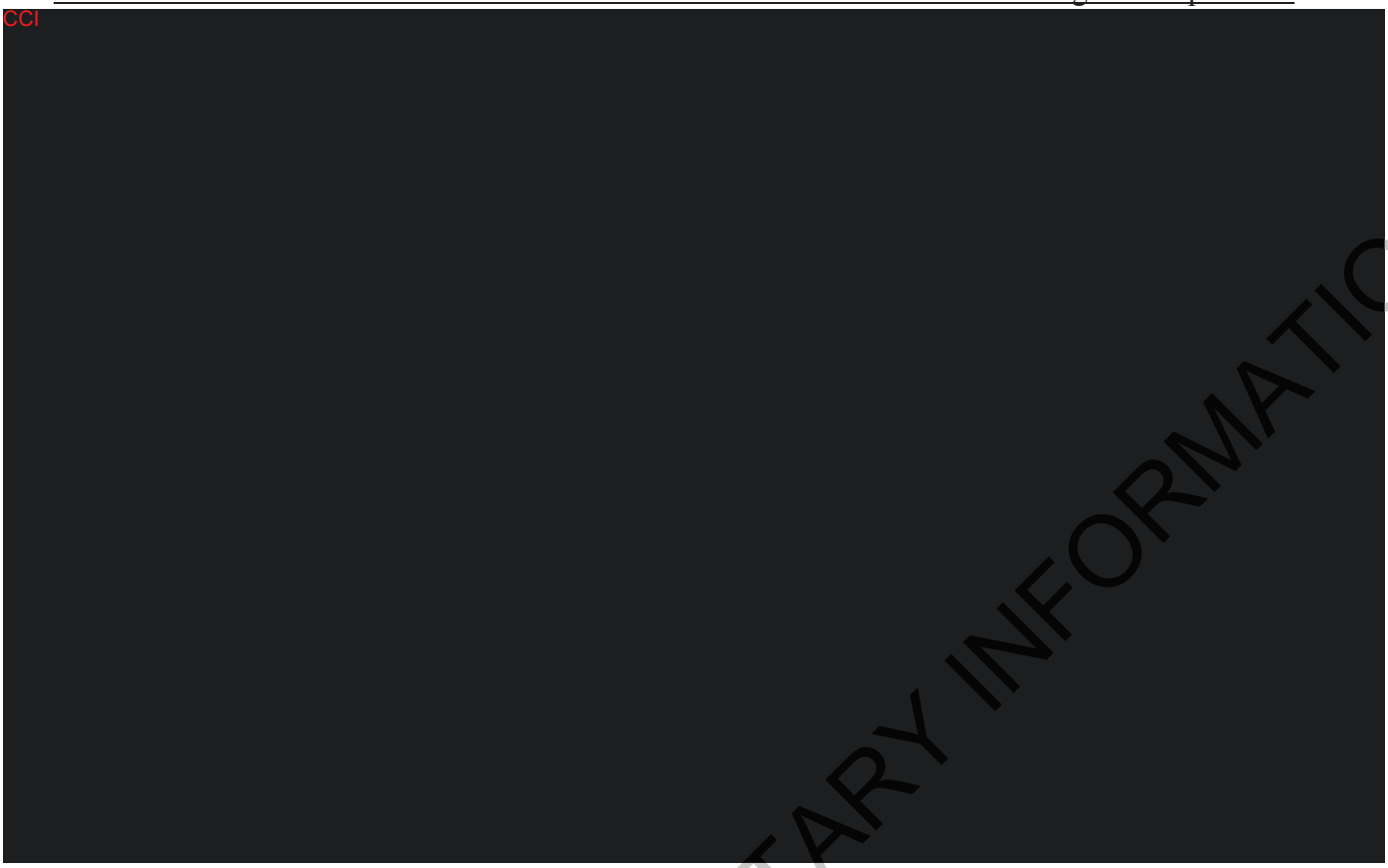
- H_3: OS in Arm 1 ≤ Arm 3 versus OS in Arm 1 > Arm 3
- H_4: OS in Arm 2 ≤ Arm 3 versus OS in Arm 2 > Arm 3

will be tested only if either one of the primary hypotheses for PFS is rejected at the interim or the final PFS analysis. In addition, the other 2 key secondary endpoints, OS at 24 months (OS 24) and ORR, will also be tested if both the PFS and OS hypotheses in the same pairwise comparison of treatment groups are rejected.

The overall type one error rate control strategy here follows the graphic approach as described by Maurer and Bretz (Maurer, 2013), and can be depicted by the following graph. The local alpha will be dynamically determined by given spending function of the group sequential design for each endpoint (Glimm, 2010; Maurer, 2013).

CELGENE PROPRIETARY INFORMATION

CCI



Of note, if Arm 1 or Arm 2 is discontinued, and the study continues with one of the tislelizumab arms and the control arm, the graph will be simplified to the left (or right) half of the graph. The edges in between the 2 OS hypotheses will be removed, and the weight for edges from the OS endpoint to the OS 24 and ORR endpoint will be updated to 1/2, but other edges and the alpha allocation for each hypothesis in the remaining half graph will stay the same as in the initial graph.

Additionally, to control the type one error due to multiple looks of OS data at the interim and the final OS analysis, a group sequential design based on an alpha spending function that approximates the O'Brien-Fleming boundary will also be implemented for either one of the OS hypotheses. The actual boundaries will depend on the number of OS events, or information time, at the time of second interim analysis. Similar alpha control approach will be implemented for the other key secondary endpoints OS 24 and ORR. Notably, if one or more hypotheses are rejected at the interim or final analysis, the superiority boundaries for the remaining unrejected hypotheses will be updated based on the alpha propagation strategy as described by Maurer and Bretz (Mauer, 2013) using the graph above.

CELGENE PROPRIETARY INFORMATION

9.3.2. Power and Sample Size

CCI [redacted] Assuming a constant enrollment rate of 30 subjects per month, and a median PFS of 9 months in the placebo arm, it will take approximately 28 months to enroll 840 subjects, and 35 months to accumulate a total of 580 PFS events.

CCI [redacted] The time for the final OS analysis when approximately 572 total OS events accumulates is projected to be 61 months.

The median PFS in the control arm (Arm 3) is based on data from historical trials with similar subjects. Ahn (2015) and Belderbos (2007) reported that the median PFS for inoperable (unresectable) stage III NSLC treated with concurrent chemoradiotherapy are 8.1 months and 8.5 months, respectively. Factoring in potential improvements in best supportive care, a conservative estimate for median PFS of 9 months for the control arm is used for the sample size and power calculation.

For the target PFS treatment effect, a hazard ratio of 0.7 is considered as a clinically meaningful improvement of PFS and is used for the sample size and power calculation. This target is considered reasonable based on the cross-trial evaluation of historical data for cCRT described above, including that from the recently published PACIFIC study results. T0 is considered as PFS from cCRT treatment and T1 as PFS from anti-PD-L1 consolidation (durvalumab) treatment for subjects who have stable disease or better following cCRT. Heuristically, the cCRT + anti-PD-1 PFS is approximated as $T = T0(T0 \leq 2) + (2 + T1)(T0 > 2)$ for first line treatment. Fitting historical medians of T0 and T1 and conducting simulations, the median PFS is close to 14.6 months, which corresponds to an approximately 38% improvement consistent with the target hazard ratio of 0.7.

A similar assessment was performed for overall survival. The median OS in the control arm is estimated at 22 months from Ahn (2015). The target hazard ratio of 0.7 is considered a clinically meaningful improvement.

CCI [redacted]

CELGENE PROPRIETARY INFORMATION

CCI

CCI

[redacted]

[redacted]

9.4. Background and Demographic Characteristics

Subjects age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race, region, and other categorical variables will be presented using frequency tabulation. Medical history data will be summarized using frequency tabulation by system organ class and preferred term.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency tabulation for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

The primary efficacy analysis will be conducted based on ITT population. The primary and key secondary endpoints will also be analyzed using per protocol population. While key analyses are described in this section, additional analyses, including subgroup analyses, will be specified in the statistical analysis plan (SAP).

CELGENE PROPRIETARY INFORMATION

9.6.1. Primary Efficacy Endpoint

The primary endpoint of progression free survival is defined as the time from randomization to the time of progression based on blinded independent reviewer assessment using RECIST v1.1 or death, whichever is earlier. Subjects without progression or death will be censored according to censoring rules similar to those described in the FDA Guidance for Industry Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (FDA, 2007). The distribution of PFS will be estimated using the Kaplan-Meier method. The comparison of PFS between treatment arms (Arm 1 versus Arm 3 or Arm 2 versus Arm 3) will be conducted using a stratified log-rank test with age[CCI]), chemotherapy regimen [CCI] [CCI]), and region ([CCI] as stratification factors. The hazard ratio (between Arm 1 or Arm 2 versus Arm 3) and the corresponding 95% confidence interval will also be provided based on a stratified Cox proportional hazard model. The median PFS (with 95% confidence interval) and estimation of PFS rate (with 95% confidence intervals) for specific time points (eg, 3 months, 6 months etc.) will be provided for each treatment arm.

9.6.2. Secondary Efficacy Endpoints

9.6.2.1. Overall Survival

The key secondary endpoint of overall survival (OS) is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of analysis will be censored at the last-known-to-be-alive date. The distribution of OS will be estimated using Kaplan-Meier method. A stratified log-rank test will be used to compare treatment groups in OS. The median OS (with 95% confidence interval) and estimation of OS rate (with 95% confidence intervals) for different timepoints will be provided by treatment arm. The hazard ratio (between Arm 1 or Arm 2 versus Arm 3) and the corresponding 95% confidence interval will also be provided based on a stratified Cox regression model.

9.6.2.2. OS at 24 Months

The key secondary endpoint OS at 24 months is defined as the proportion of subjects alive at 24 months (OS 24). The point estimate and the corresponding 95% confidence interval for each treatment arm will be estimated using Kaplan-Meier method. The treatment comparisons for OS 24 will be performed using an approach as described in Klein, 2007.

9.6.2.3. Objective Response Rate

The key secondary endpoint of objective response rate (ORR) is defined as the percentage of subjects who achieve a CR or PR based on the independent reviewer assessment using RECIST v1.1 criteria. The ORR for each treatment arm will be summarized using 95% Clopper-Pearson confidence interval. The difference in ORR between treatment arms and the associated 95% Wilson score confidence interval will be provided. A Cochran-Mantel-Haenszel (CMH) test will be used to compare ORR between treatment arms.

9.6.2.4. Other Secondary Endpoints

The proportion of subjects alive and progression free at 12 months (APF12) or 18 months (APF18) will be summarized (using the Kaplan-Meier curve) and presented by treatment arm.

CELGENE PROPRIETARY INFORMATION

For each treatment arm, the APF12 or APF18 based on the Kaplan-Meier method will be presented, along with its 95% confidence interval. Treatment comparisons for APF12 and APF18 will be based on the approach as described in Klein, 2007.

Time to distant metastasis (TTDM) will be defined as the time from the date of randomization until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST v1.1 or proven by biopsy. Time to distant metastasis will be analyzed using similar methods as described for the analysis of PFS.

The duration of response (DOR) is defined as the time from the first tumor assessment when the CR/PR response criterion is first met to the date of disease progression based on independent reviewers' assessment following RECIST v1.1 criteria.

Patient reported outcome validated instruments (EORTC QLQ-C30 with the lung module LC13) will be used to assess the selected lung cancer symptoms: appetite (item 13 of QLQ-C30), cough (items 31 to 32 of LC13), chest pain (item 40 of LC13), dyspnea (items 33 to 35 of LC13), and fatigue (items 10, 12, 18 QLQ-C30). Baseline scores, postbaseline scores and change from baseline will be provided on global domain and subdomains (as applicable) per arm. Count and percent of subjects with minimal clinically important benefit from baseline scores will be summarized per arm. Count and percent of subjects improving, with no change and worsening their baseline score will be summarized per arm. Time to minimal clinically important improvement and decline in selected scores will be examined. Missing values will be addressed according to questionnaire guidelines. Analysis for selected efficacy variables versus change in selected EORTC QLQ-C30 and LC-13 scales will also be provided to explore the relationship between clinical response and HRQoL. The details will be provided in the separate SAP.

The proportion of subjects who received at least one dose of tislelizumab or placebo in the monotherapy phase before progression based on blinded independent reviewer assessment following RECIST v1.1 criteria, will be compared for Arm 1 versus Arm 2 and 3 combined. The proportion will be summarized using point estimate and 95% Clopper-Pearson confidence interval for Arm 1 versus Arm 2 and 3. The difference between treatment arms and the associated 95% Wilson score confidence interval will be provided. A Cochran-Mantel-Haenszel (CMH) test will be used to compare the proportion.

9.7. Safety Analysis

Safety analysis will be performed based on the safety population. Safety and tolerability will be monitored through continuous reporting of AEs and serious adverse events (SAEs), laboratory abnormalities, and incidence of subjects requiring dose modifications, dose interruptions, and/or premature discontinuation of IP. The safety population will be the primary analysis population for safety analyses. Descriptive statistics will be provided for summaries of adverse events, clinical laboratory data, and other safety assessments.

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs), defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever occurs first. Treatment-emergent AEs also include all immune-related AEs (irAEs) recorded up to 90 days after the last dose of tislelizumab

CELGENE PROPRIETARY INFORMATION

or placebo, regardless of whether or not the subject starts a new anticancer therapy. All events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events will be summarized per treatment arms by MedDRA system organ class and preferred terms. Grade 3 or higher TEAEs, SAEs, TEAEs leading to dose reduction and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized per treatment arms by MedDRA system organ class and preferred terms. Additionally, adverse events of special interest for tislelizumab will be summarized in the same manner.

CCI [redacted]

CCI [redacted]

.

9.9. Other Topics

9.9.1. Data Monitoring Committee

An IDMC will be convened that will include medical oncologists with experience in treating subjects with lung cancer and a statistician, all of whom are not otherwise involved in the study conduct. During the study, the IDMC will review the safety and efficacy data in accordance with the guidelines for the preplanned interim analyses. There will be IDMC safety assessments during which the IDMC will examine unblinded safety data including but not limited to serious adverse events, adverse events, and other safety data individually and in aggregate and will provide recommendations on the continuation of the 3 arms based on safety and tolerability. [redacted]

CCI [redacted]

Enrollment may continue during these IDMC safety assessments.

An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, to the IDMC members for each scheduled meeting. Operational details for the IDMC will be detailed in the IDMC charter.

CELGENE PROPRIETARY INFORMATION

9.9.2. 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 regions 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.

Note: The SC is separate from the IDMC.

CCI [redacted]

CELGENE PROPRIETARY INFORMATION

[redacted]

CELGENE PROPRIETARY INFORMATION

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 7.2.4 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 tislelizumab, cisplatin, carboplatin, etoposide, or paclitaxel 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 subjects will be monitored for adverse events starting from the time the subject signs the ICF until 30 days after the last dose of study treatment (tislelizumab/placebo, chemotherapy, or RT), as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to study treatment. Subjects will also be monitored for immune related adverse events (serious or nonserious) starting from the time the subject signs the ICF until 90 days after the last dose of tislelizumab or placebo, regardless of whether or not the subject starts a new anticancer therapy. All AEs and SAEs considered related to RT will be collected at any time after the first dose of RT, including late radiation toxicities.

Adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

CELGENE PROPRIETARY INFORMATION

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.

CELGENE PROPRIETARY INFORMATION

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.

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

CELGENE PROPRIETARY INFORMATION

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 because 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).

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).

CELGENE PROPRIETARY INFORMATION

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.

Study participants receiving chemotherapy have a potential risk of irreversible infertility. Patients should be advised to speak to their physician for further information about their locally available options for fertility preservation.

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 120 days after the subject's last dose of tislelizumab or placebo and 180 days after the subject's last dose of chemotherapy, are considered immediately reportable events. Investigational product is to be discontinued immediately. 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 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 by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

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

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, 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 criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

CELGENE PROPRIETARY INFORMATION

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 30 days after the last dose of study treatment; until 90 days after the last dose of tislelizumab or placebo for irSAEs regardless of whether or not the subject starts a new anticancer therapy) or any SAE made known to the Investigator at any time thereafter that is suspected of being related to IP. All SAEs considered related to RT will be collected at any time after the first dose of RT, including late radiation toxicities. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

[redacted]

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.

10.5.1. Safety Queries

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

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to tislelizumab based on the Investigator's 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.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to non-Celgene IMP study drugs (cisplatin, etoposide, carboplatin, and paclitaxel) based on the following Reference Safety Information documents:

- Cisplatin- EU Summary of Product Characteristics (SmPC)
- Etoposide- EU SmPC
- Carboplatin- EU SmPC

CELGENE PROPRIETARY INFORMATION

- Paclitaxel- EU SmPC

Celgene or its authorized representative shall notify the Investigator of the following information (In Japan, Celgene KK shall notify the Heads of the Institutes in addition to the Investigators):

- 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.
- Other important safety information and periodic reports according to the local regulations.

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.)

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

CELGENE PROPRIETARY 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
- Symptomatic deterioration (global deterioration of health status)
- Withdrawal by subject
- Death
- Lost to follow-up
- Pregnancy
- Study terminated by Sponsor
- 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 from the investigational product, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

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

- Screen failure
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- 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.

CELGENE PROPRIETARY INFORMATION

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 Sponsor 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

The blind must not be broken during the course of the study **unless** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the IRT.

CELGENE PROPRIETARY INFORMATION

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 for 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 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.

[redacted]

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.

CELGENE PROPRIETARY INFORMATION

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.

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 PROPRIETARY INFORMATION

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.

CELGENE PROPRIETARY INFORMATION

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. [redacted]

CELGENE PROPRIETARY INFORMATION

- [redacted]

[redacted]

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.

CELGENE PROPRIETARY INFORMATION

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 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, European Medicines Agency, 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

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the subjects. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified,

CELGENE PROPRIETARY INFORMATION

tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing PPD or by contacting the Celgene Customer Care Center PPD

CELGENE PROPRIETARY INFORMATION

16. PUBLICATIONS

[redacted]

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

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

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

CELGENE PROPRIETARY INFORMATION

17. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

Ahn JS, Ahn YC, Kim J-H, Lee CG, Cho EK, Lee KC, et al. Multinational Randomized Phase III Trial With or Without Consolidation Chemotherapy Using Docetaxel and Cisplatin After Concurrent Chemoradiation in Inoperable Stage III Non-Small-Cell Lung Cancer : KCSG-LU05-04. J Clin Oncol 2015 Aug 20;33(24):2660-2670.

American Cancer Society. [Internet]. Non-small cell lung cancer survival rates, by stage. [updated 2017 Dec 18; cited 2018 Mar 26]. Available from: https://www.cancer.org/content/cancer/en/cancer/non-small-cell-lung-cancer/detection-diagnosis-staging/survival-rates#references.

American Joint Committee on Cancer: AJCC Cancer Staging Manual. 2017. 8th ed. New York (NY): Springer.

Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al; PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017 Nov 16;377(20):1919-29.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Aupérin A, Le Péchoux C, Pignon JP, Koning C, Jeremic B, Clamon G, et al. Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MAC3-LC) Group. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. Ann Oncol. 2006 Mar;17(3):473-83.

Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010 May 1;28(13):2181-90.

Baker S, Fairchild A. Radiation-induced esophagitis in lung cancer. Lung Cancer (Auckl). 2016; 7:119–127.

Bayman N, Blackhall F, McCloskey P, Taylor P, Faivre-Finn C. How can we optimise concurrent chemoradiotherapy for inoperable stage III non-small cell lung cancer? Lung Cancer. 2014 Feb;83(2):117-25.

CELGENE PROPRIETARY INFORMATION

Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, et al. Combined Chemoradiotherapy Regimens of Paclitaxel and Carboplatin for Locally Advanced Non–Small-Cell Lung Cancer: A Randomized Phase II Locally Advanced Multi-Modality Protocol. J Clin Oncol. 2005 Sep 1;23(25):5883-91.

Belderbos J, Uitterhoeve L, van Zandwijk N, Belderbos H, Rodrigus P, van de Vaart P, et al, on behalf of the EORTC LCG and RT Group. Randomised Trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer. Eur J Cancer. 2007;43:114-121.

CCI [redacted]

Berman AT, Simone CB. Immunotherapy in locally-advanced non-small cell lung cancer: releasing the brakes on consolidation? Transl Lung Cancer Res. 2016 Feb;5(1):138–142.

Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30A(5):635-42.

Bezjak A, Temin S, Franklin G, Giaccone G, Govindan R, Johnson ML, et al. Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. J Clin Oncol. 2015 Jun 20;33(18):2100-5.

CCI [redacted]

Borghaei H, Paz-Ares L, Horn L, Spigel D, Steins M, Ready N, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-1639.

Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell RD, et al. LBA49 Updated results from KEYNOTE-021 cohort G: A randomized, phase 2 study of pemetrexed and carboplatin (PC) with or without pembrolizumab (pembro) as first-line therapy for advanced nonsquamous NSCLC. Ann Oncol. 2017 Sep 01;28(suppl 5).

Bouazza YB, Chiairi I, El Kharbouchi O, De Backer L, Vanhoutte G, Janssens A, et al. Patient-reported outcome measures (PROMs) in the management of lung cancer: a systematic review. Lung Cancer. 2017 Nov, 113:140-51.

Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015 Feb;16(2):187–99.

CELGENE PROPRIETARY INFORMATION

Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt W, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-135.

Brogden KA, Parashar D, Hallier AR, Braun T, Qian F, Rizvi NA, et al. Genomics of NSCLC patients both affirm PD-L1 expression and predict their clinical responses to anti-PD-1 immunotherapy. BMC Cancer. 2018 Feb 27;18(1):225.

Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. CheckMate 026 Investigators. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med. 2017 Jun 22;376(25):2415-26.

Cheung MC, Hay AE, Crump M, Imrie KR, Song Y, Hassan S, et al. Committee on Economic Analysis and the Hematology Disease Site Committee, NCIC Clinical Trials Group. Gemcitabine/dexamethasone/cisplatin vs cytarabine/dexamethasone/cisplatin for relapsed or refractory aggressive-histology lymphoma: cost-utility analysis of NCIC CTG LY.12. JNCI: J Natl Cancer Inst. 2015 Apr 13;107(7):pii, djv106.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

Copur MD, Gauchan D, Ramaekers R. Durvalumab in stage III non–small-cell lung cancer. N Engl J Med. 2018 Mar 1;378(9):869.

Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011 Oct 5;103(19):1452-60. doi: 10.1093/jnci/djr325. Epub 2011 Sep 8.

Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014 Feb;124(2):687-95.

De Ruysscher D, Faivre-Finn C, Moeller D, Nestle U, Hurkmans CW, Le Pechoux C, et al. European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. Radiother Oncol. 2017 Jul;124(1):1-10.

Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997 Nov;35(11):1095-108.

CCI [redacted]

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer. 2001 Jul;37(11):1331-4.

CELGENE PROPRIETARY INFORMATION

Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys. 2011 79(1):10-18.

Fiorica F, Belluomini L, Stefanelli A, Santini A, Urbini B, Giorgi C, Frassoldati A, et al. Immune checkpoint inhibitor nivolumab and radiotherapy in pretreated lung cancer patients: efficacy and safety of combination. Am J Clin Oncol. 2018 Jan 31. doi: 10.1097/COC.0000000000000428. [Epub ahead of print]

Food and Drug Administration (FDA). Approved drugs. Pembrolizumab (Keytruda) 5-10-2017 [Internet]. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs / ucm558048.htm

Food and Drug Administration (FDA). FDA News Release. FDA expands approval of Imfinzi to reduce the risk of non-small cell lung cancer progressing. February 16, 2018. Available from: https://www.fda.gov/NewsEvents/ Newsroom/ PressAnnouncements/ucm597217.htm

Food and Drug Administration (FDA). Guidance for Industry Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics. May 2007. Available from: https://www.fda.gov/ downloads/Drugs/Guidances/ucm071590.pdf

Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst. 2013 Feb 20;105(4):256-65.

Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. KEYOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015 May 21;372(21):2018-28.

Ghandi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med. 2018 Apr 16. [Epub ahead of print]

Glimm E, Maurer W, and Bretz F. Hierarchical Testing of Multiple Endpoints in Group Sequential Trials. Statistics in Medicine. 2010;29: 219–228.

GLOBOCAN. [Internet]. Cancer incidence and mortality worldwide in 2012. [cited 2017 Feb 01]. Available from: http://globocan.iarc.fr/.

Goodman AM, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, et al. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther. 2017 Nov;16(11):2598-2608.

Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl 4): iv119–iv142.

Hanna N, Johnson D, Temin S, Baker S Jr, Brahmer J, Ellis P, et al. Systemic therapy for Stage IV non–small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017 Oct;35(30):3484-515.

Hellman MD, Ciuleanu T-E, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med. 2018 Apr 16. [Epub ahead of print]

CELGENE PROPRIETARY INFORMATION

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

CCI [redacted]

Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. J Clin Oncol. 1995 May;13(5):1249-54.

[ICRU] International Commission on Radiation Units and Measurements, Inc. Report 50. 1993.

Prescribing, recording and reporting photon beam therapy. ICRU, 7910 Woodmont Avenue, Suite 400, Bethesda, Maryland 20814, USA.

Jabbour SK, Berman AT, Simone CB 2nd. Integrating immunotherapy into chemoradiation regimens for medically inoperable locally advanced non-small cell lung cancer. Transl Lung Cancer Res. 2017 Apr; 6(2): 113–8.

CCI [redacted]

CCI [redacted]

King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Qual Life Res. 1996 Dec;5(6):555-67.

Klein JP, Logan B, Harhoff M, AndersenPK. Analyzing survival curves at a fixed point in time. Statist. Med. 2007;26:4505–4519.

CCI [redacted]

CCI [redacted]

Koller M, Warncke S, Hjermstad MJ, Arraras J, Pompili C, Harle A, et al. European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group; EORTC Lung Cancer Group. Use of the lung cancer–specific Quality of Life Questionnaire EORTC QLQ-LC13 in clinical trials: a systematic review of the literature 20 years after its development. Cancer. 2015 Dec 15;121(24):4300–23.

Kong FM, Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys. 2011 Dec 1;81(5):1442-57.

CELGENE PROPRIETARY INFORMATION

Labrijn AF, Buijsse AO, van den Bremer ET, Verwilligen AY, Bleeker WK, Thorpe SJ, et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. Nat Biotechnol. 2009 Aug;27(8):767-71.

Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. KEYNOTE-021 investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Nov;17(11):1497-508.

Lee CK, Man J, Lord S, Cooper W, Links M, Gebski V, et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma: a systematic review and meta-analysis. JAMA Oncol. 2018 Feb 1;4(2):210-6.

Liniker E, Menzies AM, Kong BY, Cooper A, Ramanujam S, Lo S, et al. Activity and safety of radiotherapy with anti-PD-1 drug therapy in patients with metastatic melanoma. Oncoimmunology. 2016 Aug 19;5(9):e1214788. eCollection 2016.

Mak KS, van Bommel AC, Stowell C, Abrahm JL, Baker M, Baldotto CS, et al. Defining a standard set of patient-centred outcomes for lung cancer. Eur Respir J. 2016 Sep;48(3):852-60.

Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches Statistics in Biopharmaceutical Research, 2013; 5:4, 311-320.

National Cancer Institute: Cancer Types. [Internet]. Non-small cell lung cancer treatment (PDQ®)-health professional version. [updated 2018 Feb 01, cited 2018 Mmm DD]. Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq.

National Comprehensive Cancer Network [Internet]. NCCN Guidelines for treatment of cancer: non-small cell lung cancer, version 3, 2018. [cited 2018 Jan 03]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Nomura M, Otsuka A, Yoshimura M, Nonomura Y, Kaku Y, Matsumoto S, et al. Cancer Chemother Pharmacol. 2018 Mar 3.

NSCLC Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ. 1995 Oct 7;311(7010):899-909.

Osoba D, Aaronson N, Zee B, Sprangers M, te Velde A. Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. Qual Life Res. 1997 Mar;6(2):103-8.

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139–44.

Peters S, De Ruysscher D, Dafni U, Felip E, Guckenberger M, Vansteenkiste JF, et al. Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-RT regimen in unresectable locally advanced NSCLC: The ETOP NICOLAS phase II trial. J Clin Oncol. 2018;36(suppl; abstr 8510).

CELGENE PROPRIETARY INFORMATION

Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. European Society for Medical Oncology (ESMO). Early-stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice guideline. Ann Oncol. 2017;28(suppl 4):iv1–iv21.

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016 Nov 10;375(19):1823-3.

Reck M, Socinski MA, Cappuzzo F, Orlandi F, Stroyakovskii D, Nogami N, et al. Primary PFS and safety analyses of a randomised Phase III study of carboplatin + paclitaxel +/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150). Poster presented at: ESMO Immuno-Oncology Congress 2017. Abstract Book of ESMO Immuno Oncology Congress. Geneva, Switzerland; 2017 December 7-10. Ann Oncol. 2017;28(suppl 11):abstract #LBA1-PR.

Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J. Atezolizumab versus docetaxel in patients with previously treated non-small-cell-lung cancer (OAK): a phase 3, open-label, multicenter randomized controlled trial. Lancet 2017; 389:255-65.

Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015 Apr 3;348(6230):124-8.

Rizvi H, Sanchez-Vega F, La K, Chatila W, Jonsson P, Halpenny D, et al. Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non-Small-Cell-Lung Cancer Profiled With Targeted Next-Generation Sequencing. J Clin Oncol. 2018 Mar 1;36(7):633-641.

Rodrigues G, Choy H, Bradley J, Rosenzweig KE, Bogart J, Curran WJ Jr, et al. Definitive radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. Pract Radiat Oncol. 2015 May-Jun; 5(3):141-8.

Rolland E, Le Pechoux C, Curran WJ, Furuse K, Fournel P, Uitterhoeve L, et al. Concomitant Radio-chemotherapy (CT-RT) versus Sequential CT-RT In Locally Advanced Non-Small-Cell Lung Cancer (NSCLC): A Meta-Analysis Using Individual Patient Data (IPD) From Randomised Clinical Trials (RCTs). Int J Rad Oncol Biol Phys. 2007;69:S5.

Samstein R, Rimner A, Barker CA, Yamada Y. Combined immune checkpoint blockade and radiation therapy: timing and dose fractionation associated with greatest survival duration among over 750 treated patients. Int J Rad Oncol. [Internet]. 2017 Oct 01; [cited 2018 Mar 28]. 99(2 Suppl):S129–S130. Available from: http://www.redjournal.org/article/S0360-3016(17)31355-X/pdf.

Santana-Davila R, Devisetty K, Szabo A, Sarapani R, Arce-Lara C, Gore EM, et al. Cisplatin and Etposide Versus Carboplatin and Paclitaxel With Concurrent Radiotherapy for Stage III Non-Small-Cell Lung Cancer: An Analysis of Veterans Health Administration Data. J Clin Oncol. 2015 Feb 20;33(6):567-574.

Senan S, Brade A, Wang LH, Vansteenkiste J, Dakhil S, Biesma B, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation

CELGENE PROPRIETARY INFORMATION

therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2016 Mar 20;34(9):953-62.

Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P, et al. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. Resuscitation. 2008 May;77(2):157-69.

Tislelizumab (BGB-A317) Investigator's Brochure. BeiGene, Ltd. Edition 5.0, February 2018.

Tsujino K, Kurata, T, Yamamoto S, Kawaguchi T, Kubo A, Isa S, et al. Is Consolidation Chemotherapy after Concurrent Chemo-Radiotherapy Beneficial for Patients with Locally Advanced Non–Small-Cell Lung Cancer? A Pooled Analysis of the Literature. J Thorac Oncol. 2013;8:1181-9.

CCI [redacted]

Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nat Rev Cancer. 2012 Mar 22;12(4):237-51.

Vokes EE, Herndon JE 2nd, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, et al, Induction Chemotherapy Followed by Chemoradiotherapy Compared With Chemoradiotherapy Alone for Regionally Advanced Unresectable Stage III Non–Small-Cell Lung Cancer: Cancer and Leukemia Group B. J Clin Oncol. 2007 May 1;25(13):1698-1704.

Vokes EE, Senan S, Treat JA, Iscoe NA. PROCLAIM: A phase III study of pemetrexed, cisplatin, and radiation therapy followed by consolidation pemetrexed versus etoposide, cisplatin, and radiation therapy followed by consolidation cytotoxic chemotherapy of choice in locally advanced stage III non–small-cell lung cancer of other than predominantly squamous cell histology. Clin Lung Cancer. 2009 May;10(3):193-8.

Wei X, Liu HH, Tucker SL, Liao Z, Hu C, Mohan R, et al. Risk factors for acute esophagitis in non-small-cell lung cancer patients treated with concurrent chemotherapy and three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2006 Sep 1;66(1):100-7.

Werner-Wasik M. Treatment-related esophagitis. Semin Oncol. 2005 Apr;32(2Suppl 3):60–6.

Yamamoto N, Nakagawa K, Nishimura Y, Tsujino K, Satouchi M, Kudo S, et al. Phase III Study Comparing Second- and Third-Generation Regimens With Concurrent Thoracic Radiotherapy in Patients With Unresectable Stage III Non–Small-Cell Lung Cancer: West Japan Thoracic Oncology Group WJTOG0105. J Clin Oncol. 2010 Aug 10;28(23):3739-45.

Zhang P, Su DM, Liang M, Fu J. Chemopreventive agents: induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis. Mol Immunol. 2008 Mar;45(5):1470-6.

CELGENE PROPRIETARY INFORMATION

18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 21: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
APF12	Alive and progression free at 12 months
APF18	Alive and progression free at 18 months
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CMH	Cochran-Mantel-Haenszel
cCRT	Concurrent chemoradiotherapy
CI	Confidence interval
CR	Complete response
CrCl	Creatinine clearance
CRT	Chemoradiotherapy
CSF	Colony stimulating factor
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
3DCRT	Three-dimensional conformal radiotherapy
4DCT	4-dimensional computed tomography
DNA	Deoxyribonucleic acid

CELGENE PROPRIETARY INFORMATION

Table 21: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
DOR	Duration of response
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire lung cancer module
EOT	End of treatment
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ESA	Erythropoiesis-stimulating agents
ESMO	European Society for Medical Oncology
EuroQol	European Quality of Life
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose - positron emission tomography
FFPE	Formalin-fixed paraffin embedded
GCP	Good clinical practice
G-CSF	Growth-colony stimulating factor
GFR	Glomerular filtration rate
GHS	Global health status
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GTV	Gross tumor volume
Gy	Gray
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen

CELGENE PROPRIETARY INFORMATION

Table 21: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICI	Immune checkpoint inhibitor
ICF	Informed consent form
ICH	International Council for Harmonisation
ICHOM	International Consortium for Health Outcomes Measurement
ICRU	International Commission on Radiation Units & Measurements
IDMC	Independent data monitoring committee
IFN-γ	Interferon- γ
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IMRT	Intensity modulated radiation therapy
INR	International normalized ratio
IP	Investigational product
irAE	Immune related adverse event
irTEAE	Immune related treatment-emergent adverse event
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
ITV	Internal target volume
IV	Intravenous
LC13	Lung cancer module 13
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multiple-gated acquisition scan

CELGENE PROPRIETARY INFORMATION

Table 21: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OS 24	Overall survival at 24 months
OTC	Over the counter
PBMC	Peripheral blood mononuclear cells
PE	Physical examination
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death protein-ligand 1
PD-L2	Programmed cell death protein-ligand 2
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PQC	Product Quality Complaint
PR	Partial response
PRO	Patient reported outcome
CCI [redacted]	[redacted]
PT	Prothrombin time
PTT	Partial thromboplastin time
PTV	Planning target volume
Q2W	Every two weeks
Q3W	Every three weeks
QA	Quality assurance
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
ROS-1	Proto-oncogene tyrosine-protein kinase ROS

CELGENE PROPRIETARY INFORMATION

Table 21: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
RT	Radiation therapy
RTOG	Radiation Thoracic Oncology Group
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering committee
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious AE
TSH	Thyroid stimulating hormone
CCI [redacted]	[redacted]
TTDM	Time to death or distant metastasis
UK	United Kingdom
ULN	Upper limit of normal
US	United States
V5	Volume of both lungs (%) receiving a dose of 5Gy or higher
V20	Volume of whole lung minus Planning Target Volume receiving at least 20 Gy of radiation in total expressed as a percent
WBC	White blood cell

CELGENE PROPRIETARY INFORMATION

APPENDIX B. PATIENT REPORTED OUTCOMES: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ☐☐☐☐
Your birthdate (Day, Month, Year): ☐☐☐☐☐☐☐☐
Today's date (Day, Month, Year): 31 ☐☐☐☐☐☐☐☐

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

CELGENE PROPRIETARY INFORMATION

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

CELGENE PROPRIETARY INFORMATION

APPENDIX C. PATIENT REPORTED OUTCOMES: EORTC QLQ - LC13

EORTC QLQ - LC13

Subjects sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body?	1	2	3	4

If yes, where

43. Did you take any medicine for pain?

1 No 2 Yes

If yes, how much did it help?	1	2	3	4

CELGENE PROPRIETARY INFORMATION

CCI

CELGENE PROPRIETARY INFORMATION

CCI

CELGENE PROPRIETARY INFORMATION

[redacted]

CELGENE PROPRIETARY INFORMATION

CCI CCI

CCI

CCI

CELGENE PROPRIETARY INFORMATION

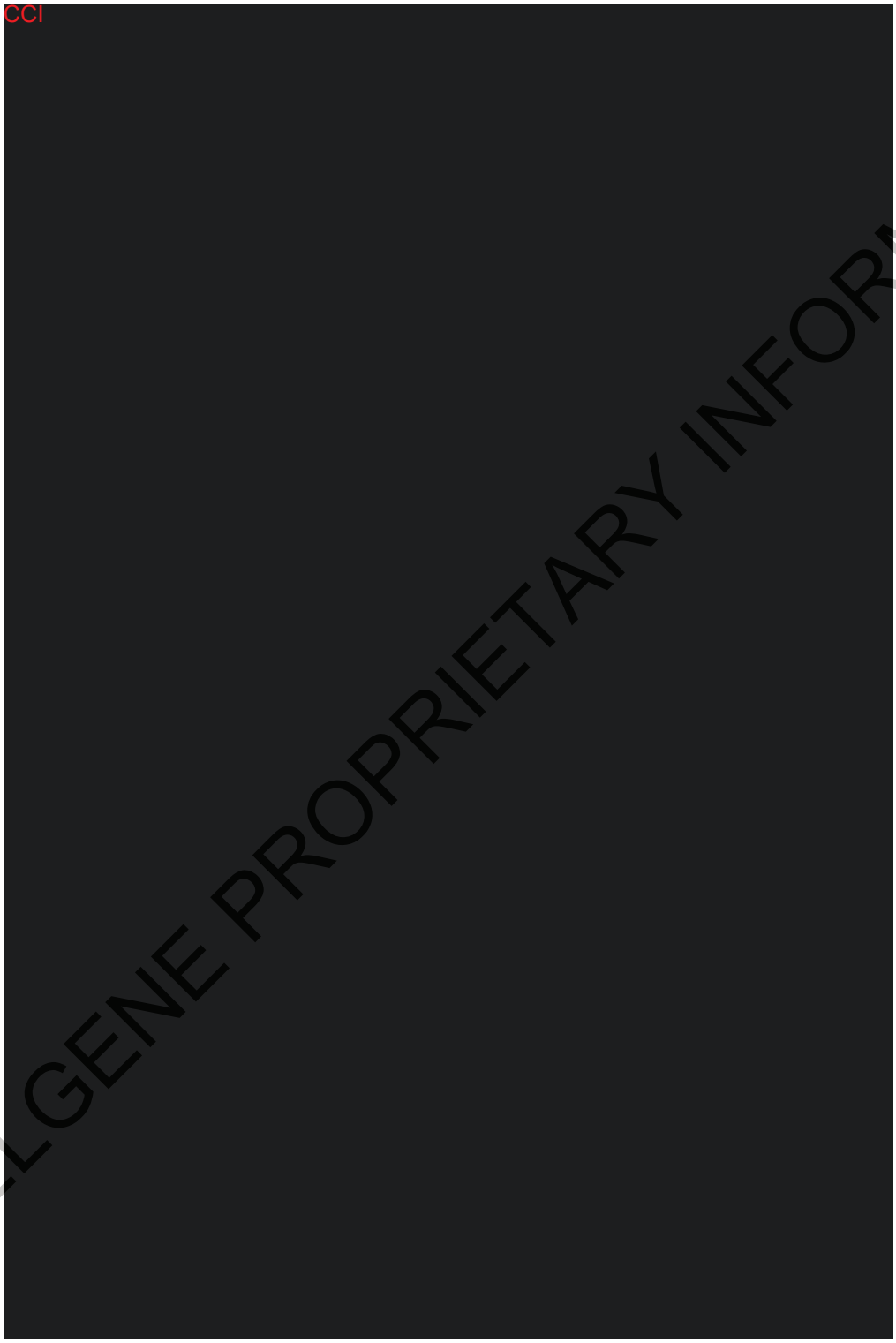
CCI

[redacted]

CELGENE PROPRIETARY INFORMATION

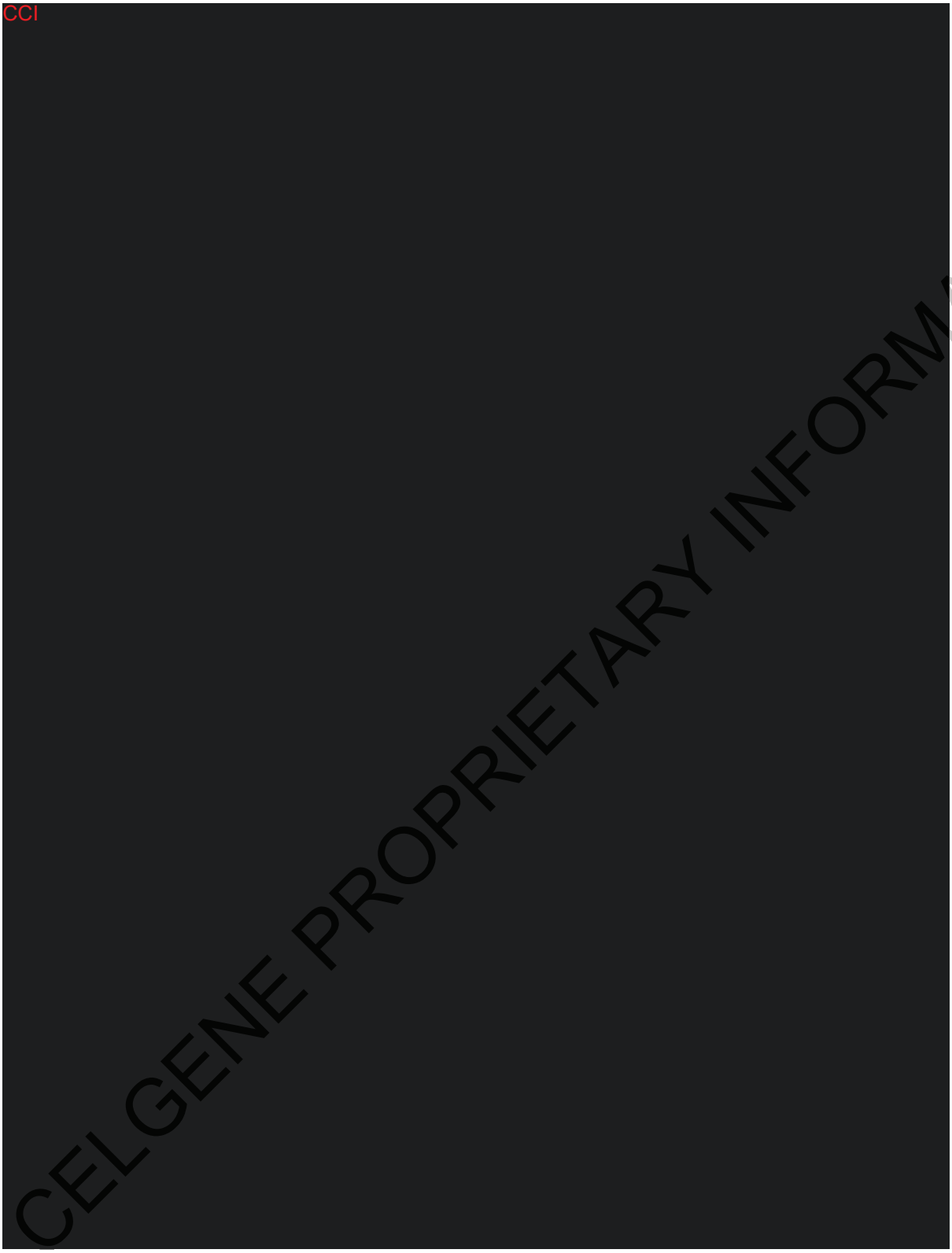
CCI CCI

CCI



CELGENE PROPRIETARY INFORMATION

CCI



CELGENE PROPRIETARY INFORMATION

APPENDIX G. CALCULATED CREATININE CLEARANCE (COCKCROFT AND GAULT 1976)

This formula should be used for calculating creatinine clearance (CrCl) from local laboratory results only. The central laboratory applies the formula and reports the value in its calculated form.

(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] X [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)

CELGENE PROPRIETARY INFORMATION

APPENDIX H. IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any irAE are intended as guidance. This document should be used in conjunction with expert clinical judgment (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

Criteria used to diagnose irAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an irAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab/placebo and the adverse event?
- How did the subject respond to withdrawal of tislelizumab/placebo?
- Did the event recur when tislelizumab/placebo was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the irAE field, associated with the AE in the eCRF should be checked.

Table 22: Recommended Diagnostic Tests in the Management of Possible Immune related Adverse Events

Immune-related Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in subjects with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All subjects presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including *D*LCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

CELGENE PROPRIETARY INFORMATION

Table 22: Recommended Diagnostic Tests in the Management of Possible Immune related Adverse Events (Continued)

Immune-related Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a subject experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye Disorders	If subjects experience acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the subject urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3-4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan, for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy.
Renal Toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: creatine kinase, erythrocyte sedimentation rate, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, CK/CK-MB, echocardiogram, troponin (troponin I and/or T), and refer to a cardiologist.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate aminotransferase; CK = creatine kinase; CK-MB = creatine kinase cardiac isoenzyme; CNS = central nervous system; CRP = C-reactive protein; CT = computed tomography; *D*LCO = diffusing capacity for carbon monoxide;

CELGENE PROPRIETARY INFORMATION

ECG = electrocardiogram; FBC = full blood count; HIV = human immunodeficiency virus; INR = international normalized ratio; LCI = liver cystosolic antigen; LFT = liver function test; LKM = liver kidney microsomal antibody; LP = liver pancreas antigen; MRA = magnetic resonance angiogram; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; SLA = soluble liver antigen; SMA = smooth muscle antibody; T4 = thyroxine; TFT = thyroid function tests; TSH = thyroid-stimulating hormone; UEC = urea electrolytes and creatinine.

Treatment of Immune-related Adverse Events

- Immune-related AEs can escalate quickly; study drug interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with subjects is required
- Immune-related AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice and contact the study medical monitor
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory irAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil)
- Consider prophylactic antibiotics for opportunistic infections if the subject is receiving long-term immunosuppressive therapy

Table 23: CCI [redacted]

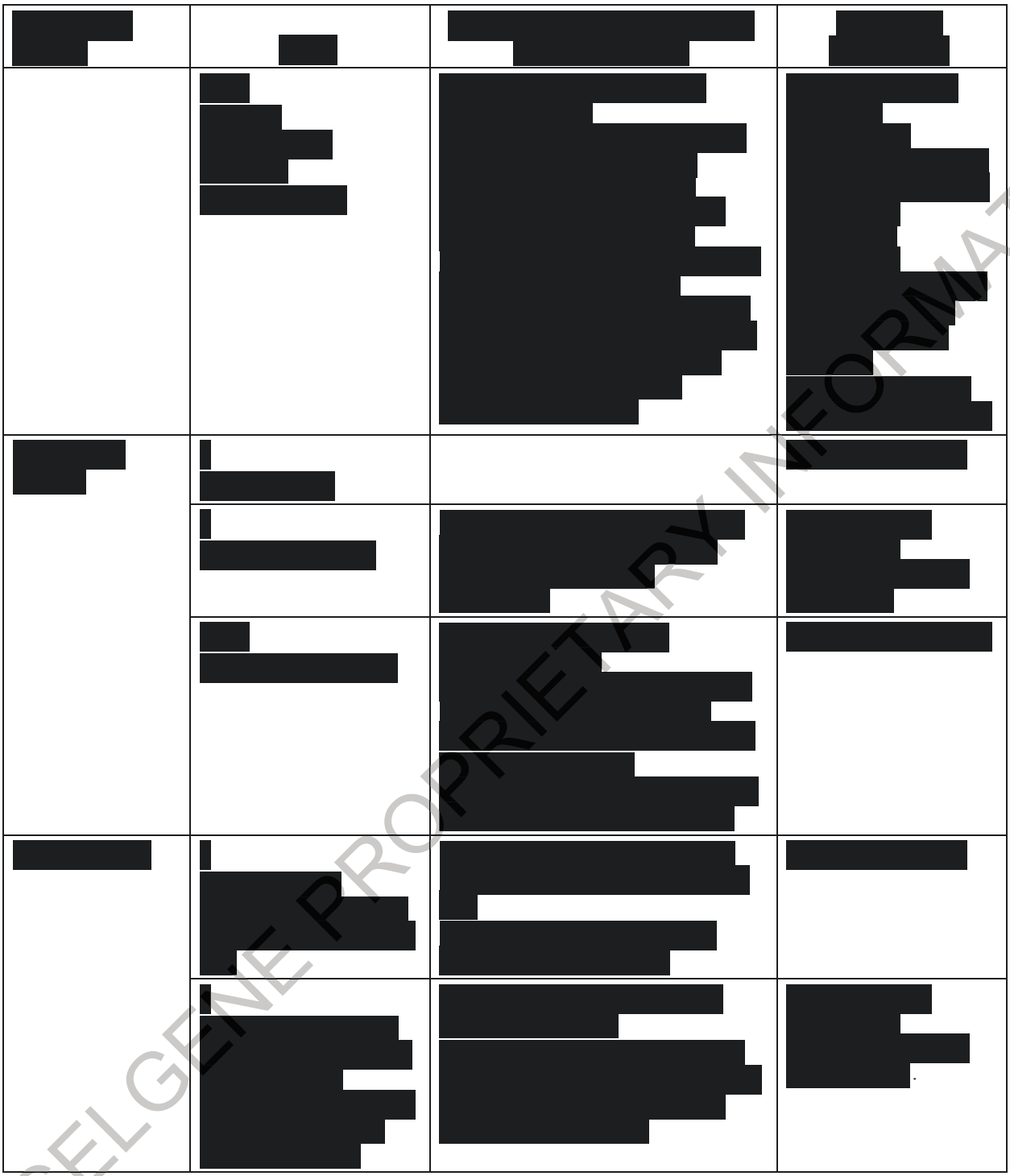
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

CELGENE PROPRIETARY INFORMATION

Table 23: CCI [redacted]

CELGENE PROPRIETARY INFORMATION

Table 23: CCI [redacted]



CELGENE PROPRIETARY INFORMATION

Table 23: CCI

CELGENE PROPRIETARY INFORMATION

Table 23: CCI

CELGENE PROPRIETARY INFORMATION

Table 23: CCI

CELGENE PROPRIETARY INFORMATION

Table 23: CCI

CELGENE PROPRIETARY INFORMATION

Table 23: CCI

CELGENE PROPRIETARY INFORMATION

Table 23: CCI [redacted]

CELGENE PROPRIETARY INFORMATION

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

The text below was obtained from Eisenhauer, 2009.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (v1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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.

Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

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

CELGENE PROPRIETARY INFORMATION

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and 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 organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

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

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal

CELGENE PROPRIETARY INFORMATION

progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are accessible by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease

CELGENE PROPRIETARY INFORMATION

specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

RESPONSE CRITERIA

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline

CELGENE PROPRIETARY INFORMATION

become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".

  - When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget 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 nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the patient has only non-measurable disease: This circumstance arises in some phase 3 trials when it is not a criterion of trial entry to have measurable disease. The

CELGENE PROPRIETARY INFORMATION

same general concept applies 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 patients 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 patient 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.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.

- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease

CELGENE PROPRIETARY INFORMATION

on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

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

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

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

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be

CELGENE PROPRIETARY INFORMATION

based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero."

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

CELGENE PROPRIETARY INFORMATION

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

CELGENE PROPRIETARY INFORMATION

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: PPD
Title: PPD
Date: Thursday, 20 September 2018, 06:57 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

CELGENE PROPRIETARY INFORMATION

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below.

CCI [redacted] This includes the following revisions:

- **Additional Independent Data Monitoring Committee (IDMC) Assessment of the Safety and Tolerability of the Cisplatin Plus Etoposide Chemotherapy Regimen**

An additional IDMC safety analysis with a minimum of 10 subjects who have completed 2 cycles of tislelizumab, cisplatin/etoposide and radiation therapy and have been on study for at least 60 days will be conducted to provide additional safety information about this specific chemotherapy combination.

CCI [redacted] had concerns regarding the tolerability of cisplatin/etoposide administered in combination with tislelizumab and radiation therapy, since this regimen is known to have increased morbidity when compared to the regimen of carboplatin and paclitaxel (Santana-Davila, 2014). Protocol Section 1.2.2.4 provides early data from Study BGB-A317-206, in which tislelizumab is administered in combination with 4 different platinum-containing doublet chemotherapy regimens (pemetrexed, paclitaxel, gemcitabine or etoposide combined with either cisplatin or carboplatin) in subjects with non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC).

While there are no safety data for tislelizumab in combination with chemotherapy and radiation, data presented at ASCO 2018 regarding the use of immune checkpoint inhibitors in combination with chemotherapy and radiation in subjects with NSCLC have not identified any new safety concerns. The NICOLAS Phase 2 trial (Peters, 2018) is exploring the safety and feasibility of combined chemotherapy (which included cisplatin in combination with etoposide, vinorelbine or pemetrexed) and radiation with nivolumab in stage III NSCLC. At the time of an early interim analysis, 49 subjects were recruited with a median follow-up of 6.6 months. The most frequently observed AEs were fatigue and anemia. No unexpected AEs or increased safety risk were observed. For the first 21 subjects, no pneumonitis grade ≥3 was observed by the end of the 3-month post radiotherapy (RT) follow-up period. The majority of these subjects (18 subjects) were on a concurrent chemotherapy and radiation schedule. This early interim safety analysis provides evidence that the addition of nivolumab to concurrent chemotherapy and radiation is safe and tolerable.

An early safety assessment across all the treatment arms in the current study would provide a meaningful basis for comparison of the relative safety of tislelizumab given concomitantly with chemotherapy and radiation. In the original protocol, CCI [redacted]. Therefore, the amendment includes an additional IDMC safety analysis with a minimum of 10 subjects who have completed

CELGENE PROPRIETARY INFORMATION

2 cycles of tislelizumab, cisplatin/etoposide and radiation therapy and have been on study for at least 60 days, to provide additional safety information about this specific chemotherapy combination.

Revised sections: Protocol Summary, Section 1.3.2 (Rationale for the Study Design), Section 3.1 (Study Design), Figure 1 (Overall Study Design), Section 9.9.1 (Data Monitoring Committee)

- **Increased Creatinine Clearance Eligibility and Dose Modification Requirements for Subjects Receiving the Cisplatin Plus Etoposide Chemotherapy Regimen**

Given the increased risk of renal injury with the combination of platinum-based chemotherapy and tislelizumab and the absence of data characterizing the risks of renal toxicity with these regimens, the FDA had concerns that the creatinine clearance (CrCl) requirement of ≥ 45 ml/min in inclusion criterion 7.d. in protocol Section 4.2 (Inclusion Criteria) was too low. The current amendment thus revises the required calculated creatinine clearance (CrCl) to ≥ 60 mL/min (Cockcroft-Gault formula) for subjects receiving cisplatin/etoposide. Since carboplatin dosing is based on area under the curve (AUC), which takes into consideration drug elimination through renal clearance, the requirement remains CrCl ≥ 45 mL/min for subjects receiving carboplatin/paclitaxel.

In addition, Table 14 (Dose Modifications for Cisplatin Based on Renal Toxicity) is amended to reflect that resumption of cisplatin dosing following a delay due to renal toxicity, and the degree of dose reduction (if needed), depend upon the return of the subject's CrCl to ≥ 60 mL/min rather than ≥ 45 mL/min.

Revised sections: Section 4.2 (Inclusion Criteria), Table 14 (Dose Modifications for Cisplatin Based on Renal Toxicity), Section 7.2.8 (Creatinine Clearance)

- **Clarification Regarding the East Asia Versus Other Stratification Factor**

As described in the protocol, this Phase 3 study will be conducted under 2 protocols. These 2 protocols are as follows:

1. Protocol BGB-A317-NSCL-001 is the main protocol [redacted]
2. Protocol BGB-A317-NSCL-001C is the companion protocol [redacted]

The data from both study protocols will be collected into one database and the statistical analyses as described in protocol Section 9 will be performed on the combined total number of subjects randomized into either the main protocol or the companion study protocol. A single independent data monitoring committee (IDMC) and blinded independent central review will be utilized for these 2 study protocols. Randomization into the study will be stratified by age [redacted], chemotherapy regimen [redacted], and region [redacted].

[redacted].

CELGENE PROPRIETARY INFORMATION

Revised sections: Protocol Summary, Section 3.1 (Study Design), Section 9.1 (Statistical Considerations – Overview)

- **Addition of Rationale for Implementing the Statistical Assumptions of the Progression Free Survival (PFS) and Overall Survival (OS) Analyses**

CCI requested that the analysis plan for the study provide a detailed description of the assumptions of the PFS and OS analyses, including the difference to be detected between arms and the estimated median PFS and OS in both arms. A justification for the assumptions of treatment effect has been added to the statistical assumptions in Section 9 of the amendment.

Revised sections: Section 9.3.2 (Statistical Considerations – Power and Sample Size)

In addition to the above changes CCI one significant change included in this amendment is summarized below:

- **Addition of timepoints for Patient Reported Outcomes Assessments**

A secondary objective in the protocol is to compare the impact of study treatment on patient-reported lung cancer symptoms (appetite loss, cough, chest pain, dyspnea, and fatigue) assessed by European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC QLQ-C30) and its lung cancer module (EORTC QLQ-LC13). C CI

In the original protocol this data is collected at screening, Day 1 of Cycles 1 through 8, at discontinuation of the study treatment, and 30 days after the last dose of tislelizumab/placebo. To fully assess patient reported outcomes for the duration of study treatment, the amendment includes data collection at screening, Day 1 of every cycle during study treatment, at discontinuation of the study treatment, and 30 days after the last dose of tislelizumab/placebo.

Revised sections: Table 3 (Study Endpoints), Table 4 (Table of Events), Section 6.2 (Procedures – Treatment Period)

This amendment also includes several other minor clarifications and corrections:

- CCI
- Deletion of the statement that the wording of the CCI will be replaced to adjust to the needs of the current study CCI
- Change of Celgene Therapeutic Area Head

CELGENE PROPRIETARY INFORMATION

- CCI [redacted]
- Clarification that subjects who have detectable HBV DNA or HCV RNA either at screening or upon repeat testing during treatment (if clinically indicated) will have the respective viral load test every 4 cycles (ie, Day 1 of Cycles 5, 9, 13, etc.) (Table 4; Section 6.1, Procedures – Screening Period; Section 6.2, Procedures – Treatment Period; Section 6.2.1, Procedures – End of Treatment; Section 6.3.1, Procedures – Safety Follow-Up)
- Update the example of other medically appropriate methods of left ventricular ejection fraction (LVEF) assessment from MRI, CT and cardiac catheterization to multiple-gated acquisition scan (MUGA), and add the description of the assessment (if clinically indicated) to the End of Treatment and 30-Day Safety Follow-up visits in order to match the Table of Events (Procedures – Screening Period; Section 6.2, Procedures – Treatment Period; Section 6.2.1, Procedures – End of Treatment; Section 6.3.1, Procedures – Safety Follow-Up)
- Clarify in a footnote that histamine H2 receptor antagonist premedications for paclitaxel can include not only cimetidine or ranitidine, but also other equivalent histamine H2 receptor antagonists (eg, famotidine) (Table 5)
- Minor formatting changes and corrections

CELGENE PROPRIETARY INFORMATION