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]

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]

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]

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

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]

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.

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.

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	-	-

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

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					

- 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.

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.

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

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.

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.

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

- 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.

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

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

CCI

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;

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

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

CCI

[redacted]

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

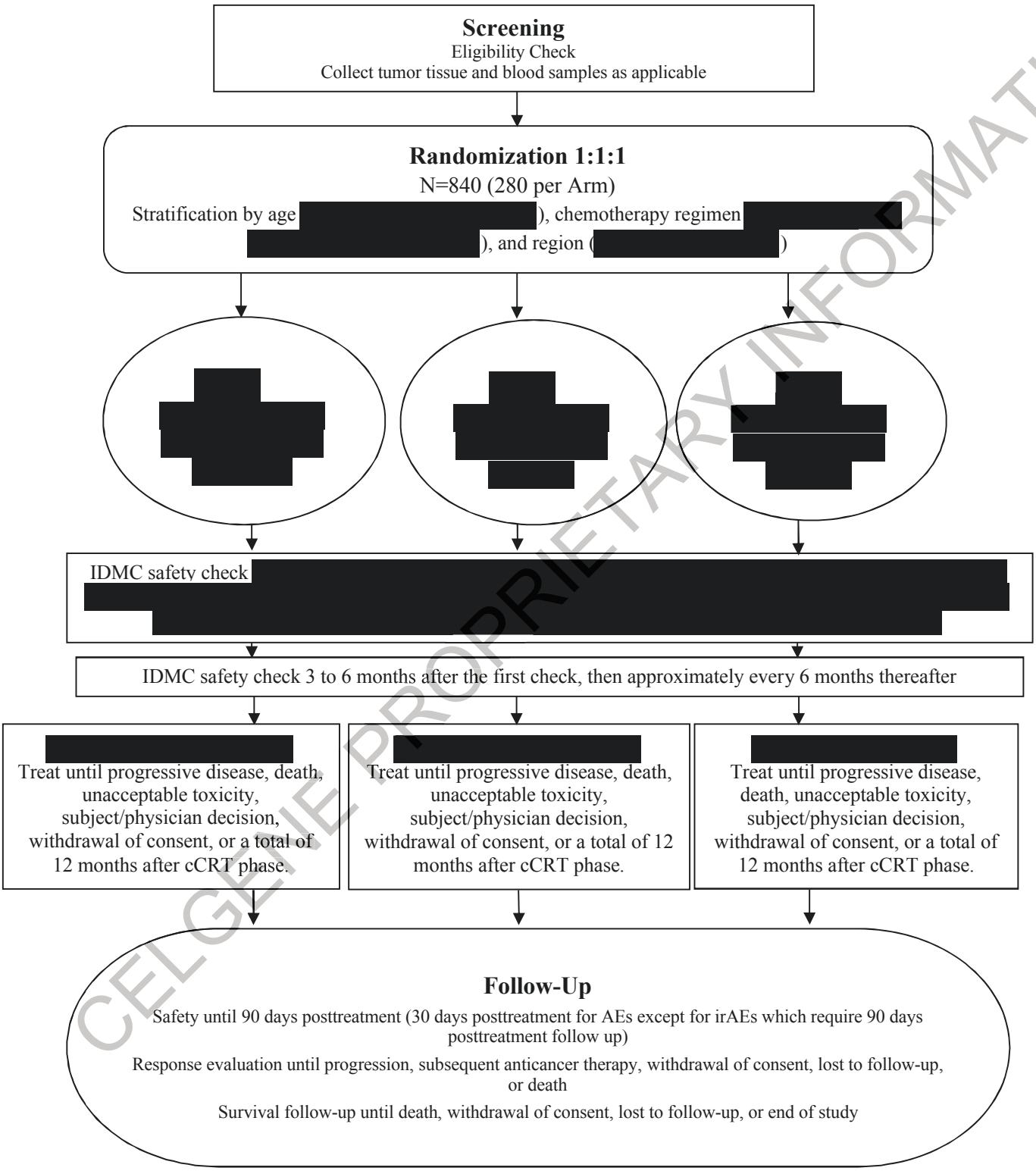
It will be important to assess treatment effectiveness both in terms of objective outcomes (eg, PFS or OS) and subjective, patient reported outcomes (PROs) to ensure that the addition of tislelizumab to cCRT followed by tislelizumab monotherapy in newly-diagnosed, unresectable locally advanced NSCLC 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.

Table 3: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	CCI		

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



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.

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	-	-

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]

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).

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

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.

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.

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

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.

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

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

CCI

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]

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