CLINICAL STUDY PROTOCOL

Protocol Title:		GRECO-1: Phase I/II, Randomized, Placebo-Controlled Study of Stereotactic Body Radiation Therapy (SBRT) and GC4711 for Centrally Located or Large, Node-Negative Non-Small Cell Lung Cancer (NSCLC)	
Protocol Number:		GTI-4711-101	
Compound:		GC4711	
Sponsor	**Sponsor Name:**	Galera Therapeutics Inc.	
	Legal Registered Address:	2 West Liberty Blvd, Suite 110, Malvern, PA 19355	
Regulatory Agency Identifier Number(s)		150,818	
Protocol Date:		**Document Version**	**Date**
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CONFIDENTIALITY NOTICE

The information contained in this protocol and all other information relevant to GC4711 are the confidential and proprietary information of Galera Therapeutics Inc. and, except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without the prior written permission of Galera Therapeutics Inc.

Study Acknowledgement

GRECO-1: Phase I/II, Randomized, Placebo-Controlled Study of Stereotactic Body Radiation Therapy (SBRT) and GC4711 for Centrally Located or Large, Node-Negative Non-Small Cell Lung Cancer (NSCLC)

This protocol has been approved by Galera Therapeutics, Inc. The following signature documents this approval.

DocuSigned by:
Jon Holmlund
Signer Name: Jon Holmlund
Signing Reason: I approve this document
Signing Time: April 21, 2022 | 5:51:16 PM EDT
4055E5E56BC84EFBBD0C864CFDA550EB

Jon Holmlund, MD
Chief Medical Officer
Galera Therapeutics, Inc.

Investigator Statement

I have read the attached protocol and agree to abide by all provisions set forth therein. I will provide copies of the protocol and other pertinent information to all individuals responsible to me who will assist with the study.

I agree to comply with the International Conference on Harmonization, Tripartite Guideline on Good Clinical Practice (ICH, GCP) in accordance with local government and applicable global and local government regulations/guidelines, for example, including 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312.

I agree to ensure that Financial Disclosure Statements will be completed before study initiation, during the studies if there are changes that affect my financial disclosure status, and one year after study completion by:

- myself (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Galera Therapeutics.

The Sponsor or its designee will have access to source documentation from which case report forms have been completed.

_____ _____

Signature of Principal Investigator Date (DD MMM YYYY)

_____

Printed Name of Principal Investigator

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1 SYNOPSIS

Name of Sponsor/Company:
Galera Therapeutics, Inc.

Name of Investigational Product:
GC4711

Title of Study:
Phase I/II, Randomized, Placebo-Controlled Study of Stereotactic Body Radiation Therapy (SBRT) and GC4711 for Centrally Located or Large, Node-Negative Non-Small Cell Lung Cancer (NSCLC)

Number of Study Center(s): Phase 1: Approximately 4 centers in the United States
Phase 2: Up to 20 centers in the United States

Estimated Enrollment Period: ~36 months

Studied period (years):	**Phase of development:** 1-2
First patient enrolled, Phase 1: Q4 2020	
Last patient completed, Phase 1: Q3 2021	
First patient enrolled, Phase 2: Q3 2021	
Estimated date last patient completed, Phase 2: Q3 2023	

Objectives: Phase I

Primary: To assess the safety of GC4711 administered intravenously (IV) in combination with 5 fractions of stereotactic body radiation therapy (SBRT) in subjects with Non-Small Cell Lung Cancer (NSCLC)

Secondary: To evaluate the efficacy, and acute and late toxicities of GC4711 + 3 or 5 fractions of SBRT

Objectives: Phase II

Primary: To determine the percentage of patients with complete or partial in-field tumor response based on the RECIST 1.1 criteria through 6 months following completion of SBRT

Secondary:

- To determine the best in-field tumor response at 6-, 12-, 18- and 24-months following completion of SBRT
- To compare progression-free survival, overall survival, local tumor control, and distant metastasis rates over a 2-year follow up period for SBRT plus GC4711 or placebo
- To assess durability of in-field complete or partial responses
- To determine acute lung toxicity after SBRT + GC4711 compared to SBRT + placebo for early-stage NSCLC
- To evaluate the rate of acute and late radiation toxicities for SBRT + GC4711 compared to SBRT + placebo

- To assess the relationship between clinical, functional and radiographical lung function changes observed after SBRT

Exploratory (Phase I and II)

- To evaluate risk of lung injury, its development pattern over time, and patient/disease and dosimetry characteristics in relation to additional GC4711
- To evaluate the pharmacokinetics of GC4711 in the study population
- To collect initial information about acute effects of GC4711, including cardiovascular events and electrocardiogram parameters

Rationale:

GC4711, a novel, water soluble, low molecular weight, manganese-containing macrocyclic ligand complex, is being developed as a 15-minute intravenously (IV)-administered treatment given in combination with stereotactic body radiotherapy (SBRT; also known as stereotactic ablative radiotherapy, or SABR) to improve efficacy and reduce normal tissue damage of high dose per fraction radiation delivery in early-stage non-small cell lung cancer (NSCLC).

The number of patients with limited NSCLC are fast increasing due to screening programs and more frequent thoracic imaging in general, but many newly diagnosed patients are not good surgical candidates; the combination of SBRT with GC4711 as a safe and efficient alternative may be of great value in lung cancer management**.**

Modern RT techniques have enabled more precise delivery of high ablative doses with improved sparing of surrounding normal tissue. For early-stage NSCLC, SBRT has become an alternative to surgery (Timmerman 2010). After initial demonstration of safety with SBRT for small peripheral NSCLC lesions, SBRT has been delivered to larger and more central lesions (Bezjak 2019), which identified SBRT dosing of 11.5 or 12 Gy x 5 fractions as associated with acceptable toxicity and with approximate 2-year rates for local control, overall survival, and progression-free survival of approximately 90%, 70%, and 55%, respectively. The practice is shifting toward 5 fractions specially for central localizations; however, a 3-fraction regimen is still accepted. Use of SBRT for larger or centrally located NSCLC is reported to increase the risk of toxicity with a larger volume of normal tissue exposure (Fakirs 2009, Woody 2015, Peterson 2016, Beak 2019). SBRT can induce inflammatory reactions and sequentially generate fibrosis and lung functional restrictions (Lu 2018). Individual risk of radiation-induced pneumonitis depends on the volume of lung treated and the radiation dose administered, as well as patient age and other treatment modalities used (immunotherapy itself has around 10% pneumonitis risk on its own (Zhao 2016, Mohamad 2018)). Central tumors have a higher complication risk because of the close relation to the major airways, esophagus, and major vessels. These tumors are treated with 5 or more fractions of SBRT (Lo 2009) to give normal tissue within the field more time to repair (Timmerman 2006). Radiation induced injury is a slowly developing process, developing radiological changes and symptoms around 3-6 months (mean 135 days) after treatment (Vide tic 2013, Takeda 2013, Jain 2018, Ferrero 2015). Approximately a quarter of patients encounter lung function decline, after a 5-fraction regimen SBRT (Stone 2015). A small portion of patients (approximately 10%) remain with a significant

decline in lung function, which can be difficult to distinguish from disease recurrence (Huang 2012). Radiological changes have been described in a larger number of patients but are not always accompanied by clinical symptoms. Historical incidence of functional and radiological lung changes is based on a 3 or 6 monthly assessment throughout the first 1-2 years after the completion of treatment. For interrelated risk-benefit evaluation, it is key to collect clinical, radiological, and functional data at these same time points, thus gathering sufficient clinical information over the first 12 months to distinguish patterns.

The action of GC4711 to convert superoxide to hydrogen peroxide has the potential to be a radiosensitizer, increasing both the efficacy and safety of SBRT. In nonclinical models, the addition of selective dismutase mimetics to SBRT regimens with or without concomitant systemic anti-cancer therapy enhanced tumor control while protecting normal tissues from radiation (Sishc 2018). Furthermore, in GC4711 nonclinical pharmacology studies, GC4711 augmented the anti-tumor activity of SBRT in NSCLC and pancreatic cancer experimental xenograft mouse models.

These observations support conducting a trial of GC4711 to reduce the potential lung toxicity of SBRT while possibly improving anti-tumor activity.

Methodology:

GTI-4711-101 is a Phase I/II study of the safety of GC4711, its effect on in-field tumor response per RECIST 1.1 and its potential to reduce radiation-related pulmonary injury due to SBRT for lymph node negative (T1 to T3N0M0) peripheral or central localized (within 2cm of the proximal bronchial tree) NSCLC. After an open-label, Phase 1, safety cohort of 5 subjects has been completed, a randomized, placebo-controlled Phase 2 portion will be conducted.

Subjects must be referred for SBRT with large peripheral lesions (>1cm-7cm) and/or central localized, node negative, non-metastatic NSCLC, and have an ECOG PS score of 0-3 (Buccheri 1996) to be considered for enrollment. Subjects with small peripheral lesions (≤1cm) are excluded, as the aim is to improve outcome in larger, central NSCLC carrying a higher risk of pneumonitis, as well as poorer local control. Feasibility of SBRT is judged by the treating physician.

SBRT is planned for the tumor location as a dose of 5 fractions of 10-12 Gy or 3 fractions of 18-20 Gy (Phase 2 only). SBRT fractions will be given sequentially, and within 180 minutes from the end of the GC4711 or placebo infusion. Between fractions, a minimum of 18 hours and a maximum of 96 hours are permitted. All fractions should be given within 10 calendar days (+3 days in the case of a holiday or technical issue).

Phase 1: In the Phase 1 portion, 5 subjects will each receive 100 mg of GC4711 by 15-minute IV infusion, before each SBRT fraction, beginning the day of the first fraction and ending the last day of SBRT (5 doses in total). SBRT is administered within 180 minutes (3 hours) of the end of the GC4711 infusion.

All 5 subjects will be monitored for dose limiting toxicity (DLT) occurring during treatment with SBRT and GC4711 or within 30 days post-therapy. DLT is defined (using the National

Cancer Institute−Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading scale) as Grade 3-5 AEs occurring from Day 1 to 30 days post SBRT completion, and *excluding* the following:

- AEs clearly related to disease progression or intercurrent illness
- Grade 3 fatigue for 7 days or less,
- Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
- Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
- Hematological grade 3-4 toxicities except for the following:
    - Grade 4 neutropenia lasting >7 days.
    - Grade 3 thrombocytopenia with clinically significant bleeding.
    - Grade 4 anemia and grade 4 thrombocytopenia

Safety will be judged unacceptable if 2 or more (i.e., no more than one) of the 5 subjects develop a DLT. Safety will be reviewed by a Safety Review Committee (SRC) consisting of the Medical Monitor, the Principal Investigator from each Phase 1 site, and additional designees by the Sponsor or the site Principal Investigators.

Phase 2: After the SRC has confirmed acceptable safety for Phase 1, a Phase 2, randomized, placebo-controlled study will be initiated, wherein approximately 66 subjects referred for SBRT with early stage large and/or central localized NSCLC will be randomized in a 1:1 ratio to receive either GC4711 100 mg or placebo given intravenously (IV) over 15 minutes before each fraction of SBRT, beginning the day of the first fraction of SBRT and ending the last day of SBRT.

The primary endpoint will be the difference in in-field RECIST response rate at 6 months post SBRT completion.

The secondary endpoints will include overall response, pulmonary function, pneumonitis assessed clinically and radiographically, and time to event endpoints (PFS, OS, Local and Distant Control).

Detailed information on dose-volume exposure, co-treatment and sensitivity profiles of existing obstructive lung disease will be collected for pneumonitis-risk analyses. Pharmacokinetic (PK) sampling and cardiac monitoring will be performed on each subject with two separate doses of GC4711 (or placebo) collecting blood samples pre-infusion and post-infusion for each.

Number of Subjects:

Phase 1: 5 subjects

Phase 2: Approximately 66 subjects (~33 per arm, GC4711 or placebo)

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Male or female subjects at least 18 years of age.
2. Ability to understand and the willingness to sign a written informed consent.

3. Histological or biopsy proven Non-Small Cell Lung Cancer. For peripheral lesions, cytology and/or clear imaging-guided suspicion is accepted if histology cannot be obtained.
4. ECOG performance status of 0-3.
5. Node negative (T1 to T3N0M0), centrally located (within 2cm in all directions around the proximal bronchial tree, including ultra-central tumors, abutting the bronchial tree or trachea) or large (>1-7cm) Non-Small Cell Lung Cancer (NSCLC), judged acceptable for SBRT by the treating Investigator. Staged with FDG-PET/CT, brain CT or MRI with contrast and/or mediastinoscopy, measurable disease as defined by RECIST 1.1.
6. Adequate end-organ function, based on routine clinical and laboratory workup:
    a. ANC >1,000 cells/µl, Platelets ≥ 75,000 cells/µl, Hemoglobin ≥ 7.0 g/dl
    b. Serum creatinine ≤ 2 mg/dL or calculated creatinine clearance ≥ 30 ml/min
    c. Total bilirubin ≤ 1.5 x ULN (or direct bilirubin below the ULN), AST and ALT ≤ 2.5 x ULN
7. Males and females of must agree to use effective contraception starting prior to the first day of treatment and continuing after the last dose of GC4711/Placebo for 30 days (females) and 90 days (males).

Exclusion Criteria

1. Subjects with confirmed nodal and/or distant disease (including brain) using standard workup (per investigator).
2. Subjects with peripheral lesions of 1cm or smaller
3. Prior treatment with immunotherapy within 3 months prior to Day 1 dosing.
4. Prior intra-thoracic radiotherapy or surgery with substantial overlap to planned radiation fields as determined by the treating radiation oncologist.
5. Subjects not recovered/controlled from prior treatment-related (chemotherapy or targeted therapy) toxicities judged by treating physician.
6. Uncontrolled malignancy other than lung cancer that requires active treatment or is deemed by the treating physicians to be likely to affect the subject's survival duration.
7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to GC4711.
8. Uncontrolled intercurrent illness including, but not limited to, active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements.
9. Participation in other clinical trials actively testing new anti-cancer treatments, unless previously written approval is provided by the Sponsor.

10. Requirement for concurrent treatment with nitrates or other drugs that may, in the judgment of the treating investigator, create a risk for a precipitous decrease in blood pressure.
11. Female subjects who are pregnant or breastfeeding.
12. Any other conditions that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study.

Duration of Treatment:

Phase 1: SBRT is administered in 5 sequential fractions of 10-12 Gy with each fraction preceded by once daily (QD) doses of GC4711 (5 doses) from the start to the last fraction

Phase 2: SBRT is administered in 5 sequential fractions of 10-12 Gy or 3 sequential fractions of 18-20 Gy with each fraction preceded by once daily (QD) doses of GC4711/placebo (3 or 5 doses) from the start to the last fraction

Reference Therapy, Dosage and Mode of Administration:

Phase 1 will use open-label GC4711 to be given as a 15-minute, 100 mL IV infusion. GC4711 100 mg QD should be completed within 180 minutes prior to SBRT (5 doses).

Phase 2 will include two treatment arms:

- **Arm A:** GC4711 100 mg (15 min, 100 mL IV infusion to complete within 180 minutes prior to SBRT) administered before each SBRT, from the first dose of SBRT to the last fraction of SBRT.
- **Arm B**: Placebo (15 min, 100 mL normal saline IV infusion) given in combination with SBRT as described for Arm A. Normal saline should be provided by the site's unblinded pharmacists.

SBRT will deliver 5 fractions of 10-12 Gy or 3 fractions of 18-20 Gy to confirmed tumor area), no elective fields are given. Between fractions, a minimum of 18 hours and a maximum of 96 hours are permitted. All fractions should be given within 10 calendar days (+3 days in the case of a holiday or technical issue).

Criteria for Evaluation:

- NCI-CTCAE version 5.0 for Adverse Events and clinical pneumonitis evaluation

  https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
- RTOG Pulmonary toxicity scale (Stone 2015) for decline in DLCO
- CT (chest/abdomen/pelvis) evaluation using RECIST 1.1 (Eisenhauer EA 2009) for tumor evaluation
- CT (chest) for radiographic evaluation of pneumonitis
- FVC, FEV1, DLCO, SpO2

Safety Monitoring and Toxicity Management:

Adverse/Serious Adverse Event (AE/SAE) assessments are categorized using CTCAE version 5.0. Subjects in Phase 1 will be monitored for DLTs as outlined above for 30 days post SBRT completion.

Additionally, all subjects in Phase 1 and Phase 2 will be monitored 90 days post-SBRT for all adverse events to evaluate acute toxicities, and monitored for 1-year post-SBRT completion for specific late toxicities as defined in Section 7.4 Late Radiotherapy Toxicities.

Toxicities that will require infusion modification of GC4711 or placebo include the following:

- Grade 2 or greater hypotension occurring within 1 hour of the end of GC4711 or placebo infusion
- Other Grade 3 or greater AEs judged by the investigator to be possibly attributable to the study infusion.

Patients who experience a toxicity noted above during or shortly after the infusion of GC4711/placebo should have their infusion times increased to 30 minutes.

If the toxicity recurs, the infusion time should be increased to 45 minutes, and may be increased to 60 minutes if hypotension occurs with a 45-minute infusion.

If toxicity occurs with a 60-minute infusion, the patient should be discontinued from further treatment with GC4711/placebo but should remain on study for all other protocol interventions (SBRT) and assessments.

Concomitant Medications/Treatments:

Investigators may prescribe concomitant medication or supportive care deemed necessary. All medications taken from 30 days prior to dosing through 90 days post completion of SBRT should be documented in source records and in the CRF.

After 3 months post completion of SBRT, only medications used to treat respiratory disease or late radiation toxicities (see section 7.4) should be recorded through 12 Months, including inhalers, steroids, oxygen supply, etc.

Any new anti-cancer therapy given in follow-up should be recorded in the CRF through 24-months post-SBRT or until tumor progression has been recorded.

Supportive care includes antiemetic prophylaxis, hematopoietic growth factor as used per ASCO guidelines, systemic antibiotics, hydration to prevent renal damage etc., consistent with local standard of practice, with the following exceptions:

Prohibited medications/treatments:

- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildenafil, tadalafil, or similar agents) or other drugs that in the judgment of the treating Investigator could create a risk of a precipitous decrease in blood pressure are prohibited until at least 24 hours after the last dose of GC4711/placebo.

- Approved or investigational anti-cancer therapy (e.g., chemotherapy, immunotherapy, targeted therapy, hormone, and biologic therapy) given during SBRT other than the protocol regimen

Statistical Considerations:

In Phase 1 portion of the study, 5 subjects will be treated and monitored for DLTs. DLT is defined above and in Section 7.5.

Safety is considered acceptable if no more than one subject experiences a DLT during treatment or within the 30-day post-therapy safety observation period.

In Phase 2, approximately sixty-six (66) participants, randomized 1:1 to GC4711 or placebo, will be recruited to achieve 60 evaluable subjects, assuming a 10% drop-out.

Sample size in Phase 2 is selected to provide a reasonably precise estimate of the treatment effect as measured by the width of a two-sided 90% confidence interval around the difference in in-field tumor response as well as to provide other efficacy data that can used in planning future studies. With 30 patients/arm the half-width of the 90% confidence interval. To supplement the routine monitoring outlined in this protocol, a Safety Review Committee (SRC) will periodically review safety data and related delays in SBRT administration. See Section 8.6 for details.

Table 1 Schedule of Activities

Procedure	Screening [a]	ACTIVE TREATMENT PERIOD					POST SBRT FOLLOW-UP			
		D1	D2	D3	D4	D5	D12 or Early Term [b]	30- and 90-days post SBRT [c]	M6, M12 [c]	M18, M24 Post-SBRT [d,]
Informed consent	X									
Inclusion and exclusion criteria [e]	X									
Registration/Randomization (Phase 1/Phase 2) [e]	X									
Medical history (includes smoking history)	X									
Demography	X									
Complete PE including height and weight	X								X	
ECOG Performance Status	X								X	
Vital signs [f]	X	X	X	X	X	X				
PK Blood samples [g]		X		X						
12-lead ECG [h]	X	X		X						
AE/SAE review [i]		X	X	X	X	X	X	X	X	
Concomitant medications/treatments and smoking review [j]	X	X	X	X	X	X		X	X	X
Survival Status								X	X	X
Serum pregnancy test (WOCBP only)	X									
Serum chemistry panel	X						X			
Complete blood count	X						X		X	
PT/INR, aPTT	X									
PFTs – SpO2, FEV1, FVC and DLCO [k, n]	X								X	
CT chest for pneumonitis scoring [k]	X								X	X
CT (chest, abdomen, pelvis) [k]	X								X	X
GC4711/Placebo IV infusion [l]		X	X	X	X[l]	X[l]				
SBRT administration [m]		X	X	X	X[m]	X[m]				

AE = adverse event, BP = blood pressure, CBC = complete blood count, CT = computed tomography, CTCAE = Common Terminology Criteria for Adverse Events, DLCO = diffusion capacity of lung for carbon monoxide, ECG = electrocardiogram, ECOG PS = eastern cooperative oncology group performance status, FEV1 = forced expiratory volume in 1 second, FU = Follow-up, , IV = intravenous, PE = physical examination, PET = positron emission tomography, PFTs = pulmonary function tests, PK = pharmacokinetics, SAE = serious adverse event.

a Screening evaluations should occur within 21 days of Treatment Day 1, except where otherwise noted

b The Day 12 visit should occur 7 days after the last dose of SBRT ±5 days

c The 30- and 90- day post SBRT completion visits should occur on or within 7 days after target date and may be performed remotely via telemedicine visits. The Months 6 and 12 post SBRT completion visits should occur ±7 days of target date.

d The Month 18 and 24 post SBRT visits should occur ±14 days of target date.

e Registration/Randomization should occur after all screening assessments are performed, eligibility is confirmed, and within 7 days of the first dose of SBRT. Confirmation of eligibility should include confirmation of diagnosis, histology and exclusion of distant disease by standard practice.

f BP and HR should be taken prior to each infusion, monitoring possible hypotensive symptoms, please repeat before going from infusion to radiation site.

g PK blood samples should be drawn pre-and post- - infusion on Day 1 and Day 3. The end of infusion PK draw should be drawn within 10 minutes after the end of infusion and the ECG should be +/- 10 minutes from the PK draw.

h The ECGs will be collected in triplicate pre- and post-infusion as close to PK draws as possible. The end of infusion PK draw should be drawn within 10 minutes after the end of infusion and the ECG should be +/- 10 minutes from the PK draw. A 12-lead ECG recording will be conducted using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

i AE/SAE collection will occur through 30 days post SBRT completion for treatment related adverse events, will continue through 90 days post SBRT completion for acute toxicities (all AEs/SAEs) and 1-year post SBRT completion for late radiation toxicities. Please see Section 7.4 for the definition of late radiation toxicities. The DLT period is through 30 days post-SBRT for Phase 1 subjects. Please see Section 7.5 for details on the DLT definition.

j All medications taken from 30 days prior to dosing through 90 days post SBRT completion should be documented in source records and CRF. After 90 days post-SBRT, only medications used to treat late radiation toxicities should be recorded through 12 Months post SBRT completion, including inhalers, steroids, oxygen supply, etc. Additionally, any new anti-cancer therapy given in follow-up should be recorded in the CRF through 24 months post-SBRT or disease progression.

k Imaging assessments performed as part of standard of care within 56 days of dosing will be accepted. Investigator Response Assessment should follow RECIST 1.1. Suspicion of progression should be confirmed with PET at 6 months. Radiographic assessment of pneumonitis will occur by evaluating for presence of descriptors listed in the table in Appendix 4.

l GC4711 or placebo will be given prior to each dose of SBRT starting the first day of SBRT through the last day of SBRT. GC4711/placebo infusion should be completed within 180 minutes prior to the start of SBRT. For patients treated with a 3-fraction SBRT regimen, only 3 doses of GC4711 will be administered.

m SBRT will be administered within 180 minutes after completion of GC4711/placebo. A minimum of 18 hours and a maximum of 96 hours are permitted between fractions. All fractions should be given within 10 calendar days (+5 days in the case of a holiday or technical issue).

n Pulmonary function testing (PFT) to be conducted at Months 6 and 12 only.

2 INTRODUCTION

2.1 Radiotherapy for Non-Small Cell Lung Cancer

Lung cancer is the leading cause of death in the United States, with approximately 135,000 deaths predicted in 2020 (Ettinger 2020). As recently as 2015, the 5-year survival rate for non-small cell lung cancer (NSCLC) was 25% (Ettinger 2020). While surgery for early-stage disease remains the preferred treatment, advances in noninvasive treatment modalities, such as targeted therapy, immunotherapy, and modified forms of radiotherapy (RT), have contributed to improved outcomes (Ettinger 2020). Stereotactic body radiotherapy (SBRT; also known as stereotactic ablative radiotherapy, or SABR) is an RT regimen that targets tumors with image-guided, short dose-intensive ablative courses of radiation, in contrast to conventionally fractionated RT (Timmerman 2010). SBRT is a current accepted alternative for surgery of peripheral lung lesions (Stephans 2018, Timmerman 2010, Prezzano 2019) and can be an alternative for larger or central tumors in a 5-fraction regimen in more fragile patients for whom chemo-radiation or surgery presents too great a risk of complications (Peterson 2016, Bezjak 2019, Ettinger 2020).

Modern RT techniques have enabled more precise delivery of high ablative doses with improved sparing of surrounding normal tissue. For early stage NSCLC, SBRT has become increasingly used as standard of care (Timmerman 2018). After initial demonstration of safety with SBRT for small peripheral NSCLC lesions, SBRT has been delivered to larger and more central lesions (Bezjak 2019), which identified SBRT dosing of 11.5 or 12 Gy x 5 fractions as associated with acceptable toxicity and with approximate 2-year rates for local control, overall survival, and progression-free survival of approximately 90%, 70%, and 55%, respectively. Use of SBRT for larger or centrally located NSCLC is reported to increase the risk of toxicity with a larger volume of normal tissue exposure (Fakiris 2009, Woody 2015, Peterson 2016, Bezjak 2019). SBRT can induce serious inflammatory reactions depending on dose and volume given to the lung and generate fibrosis and lung functional restrictions (Lu 2018). SBRT delivering a Biological Equivalent Dose of over 100 Gy to the lung is associated with grade 2 or worse pneumonitis in approximately 15% of patients (Lu 2018).

Individual risk of radiation-induced pneumonitis depends on the volume of lung treated and the radiation dose administered, as well as patient characteristics and other treatment modalities used (immunotherapy itself has around 10% pneumonitis risk on its own (Mohamad 2018). The risk of clinical pneumonitis requiring medical intervention has been reported to be 9% to 28% after lung SBRT (Kang 2015, Palma 2013, Yamashita 2014, Timmerman 2018). Many more patients show radiological changes, which can often disturb response evaluation, as well as show milder changer which itself can limit retreatments for metastatic disease in the same lung (Larici 2011, Kang 2015). Significant (≥ grade 3) rates of pneumonitis have been reported varying from > 10% to 21% (Timmerman 2006, Baumann 2009, Stephans 2018). Chemotherapy or/and immunotherapy carry their own pneumonitis risk and cumulative pneumonitis risk together with SBRT is observed and feared (Zhao 2016, Mohamad 2018, Palma 2013).

With improved systemic treatment, lung cancer patients are also living long enough to manifest late pulmonary toxicity after RT (Larici 2011). Moreover, in patients with recurrent disease, re-challenging RT also becomes technically possible. Based on nonclinical data, fibrosis obtained following the first SBRT treatment can significantly limit future treatment options. Due to their close relation to major airways, esophagus and major vessels, central tumors have a higher complication risk from radiotherapy, and are in general treated with 5 or more fractions of SBRT (Lo 2009) allowing normal tissue in the field more time to repair (Timmerman 2006).

In this trial, we target larger and/or central tumors associated with a higher pneumonitis and local failure risk, as well as a more fragile patient population. A sequential SBRT regimen of 5 fractions or 3 fractions for larger peripheral lesions delivering dose up till biologically equivalent (total) dose (BED) of 100Gy aligns with the standard dose for larger and/or central lesions (Bejzak 2015, Timmerman JAMA 2010). The practice is shifting toward 5 fractions specifically for central localizations; however, for larger peripheral lesions, a 3-fraction regimen is still accepted.

The RTOG 0813 trial identified SBRT dosing of 11.5 or 12 Gy x 5 fractions as associated with acceptable toxicity and with approximate 2-year rates for local control, overall survival, and progression-free survival of approximately 90%, 70%, and 55%, respectively (Bezjak 2019). Other studies (Stone 2015, Mohamad 2018) reported control rates around 70% and PFS 50-60% at 2 years.

Radiation-induced lung injury is a slowly developing process, mostly manifesting as radiological changes only and transient symptoms around 4-6 months (mean 135 days) after treatment (Jain 2018, Ferrero 2015). Clinically scored and symptomatic pneumonitis is seen in approximately 10% of patients 6 months after SBRT (Kang 2015, Yamashita 2014, Mohamad 2018). Stone et al (2015) referred to DLCO decline as the most objective measure of lung toxicity, referring to an observed decline (grade 1 or more) in 20-30% of patients. While a small decline is not seen as clinically significant, it is predictive for more severe accumulative toxicity risk in cases of pre-existing lung disease or in those with subsequent need for re-treatment in the thoracic area. Radiological changes in lung parenchyma are observed in over 40% of SBRT patients (Kimura 2006, Timmerman 2018).

Approximately a 25% of patients experience declines in DLCO, reported after a 5-fraction regimen SBRT (Stone 2015). Slow decline in lung function and radiological changes are described after SABR/SBRT leaving a small portion of patients (mean 10%) with persistent significant decline at one year, which can be difficult to distinguish from recurrence (Huang 2012). Both lung function testing and radiographical changes are directly related clinical scoring at 3 months (Tadasuke 2020), explaining a gradual change from radiological to functional and finally clinical symptomatic SBRT complication related to dose and volume treated.

Both radiological and clinical data are needed to create future guidelines around lung SBRT (Mohamad 2018, Tadasuke 2020, Palma 2013). Complementary drugs such as GC4711 may add important value by increasing efficacy and reducing pneumonitis risk.

2.2 Investigational Medicinal Product

GC4711 is a novel, water soluble, low molecular weight, manganese-containing macrocyclic ligand complex whose catalytic activity for the dismutation of superoxide to hydrogen peroxide mimics that of naturally occurring superoxide dismutase (SOD) enzymes. GC4711 is a member of a new pharmacologic class of drugs termed selective dismutase mimetics and is being developed for administration as an intravenous (IV) infusion. The action of GC4711 to convert superoxide to hydrogen peroxide protecting normal lung tissue and potentiating antitumor response to SBRT.

SOD enzymes are expressed in the cytoplasm (SOD1 Cu/Zn-based), mitochondria (SOD2, Mn-based), and extracellular spaces (SOD3, Cu/Zn- ($O_2^{\bullet-}$) based) of mammalian cells (Fridovich 1997). These enzymes eliminate superoxide ($O_2^{\bullet-}$) by converting it to hydrogen peroxide which is then further detoxified by peroxidase enzymes to oxygen and water (Fukai 2011, Miller 2012). In certain inflammatory disease states and during RT and chemotherapy for cancer, native SOD enzyme activity can be overwhelmed due to excessive superoxide production resulting in normal tissue damage (Mapuskar 2019). Thus, the removal of excess superoxide with supraphysiological levels of SOD activity can protect normal tissues from therapeutic radiation damage as has been demonstrated by multiple lines of evidence (Greenberger 2007). Likewise, selective dismutase mimetics, specifically GC4711 analogues, have been shown to reduce normal oral mucosa damage due to radiation (Murphy 2008, Anderson 2019).

Hydrogen peroxide is more toxic to tumor cells than to normal cells. This cancer cell sensitivity may reflect lower expression levels of catalase, glutathione peroxidase and other enzymes that degrade hydrogen peroxide in the cancer cell (Oberley 1997), a translocation of catalase (Bohm 2015), or susceptibility of cancer metabolism. In irradiated tissue, radiation directly and indirectly generates additional superoxide which is then converted by SOD enzyme or dismutase mimetic to additional hydrogen peroxide. The amount of superoxide generated is related to RT fraction dose size, and thus the amount of hydrogen peroxide produced by the dismutase mimetic is also proportional to fraction dose size. As hydrogen peroxide increases with fraction dose size, it can reach levels that have significant anti-tumor effects (Greenberger 2007, Sishc 2018, Sishc 2019). For example, the overexpression of manganese SOD (MnSOD, or SOD2) by plasmid liposomes in multiple mouse organs was shown to protect normal cells from radiation damage while increasing the radio-sensitivity of tumor cells, indicating that normal cells were protected from superoxide damage while tumor cells were susceptible to hydrogen peroxide (Greenberger 2007).

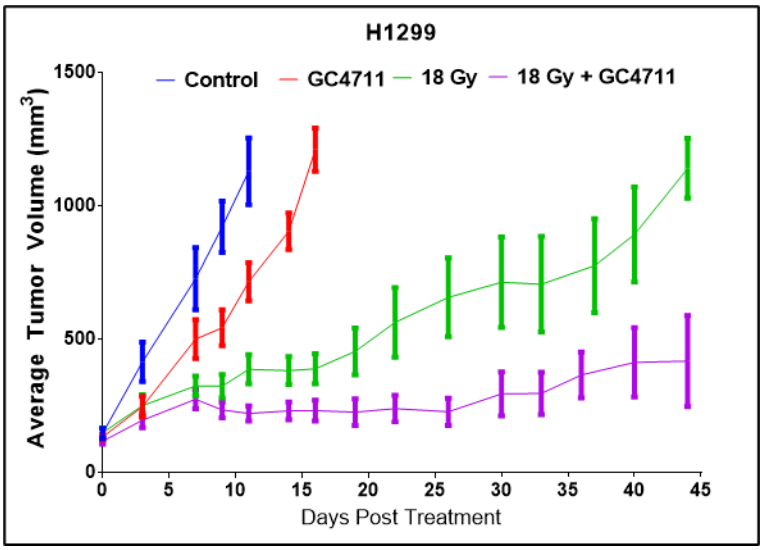
2.2.1 GC4711 Nonclinical Data

In nonclinical models, the addition of selective dismutase mimetics to SBRT regimens with or without concomitant systemic therapy enhanced antitumor activity while protecting normal tissues from radiation (Sishc 2019). The nonclinical development program for GC4711 is supported by previous findings in experimental NSCLC mouse xenograft models with GC4419, an analogue of GC4711 that is in clinical development to reduce the incidence and severity of oral mucositis due to radiation therapy for head and neck malignancies (Anderson 2019).

Additional studies provided support for the hypotheses that dismutase mimetics (1) act as radiosensitizers in a hydrogen peroxide-dependent manner, and (2) act as a radioprotector reducing damage caused to normal lung tissue (Sishc 2018).

In a series of nonclinical studies, GC4711 was evaluated for its ability to potentiate the antitumor effects of SBRT in experimental mouse xenograft models of lung and pancreatic cancers. In the human H1299 NSCLC model, GC4711 alone, administered once daily at 24 mg/kg for 5 consecutive days, significantly delayed H1299 tumor growth in the xenografted mice compared with vehicle control animals (Figure 1). The administration of SBRT alone on Day 1 at 18 Gy had an even greater effect on tumor growth. The combination treatment of 24 mg/kg GC4711 administered on Days 1 to 5 and 18 Gy SBRT on Day 1 demonstrated an additive effect on tumor growth, resulting in smaller average tumor volumes compared with GC4711 or SBRT alone.

Figure 1 GC4711 Potentiated the Antitumor Effects of SBRT in a Human NSCLC Model



NSCLC = non-small cell lung cancer; SBRT = stereotactic body radiotherapy.
H1299 cells (ATCC® CRL-2553™) were implanted by subcutaneous (SC) injection into the flank of 6-week old female nu/nu mice. When the average tumor size per group reached 100 mm^3, treatments were initiated. A single SBRT dose (18 Gy) was administered once on Day 1. Control and GC4711 groups (n = 9-12 animals per group) received the vehicle (10 mM sodium bicarbonate in saline) or 24 mg/kg GC4711 in vehicle by intraperitoneal (IP) injections approximately 30 minutes before the 18 Gy SBRT dose and on Days 2 through 5. Tumor dimensions were measured 2 times per week by caliper and tumor volumes calculated. Tumor volumes expressed as the group mean +/- standard error of the mean.

The inclusion of radiation dose holidays in the H1299 model did not decrease the inhibitory effect of the GC4711-SBRT combination. In addition, in focal irradiation models in non-tumor bearing mice the GC4711 analogue, GC4419, potently reduced normal lung damage at single RT doses up to 60 Gy (Sishc 2018).

SBRT greatly increases cellular superoxide concentrations, which these selective dismutase mimetics exploit to generate high levels of hydrogen peroxide, creating a highly toxic environment for tumor cells. The hypothesis that the antitumor response was driven by the overwhelming and persistent production of hydrogen peroxide is supported by the observation that the dismutase mimetic-enhanced radiation response of tumors derived from H1299CAT cells (doxycycline-inducible catalase overexpressing) and treated accordingly with doxycycline, was completely abrogated (Sishc 2018). The conversion of superoxide to hydrogen peroxide catalyzed by dismutase mimetics renders tumor cells more sensitive to the effects of SBRT, positively impacting tumor cure rates in nonclinical in vivo models.

That GC4711 administration will also protect normal tissues from radiation-induced damage is supported by studies with the GC4711 analogue, GC4419 (Sishc 2018). In these studies, GC4419 acted as both a protector and mitigator of radiation-induced damage. A single pretreatment with GC4419 significantly reduced the fibrotic density of focally irradiated murine lung tissue (54 Gy and 60 Gy, single dose). Furthermore, daily post-irradiation dosing of GC4419 also further reduced lung fibrosis dependent upon the total duration of daily delivery.

Four GLP 14-day repeat-dose studies with 14-day non-treatment recovery periods were conducted in SD rats and beagle dogs using either 15- or 60-minute GC4711 IV infusions in each species. In GLP toxicology studies conducted in rats, GC4711 had no test item-related adverse effects on CNS or respiratory parameters when administered as repeat-dose 15-minute IV infusions; furthermore, in single- and repeat-dosing safety pharmacology studies performed with GC4711 in dogs, no adverse CV effects occurred following 15-minute IV infusions, the intended route of administration in human subjects.

Key safety findings in the GLP toxicity studies were as follows:

- GC4711 was overall well tolerated in SD rats and beagle dogs in all repeat-dose studies.
- Mortality was observed in 2 rats in the 15-minute infusion study at the high dose of 16 mg/kg/day and was of unknown relationship to GC4711.
- Adverse effects included weight loss, which was observed in rat 15- and 60-minute infusion studies at the high dose of 16 mg/kg/day (15-minute infusion), and the middle and high doses of 18 mg/kg/day and 24 mg/kg/day (60-minute infusion), respectively. The rat adverse effects were reversible during the 14-day recovery period.
- The NOAEL was considered to be 8 mg/kg/day for rats and 9 mg/kg/day for dogs in the 15-minute GC4711 infusion studies. The NOAEL was considered to be 12 mg/kg/day for rats and 12.5 mg/kg/day for dogs in the 1-hour GC4711 infusion studies.
- There were no indications of clastogenicity or genotoxicity associated with administration of GC4711.

For additional information, please refer to the GC4711 Investigator's Brochure.

2.2.2 GC4711 Clinical Data

The clinical development of GC4711 comprises one completed and two ongoing clinical studies. Initially, the safety and plasma exposure of healthy volunteers to GC4711 was compared to that of the analogue, GC4419, which is in development for reduction of RT-induced oral mucositis (Study GTI-4711-001). Based on their structural similarities, it was hypothesized that, at equimolar doses administered by the same route and schedule, the safety and plasma exposure of GC4711 and GC4419 in human subjects would be substantially similar. This was demonstrated in GTI-4711-001, facilitating further work to identify GC4711 doses of interest for clinical study in light of prior experience with GC4419. Additional information regarding the safety and pharmacokinetic results of this completed study are available in the Investigator's Brochure.

In addition, safety data with GC4711 have been obtained at a dose of 30 mg by 60-minute IV infusion in an ongoing study (Study GTO-003) in which the bioavailability of various candidate oral formulations of GC4711 is being assessed to identify a suitable formulation for future clinical development.

The principal study supporting the proposed dosing of GC4711 in the current Phase 1/2 study was a Phase 1 Study (Study GTI-4711-002). In this study, serial cohorts of healthy volunteers received IV GC4711 or placebo by 15-minute IV infusion period at a single dose up to 120 mg of GC4711, then by multiple infusions once daily for 14 days at 90 mg/day.

In Study GTI-4711-002, a total of 10 subjects were enrolled in each cohort and were randomized at a 6:4 ratio to receive GC4711 or placebo treatment. All cohorts included a sentinel cohort consisting of 2 subjects (1 GC4711, 1 placebo) who were observed for at least 24 hours with safety data reviewed by the treating investigator before dosing the rest of the subjects in the cohort. In the SAD cohorts (Cohorts 1-6), GC4711 or placebo was administrated as a single dose on Day 1 at 30, 60, 75, 90, 105, or 120 mg. In the multiple dose cohort (Cohort 7), GC4711 or placebo was administrated once daily for 14 days at 90 mg/day.

In Study GTI-4711-002, the PK profile of GC4711 following 15-minute IV infusion at doses from 30 mg to 120 mg as a single dose and 90 mg/day for 14 days in Study GTI-4711-002 is characterized by:

- Quantifiable plasma concentrations up to 6 to 12 hours across all dose cohorts.
- Greater than dose proportional behavior for the C_{max} and AUC of GC4711 across single dose administration cohorts. For GC4711 this behavior may be attributed to the fact that the first dose (30 mg) was not measurable for a long period of time, resulting in a much lower AUC.
- The $t_{1/2}$ for GC4711 was approximately 2 hours.
- Low levels of exposure to the GC4711 metabolites GC4764 and GC4765, with metabolite to parent ratios of < 6% and 1.2%, respectively across all dose cohorts. Based on the combination of low prevalence and biological activity in nonclinical studies, these metabolites do not appear to be of clinical significance in human patients.

- No marked accumulation of GC4711 was observed by Day 8 following daily administration of 90 mg/day.

The safety of GC4711 has been established following administration by IV infusion in healthy volunteers. Overall, the safety profile of GC4711 was comparable following single 15-minute IV infusion doses up to 120 mg and multiple 15-minute IV infusion doses of 90 mg/day for 14 days. Consistent with the mechanism of action of GC4711 (specifically, potentiation of nitric oxide (Kasten 1995)), transient orthostatic symptoms (e.g., headache, dizziness, light-headedness), hypotension, facial tingling or paresthesia were expected and consistently observed. Reports of paresthesia appeared to be dose-related; however, it was mild to moderate in intensity and was not treatment-limiting. All TEAEs reported have been Grade 1 or Grade 2 in intensity. None of the TEAEs were graded serious and there were no deaths. None of the clinical laboratory evaluations resulted in any clinically significant abnormalities. Please see the Investigator's Brochure for further details.

Assessment of ECG data from the single ascending dose cohort of the ongoing Phase 1 study (Study GTI-4711-002), demonstrated that there were no clear dose-related trends, nor changes in ECG measures nor interpretation from normal to abnormal, which were clinically significant. Overall, there were 3 subjects (1 [16.7%] at 30 mg and 2 [33.3%] at 120 mg) who reported ECG changes that were all judged not clinically significant. This addressed shifts in QT interval at 2 hours post end of infusion relatively to baseline (-5.3 msec for the subject in the 30 mg group and +5.0 and +16.7 msec for the subjects 120 mg group, respectively) and QTcF interval (-5.3 msec for the in the subject in the 30 mg group and +9.0 and +7.7 msec for the subjects 120 mg group, respectively). Although, rated as clinically non-significant, ECG and QT intervals are to be closely followed when patients are first exposed to GC4711.

Overall, the safety profile of GC4711 from healthy volunteer populations is acceptable to further investigate safety testing in NSCLC patients.

2.3 GC4711 Benefit/Risk Assessment

The safety of GC4711 has been established in healthy subjects following administration via 15-minute and 60-minute IV infusions. There were no unexpected safety findings, and the overall safety profile of GC4711 was comparable following single 15-minute IV infusion doses up to 120 mg and multiple 15-minute IV infusion doses of 90 mg/day for 14 days. Further, a crossover study in healthy human subjects demonstrated similar safety and plasma exposure to the MnPAM dismutase mimetic analogues GC4711 and GC4419 administered via IV infusion at approximately equimolar doses. A 100 mg dose of GC4711 is approximately equimolar to the 90 mg dose of GC4419 used in the pilot SBRT combination trial in patients with pancreatic cancer and in the IMRT combination oral mucositis clinical trials in head and neck cancer.

Therefore, based on non-clinical pharmacology studies and previously collected clinical data, GC4711 is an appropriate experimental drug candidate in combination with SBRT as a safe and effective alternative in lung cancer management.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Phase 1	
Primary	
- To assess the safety of GC4711 administered intravenously (IV) in combination with 5 fractions of stereotactic body radiation therapy (SBRT) in subjects with Non-small Cell Lung Cancer (NSCLC)	- Number of dose-limiting toxicities (DLTs) occurring during treatment with SBRT and GC4711/placebo or within 30 days post-SBRT
Secondary	
- To evaluate the efficacy, and acute and late toxicities of GC4711 + 5 fractions of SBRT	Measurement of the following parameters over 24 months after SBRT - Efficacy: o Progression Free Survival (PFS) o Overall Survival (OS) o Local and regional control o Distant Metastases (DM) rate Measurement of the following parameters over 12 months after SBRT: - Toxicity: o Changes in pulmonary function testing: Pulse oximetry (SpO2), forced vital capacity [FVC], first expiratory volume in the first second [FEV1], DLCO, clinical and radiological pneumonitis scorings. o Frequency, duration and severity of AEs and SAEs o ECG and Pharmacokinetics monitoring of GC4711
- To evaluate the long-term toxicity of GC4711 + 5 fractions of SBRT	- Late radiotherapy (RT) Toxicities (including clinical and radiographic pneumonitis, esophagitis, pulmonary fibrosis, rib fractures) up to 12 months following the completion of SBRT

OBJECTIVES	ENDPOINTS
Phase 2	
Primary	
- To determine the percentage of patients with complete or partial in-field tumor response through 6 months following SBRT	- Percent of patients with a best RECIST response of CR or PR amongst all responses through Month 6
Secondary	

- To determine the degree of in-field tumor response at 6, 12, 18 and 24 months following completion of SBRT
- To compare progression-free survival, overall survival, local tumor control, and distant metastasis rates over a 2-year follow up period for SBRT plus GC4711 or placebo
- To assess durability of in-field complete or partial responses
- To determine acute lung toxicity after SBRT + GC4711 compared to SBRT + placebo for early-stage NSCLC
- To evaluate the rate of acute and late radiation toxicities for SBRT + GC4711 compared to SBRT + placebo
- To assess the relationship between clinical, functional and radiographical lung function changes observed after SBRT
-
	- Percent reduction of in-field tumor at Months 6, 12, 18 and 24
	- Number of participants with CR+PR
	- Number of participants experiencing grade 1 or higher in diffusion capacity of lung for carbon monoxide (DLCO), measured by RTOG scale, at 6-months after the completion of SBRT
	- Measurement of the following parameters over 12 months after SBRT
	  - Changes in pulmonary function testing (pulse oximetry [SpO2], forced vital capacity [FVC], first expiratory volume in the first second [FEV1], DLCO), clinical and radiological pneumonitis scoring
	  - Reporting of observed adverse events in patients
	  - Late Radiation Toxicities (including clinical and radiographic pneumonitis, esophagitis, pulmonary fibrosis, rib fractures, plexopathy, cardiac and vascular events) up to 12 months following the completion of SBRT
	- Measurement of the following parameters over 24 months after SBRT
	  - Progression Free Survival (PFS)
	  - Overall Survival (OS)
	  - Local and regional control
	  - Distant Metastases (DM) rate

OBJECTIVES	ENDPOINTS
	-
Exploratory (Phase 1 and 2)	
- To evaluate lung injury risk over time - To evaluate the relation between clinical, functional and radiographical lung function changes and patient/disease and dosimetry characteristics - To evaluate the pharmacokinetics of GC4711 in the study population - To collect initial information about acute effects of GC4711 on electrocardiogram parameters	- Lung functional decline over time - Risk factor analysis for decline in lung function, imaging and clinical scoring of pneumonitis, including dosimetry, disease and patient characteristics (smoking, medical history) - ECG and Pharmacokinetics monitoring of GC4711

4 STUDY DESIGN

4.1 Overall Design

GTI-4711-101 is a Phase I/II study of the safety of GC4711, and its potential to reduce radiation-related pulmonary injury, in combination with SBRT for clinical Stage I/II lymph node negative (T1 to T3N0M0) and/or central localized NSCLC.

After an open-label, Phase 1, safety run-in cohort of approximately 5 subjects has been completed, a randomized, placebo-controlled Phase 2 portion will be conducted.

Subjects must be referred for SBRT with peripheral lesions (>1-7 cm) or central localized (within an all direction, 2 cm- zone around the proximal bronchial tree, including ultra-central lesions, abutting the proximal bronchial tree or trachea) and node negative, non-metastatic NSCLC and have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0-3 to be considered for enrollment (Buccheri 1996). Subjects with small peripheral lesions (≤1cm) are excluded, as we aim to improve outcome in larger, central NSCLC carrying a higher risk of pneumonitis and other RT related toxicities (including esophagitis, rib fractures, fistulae, stenosis, plexopathy, pericarditis, vascular events, etc. see Section 7.4), as well as local control failure. Feasibility of SBRT is judged by the treating physician. SBRT is planned on the tumor location for a dose of 10-12 Gy per 5 fractions, delivered on 5 sequential days or a dose of 18-20 Gy per 3 fractions (minimum of 18 and maximum of 96 hours between fractions for either regimen). All fractions should be given within 10 calendar days (+5 days in the case of a holiday or technical issue).

Phase 1: 5 subjects will each receive 100 mg of GC4711 by 15-minute IV infusion, before each SBRT fraction, beginning the day of the first fraction and ending the last day of SBRT (5 doses in total). SBRT is administered within 180 minutes (3 hours) of the end of the GC4711 infusion. All 5 SBRT doses should be given within 10 calendar days. All 5 subjects will be monitored for dose limiting toxicity (DLT) for 30 days post SBRT plus GC4711. DLT is defined in Section 7.5.

Safety will be judged unacceptable if 2 or more (i.e., no more than one) of the 5 subjects develop a DLT. Safety will be reviewed by a Safety Review Committee (SRC) consisting of the Medical Monitor, the Principal Investigator from each Phase 1 site, and additional designees by the Sponsor or the site Principal Investigators.

Phase 2: After the SRC has confirmed acceptable safety in the Phase 1, a Phase 2, randomized, placebo-controlled study phase will be initiated, wherein approximately 66 subjects referred for SBRT with early stage large and/or central localized NSCLC will be randomized in a 1:1 ratio to receive either GC4711 100 mg or placebo given IV over 15 minutes on each day that SBRT is given, beginning the day of the first fraction of SBRT and ending the last day of SBRT,. SBRT is administered within 180 minutes (3 hours) of the end of the GC4711 infusion. A minimum of 18 hours and a maximum of 96 hours are permitted between factions. All fractions should be given within 10 calendar days (+3 days in the case of a holiday or technical issue).

All subjects will be evaluated for changes in the in-field tumor for 24 months following completion of SBRT. The primary endpoint will evaluate the percentage of patients with complete or partial in-field tumor response through 6 months following SBRT. In addition, as a secondary endpoint, the percent of subjects with overall responses (PR + CR) per RECIST 1.1 will be evaluated.

All subjects will be evaluated by changes in the diffusion capacity of lung for carbon monoxide (DLCO), as assessed by the RTOG grading scale monitored at 6 months and 12 months. The secondary endpoints will evaluate all lung function parameters. Pneumonitis will also be assessed both clinically and radiographically (CTCAE 5.0).

All subjects will be followed for 30 days post SBRT completion for treatment related adverse events, 90 days post SBRT completion for acute radiation toxicity and for 12 months post SBRT completion for late radiation toxicity, and will be followed for 24 months post SBRT completion for local and regional disease control (LC), Progression Free Survival (PFS), Overall Survival (OS) and Distant Metastases (DM) rate.

Detailed information on the Radiation Therapy Quality Assurance (RTQA) (Phase 1 only) and dose-volume exposure, concomitant medications and existing obstructive lung disease will be collected for pneumonitis-risk analyses.

Pharmacokinetic (PK) sampling and cardiac monitoring will be performed on each subject with two separate doses of GC4711 (or placebo) collecting blood samples pre-infusion post-infusion and 24 hours post-infusion (Phase 1 only) for each.

In Phase 2, the Sponsor will perform routine reviews of the safety data at an interval no less than quarterly and after the 20th randomized subject reaches the 30-day follow up timepoint, whichever occurs first. See Section 8.6 for details.

4.2 Study Duration for Participants

The study duration for participants is expected to be approximately 25 months. This includes a 21-day screening period, a treatment period of approximately 5-10 days, and long-term follow-up for 24 months. All subjects are evaluated 30 days after SBRT and 6, 12, 18 and 24 months post-SBRT.

If a participant experiences progressive disease prior to 24 months post-SBRT completion, they will continue for survival follow-up until end of study (24 months following the last administration of SBRT). No additional tumor assessments will be required after progression; however, adverse events for long term radiation toxicities will continue through 12 months post SBRT completion and survival follow up will continue through 24 months post SBRT completion.

4.3 Number of Participants

Approximately 71 participants will be enrolled in the study. This includes 5 in the Phase 1 portion and approximately 66 in the Phase 2 portion

4.4 Replacement of Participants

In Phase 1, if a subject is withdrawn from the study prior to completing GC4711/Radiotherapy and 30 days of follow-up without experiencing a DLT prior to withdrawal, an additional subject may be added.

In Phase 2, patients who are randomized but do not receive study drug may be replaced.

4.5 Number of Sites

Phase 1: Up to 4 sites in the US will participate in the Phase 1 portion.

Phase 2: Up to 20 sites in the US will participate in the Phase 2 portion.

4.6 End of Study Definition

End of Study (Individual Participant): A participant is considered to have ended participation in the study if he/she has completed all phases of the study including the month 24 follow-up or who as withdrawn consent from all study participation or who has died.

Primary Completion: The primary completion date is defined as the date when the last participant is assessed or receives an intervention for the final collection of data for the primary endpoint(s) for the purposes of conducting the primary analysis. For Phase 1, this is defined as 30 days post SBRT. For the Phase 2, this is defined as 6 months post SBRT.

End of Study (End of trial): The date the final participant was examined or received an intervention/assessment for purposes of final collection of data for the primary, secondary or exploratory outcome measures.

4.7 Rationale for Study Design

In non-clinical development, GC4711 has shown the potential of increasing efficacy of high dose RT as well as limit associated inflammatory and fibrotic normal tissue reactions. As SBRT is a commonly used high dose RT treatment for early NSCLC, in this trial, we combine

GC4711/placebo with this national standard SBRT indication. Though SBRT has been shown to be effective in the treatment of small peripheral NSCLC (Timmerman 2010), its use for larger and/or central lesions has been associated with an increased risk of toxicity and less favorable local control (Stanic 2014, Bezjak 2015). By combining GC4711 with the 5-fraction regimen (Timmerman 2006, Lo 2010, Ettinger 2020), this study will assess both tolerability of the regimen and disease control. In addition to the routine efficacy parameters of local and regional control, control of distant metastatic rate, progression free survival (PFS) and overall survival (OS), we will also examine the effects of SBRT and GC4711 on response rate by the RECIST 1.1 criteria and degree of in-field tumor response.

Lung damage is the most common reported adverse effect and close monitoring of pneumonitis in this trial can be compared to extensive historical data (Timmerman 2006, 2010 and 2018). Radiation induced injury is a slow developing process, showing most radiological changes and symptoms around 3-6 months after treatment (Takeda 2013, Videtic 2013, Jain 2018, Ferrero 2015). Approximately 25% of patients treated with a 5-fraction regimen of SBRT encounter lung function decline (Stone 2015), of which a small portion (mean 10%) remain with a significant decline, which can be difficult to distinguish from recurrence (Huang 2012). Radiological changes have been described in larger number of subjects but are not always translated in clinical symptoms. Safety of GC4711 is the primary endpoint of the phase 1 portion and acute and late RT toxicities, as well as disease outcome are monitored as secondary endpoints in phase 2.

4.8 Rationale for GC4711 Starting Dose

The proposed dosing regimen for this study will consist of 100 mg IV of GC4711 administered over 15 minutes prior to each SBRT fraction. Patients will be required to receive a total of 3 x 18-20 Gy or 5 x 10-12 Gyfor a total 50 to 60 Gy. Following the healthy human volunteer study (GTI-4711-002), IV administration of GC4711 was found to be well-tolerated following a single administration at dose levels up to 120 mg and following repeated dosing of 90 mg/day for 14 days or a total weekly dose of 630 mg. Therefore, GC4711 at a dose of 100 mg x 3 or 5 doses (aligning with SBRT regimen) is expected to be tolerated by this patient population.

This dose level is also supported by nonclinical safety studies. Based on the STD10 (the dose in non-clinical studies that was severely toxic to 10% of the rodents) and the highest non-severely toxic dose (HNSTD) calculations using the GLP 14-day rat (Study 1324-4711-0520) and dog (Study 1325-4711-0520) toxicology studies, a 90 to 96 mg/patient starting dose of GC4711 are supported.

Further, GTI-4711-001 demonstrated substantially similar safety and pharmacokinetics of GC4711 and GC4419. Acceptable safety of a 90 mg dose of GC4419 (approximately equimolar to 100 mg of GC4711) has been observed with GC4419 administered to head and neck cancer patients, M-F for up to 7 weeks, in combination with intensity-modulated radiotherapy (IMRT) and concurrent cisplatin (Anderson 2019). Adverse effects associated with either drug have been transient in clinical trials or have not appeared to be worse with repeat dosing (Anderson 2019).

5 SELECTION AND WITHDRAWAL OF SUBJECTS

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 1).

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Male or female subjects at least 18 years of age.
2. Ability to understand and the willingness to sign a written informed consent.
3. Histological or biopsy proven NSCLC. For peripheral lesions, cytology and/or clear imaging-guided suspicion is accepted if histology cannot be obtained.
4. ECOG performance status of 0-3.
5. Lymph node negative (T1 to T3N0M0), centrally located (within 2cm in all directions around the proximal bronchial tree, including ultra-central tumors, abutting the bronchial tree or trachea) or large (>1-7cm) Non-Small Cell Lung Cancer (NSCLC) , judged acceptable for SBRT by the treating Investigator. Staged with FDG-PET/CT, brain CT or MRI with contrast and/or mediastinoscopy, measurable disease as defined by RECIST 1.1. (See Figure 2 below).
6. Adequate end-organ function, based on routine clinical and laboratory workup:
    a. ANC >1,000 cells/µl, Platelets ≥ 75,000 cells/µl, Hemoglobin ≥ 8.0 g/dl
    b. Serum creatinine ≤ 2 mg/dL or calculated creatinine clearance ≥ 30 ml/min
    c. Total bilirubin ≤ 1.5 x ULN (or direct bilirubin below the ULN), AST and ALT ≤ 2.5 x ULN
    d. International normalized ratio (INR) (or prothrombin time (PT)) and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless participant is receiving anticoagulant therapy, if values are within the intended therapeutic range
7. Males and females of must agree to use effective contraception starting prior to the first day of treatment and continuing after the last dose of GC4711/Placebo for 30 days (females) and 90 days (males).

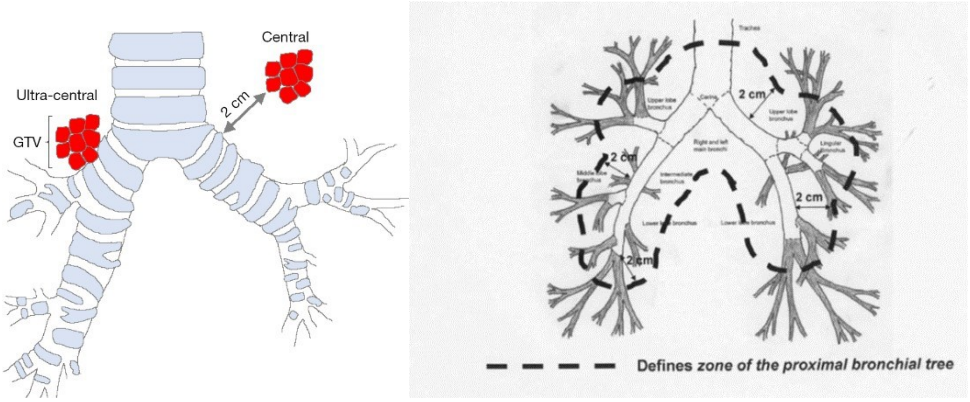


Figure 2 Anatomy of central and ultra-central lung tumors

Timmerman and colleagues defined central lung tumors as those located within 2 cm of the proximal bronchial tree (Timmerman 2006). Here defined ultra-central lung tumors as those abutting the proximal bronchial tree or trachea (Lo 2010, Chaudhuri 2015, Chang 2018).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Subjects with confirmed nodal and/or distant disease (including brain), according to standard workup by local investigator.
2. Subjects with peripheral lesions of 1cm or smaller
3. Prior treatment with immunotherapy within 3 months prior to Day 1 dosing.
4. Prior intra-thoracic radiotherapy or surgery with substantial overlap to planned in former radiation fields as determined by the treating radiation oncologist.
5. Subjects not recovered/controlled from prior treatment-related (chemotherapy or targeted therapy) toxicities judged by treating physician.
6. Uncontrolled malignancy other than lung cancer that requires active treatment or is deemed by the treating physicians to be likely to affect the subject's survival duration.
7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to GC4711.
8. Uncontrolled intercurrent illness including, but not limited to, active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements.
9. Participation in other clinical trials actively testing new anti-cancer treatments unless previous written approval provided by the Sponsor.
10. Requirement for concurrent treatment with nitrates or other drugs that may, in the judgment of the treating investigator, create a risk for a precipitous decrease in blood pressure.

11. Female subjects who are pregnant or breastfeeding.
12. Any other conditions that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study.

5.3 Screen Failures

A subject is considered as a screen failure if the subject signs the ICF but withdraws consent or is deemed ineligible prior to registration/randomization. The reason why the subject was precluded from the clinical study will be recorded in the medical record and eCRF. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

5.4 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Subject Study Withdrawal: A subject has the right to withdraw from the study at any time for any reason. Subjects who withdrawal consent from study treatment and/or study assessments early should be encouraged to continue with survival and late toxicity follow-up, if feasible.

Subject Study Discontinuation: The Investigator or Sponsor may also, at his/her discretion, discontinue a subject from participating in this study at any time.

Study Intervention Discontinuation: A subject may discontinue study treatment but remain in the study for follow-up for any of following reasons:

- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, etc.)
- The subject was "lost to follow-up"
- Unacceptable adverse event necessitating treatment cessation
- More than three infusion modifications of GC4711/placebo
- Subject requests to withdrawal from the study treatment
- Subject becomes pregnant
- Other reasons (reason must be specified, for example: the subject moved, investigator decision, Sponsor decision to terminate trial, etc.)

If a subject discontinues from the study treatment early (did not complete SBRT regimen and/or receive all protocol required infusions of study drug), they will continue to be followed for progression, toxicities and survival as outlined in the SOA.

The primary reason and date for ceasing treatment, discontinuation and/or subject withdrawal will be clearly documented in the subject's medical record and recorded on the appropriate CRF page.

Discontinuation of specific study sites or of the study are handled as part of

Appendix 1.

6 INVESTIGATIONAL PRODUCT AND TREATMENT OF SUBJECTS

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Refer to the GC4711 IB and Pharmacy Manual for more detailed information regarding the storage, preparation, destruction, and administration of each treatment.

The site pharmacists will be unblinded to the treatment assignments. The Principal Investigator and remainder of the site staff will be blinded to treatment assignment. The Unblinded Pharmacist should take every precaution to prepare the study treatment in a blinded fashion and out of site from the Blinded site clinical staff. The Blinded Clinical Staff should be mindful of the steps in place to maintain the blind.

6.1 Investigational Product: GC4711/Placebo

GC4711 Dosage Formulation and Preparation

GC4711 IV drug product is formulated as a lyophilized solid in a vial and reconstituted shortly before administration with a provided 26 mM sodium bicarbonate aqueous buffer diluent. Sterile drug product and diluent will be provided by Galera Therapeutics Inc., and the drug product will be supplied as 120 mg in 3 mL clear glass vials and reconstituted by adding 1.10 mL of the provided diluent to yield 100 mg/mL reconstituted drug product. GC4711 (reconstituted solution) will be prepared by the unblinded pharmacist, diluted in normal saline (0.9% NaCl) to obtain a 100 mL dosing solution for IV infusion. 100 mL Normal saline (0.9% NaCl) for IV infusion, supplied by the site, will be used as placebo.

GC4711 Dosage, Administration, and Schedule

Phase 1:

100 mg/day of GC4711 IV will be given over 15 minutes, starting from the first to the last SBRT treatment. GC4711 will be given before SBRT with a maximum of 180 minutes between end of infusion and the start of SBRT.

Phase 2:

- **Arm A:** 100 mg/day of GC4711 will be given via IV infusion over 15 minutes, prior to each SBRT dose, from the first to the last SBRT treatment. On days of SBRT, GC4711 will be administered with a maximum of 180 minutes between the end of infusion and the start of SBRT.

- **Arm B:** Placebo (normal saline) will be administered via IV infusion over 15 minutes to be completed with a maximum of 180 minutes prior to SBRT as for Arm A.

A total of 100 mL of GC4711 or Placebo (normal saline) will be infused IV over a 15-minute period using a programmable pump, when feasible. Each infusion should be given before each of the SBRT treatments (Table 1 Schedule of Activities). In situations where SBRT is not given following study drug infusion, an additional dose of GC4711/placebo may be given prior to the rescheduled fraction.

GC4711 Drug Packaging and Labeling

GC4711 with diluent will be provided by Galera as single-use vials for daily doses to be administered IV concurrent with SBRT. The drug product is supplied as 120 mg in 3 mL clear glass vials along with 26 mM sodium bicarbonate buffer diluent which is packaged in a 3 mL clear glass vial. Each vial will be labeled with the appropriate language, including the required regulatory text.

Normal saline will be provided and prepared by the site institutional pharmacy for subjects assigned to placebo in the Phase 2 portion of the study.

Maintenance of the Blind

All staff at the site should be designated as either blinded or unblinded. For Phase 2, the site pharmacists will be unblinded to the treatment assignments assigned within the Randomization and Trial Supply Management (RTSM) System.

Unblinded pharmacy staff will be responsible for management and accountability of investigational product and preparation of study drug in a blinded fashion. The unblinded pharmacy staff will ensure the double-blind nature of this study and will not share the treatment assignment directly or indirectly (IP Accountability Logs, IV bag labels, etc.) with the blinded site staff. Sites should be able to provide documentation regarding how the blind is maintained at their sites.

The site pharmacists will obtain treatment assignments for subjects via the Randomization and Trial Supply Management System (RTSM) through their unique username and password, which should not be shared. Blinded staff will not have access to the treatment assignments via the RTSM. Preparation of the assigned treatment group (GC4711 or placebo) can also be found in the Pharmacy Manual.

Investigational Product Storage and Accountability

GC4711 should be stored in the pharmacy at -15°C to -25°C. The sodium bicarbonate aqueous buffer diluent will also be stored in the pharmacy. The diluent must be stored under refrigerated conditions (2 to 8ºC) and must not be frozen. The storage temperature should be monitored and recorded daily as per site SOPs to ensure temperatures are maintained per above. Copies of

temperature monitoring logs will be made available to the CRA upon request. The sponsor must be notified of any deviation from the specified storage conditions.

Study drug must always be kept in a secure place with access limited to the unblinded pharmacy staff under the appropriate storage conditions. All unblind personnel involved in the dispensing of study drug should be aware of its location. Any deviations in accountability and/or storage should be reported to the site CRA immediately.

Study Intervention Compliance

Study drug will be administered under the supervision of study site personnel. The infusion volume and timing of each dose will be recorded. Accidental overdoses should be reported to the Sponsor/designee promptly.

6.2 Stereotactic Body Radiation Therapy (SBRT)

SBRT Dosage, Administration, and Schedule

Patients will be evaluated by the treating radiation oncologist at the local site. Based on location and size of the tumor, dose planning will be determined by clinical appropriateness that balances ablation of the lesion(s) while respecting normal tissue constraints including for ultra-central lesions the volume criterium of the contoured proximal bronchial tree less than 0.03cc =<52.5Gy (Bejzak 2019).

Table 2 Organ Constrains for a 3-Fraction SBRT Regimen

Serial Tissue	Volume (cc)	Volume Max (Gy)	Max Point Dose (Gy)[2]	Endpoint (≥Grade 3)
Esophagus[1]	<5	27.9	32.4	Esophagitis
Brachial Plexus	<3	22	26	Neuropathy
Heart/Pericardium	<15	24	30	Pericarditis
Great vessels	<10	39	45	Aneurysm
Trachea and Large Bronchus[1]	<5	39	43	Impairment of pulmonary toilet
Bronchus smaller airways	<0.5	25.8	30	Stenosis with atelectasis
Rib	<5	40	50	Pain or fracture
Lung (Right & Left)	1500 for males; 950 for females[3]	10.8		Basic Lung Function
Lung (Right & Left)			V-11.4Gy<37%	Pneumonitis
Spinal cord	<0.35	15.9	22.5	Myelitis

Abbreviations:
1. Avoid circumferential irradiation
2. "point" defined as 0.035cc or less
3. or one-third of the "native" total organ volume (prior to any resection or volume reducing disease), whichever is greater:

- Exceeding these dose tolerances by more than 2.5% constitutes a minor protocol violation.

- Exceeding these dose tolerances by more than 5% constitutes a major protocol violation.

Table 3 Organ Constraints for a 5-Fraction SBRT Regimen

Serial Tissue	Volume (cc)	Volume Max (Gy)	Max Point Dose (Gy)[2]	Endpoint (≥Grade 3)
Esophagus[1]	<5	32.5	38	Esophagitis
Brachial Plexus	<3	27	32.5	Neuropathy
Heart/Pericardium	<15	32	38	Pericarditis
Great vessels	<10	47	53	Aneurysm
Trachea and Large Bronchus[1]	<5	45	50	Impairment of pulmonary toilet
Bronchus smaller airways	<0.5	32	40	Stenosis with atelectasis
Rib	<5	45	57	Pain or fracture
Lung (Right & Left)	1500 for males; 950 for females[3]	12.5		Basic Lung Function
Lung (Right & Left)			V-13.5Gy<37%	Pneumonitis
Spinal cord	<0.35	22	28	Myelitis

Abbreviations:
1. Avoid circumferential irradiation
2. "point" defined as 0.035cc or less
3. or one-third of the "native" total organ volume (prior to any resection or volume reducing disease), whichever is greater:
    - Exceeding these dose tolerances by more than 2.5% constitutes a minor protocol violation.
    - Exceeding these dose tolerances by more than 5% constitutes a major protocol violation.

By protocol prescription, the RT regimen consists of a 5-fraction treatment with doses between 10-12 Gy per fraction (Bejzak 2015) or 3-fraction treatment with doses of 18-20 Gy per fraction to the FDG-PET+ areas delineated as gross tumor volume (GTV). This target volume can be translated into an iGTV by including correction for 4D movement, no clinical target margins (CTV) are used. An additional 0.5 cm in the axial plane and longitudinal plane (craniocaudal) will be added to the GTV to constitute the planning target volume (PTV), while iGTV is reconstructed a 0.3cm margin is accepted. Larger margins may be used in cases where greater motion of the hemidiaphragm is observed in simulation despite standard maneuvers to diminish motion. No (nodal) elective field is given.

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity correction. Successful treatment planning will require accomplishment of all the following criteria:

- Maximum dose: The treatment plan should be created such that 100% (60Gy) corresponds to the maximum dose delivered to the patient. This point must exist within the PTV.
- Prescription isodose: The prescription isodose surface must be >60% and < 90% of the maximum dose (60 Gy) covering the PTV.
- Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the PTV is conformally covered by the prescription isodose surface (PTV

V95%RX=100%) and 99% of PTV receives a minimum of 90% of the prescription dose (PTV V90%RX>99%).

Fractions should be given within 180 minutes from the end of the GC4711/placebo infusion. A minimum of 18 and maximum of 72 hours is permitted between fractions. Additionally, in case of machine break-down a 96-hour window is allowed. All fractions must be given within a maximum of 10 calendar days (+3 days in the case of a holiday or technical issue).

If SBRT administration is interrupted on any given day due to a machine break-down or other unforeseen circumstances, the rest of the treatment or a new SBRT session must be given as soon as possible. Rescheduling and SBRT dosing will be determined by the patient's treating physician in accordance with standard of care and covered with extra GC4711/placebo dosing. In case of a 6th fraction and/or dose of GC4711/Placebo may be given.

Anti-emetic and anti-diarrheal prophylaxis and hematopoietic growth factor use should be administered per ASCO guidelines.

Critical Organ Dose-Volume Limits

In order to verify dose-volume limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instructions for the contouring of these organs are as follows:

- **Spinal Cord:** contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing every CT slice to at least 10 below the inferior extent of the PTV.
- **Esophagus**: contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing every CT slice to at least 10 below the inferior extent of the PTV.
- **Brachial Plexus:** defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib.
- **Heart:** contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.
- **Trachea and Proximal Bronchial Tree:** contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be

divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree. Differentiating these structures in this fashion will facilitate the eligibility requirement for excluding patients with tumors within 2 cm of the proximal bronchial tree (see below).

- **Proximal Trachea:** Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree (see the diagram definitions below).
- **Proximal Bronchial Tree:** include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in the diagram in Figure 2. The following airways will be included according to standard anatomic relationships: the distal 2 cm of RTOG 0618 (Timmerman 2018) trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.
- **Whole Lung:** Planning CT need to cover both entire lung volumes. Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.
- **Skin:** defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is present in these locations (e.g., the scalp on the top of the head).
- All relevant normal tissue structures (e.g. spinal cord, lungs, heart, esophagus, brachial plexus, trachea and proximal bronchial tree, skin, etc.) are required in both planning images, as well as dose-volume histogram, for further contouring help see RTOG contouring atlas (https://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx).

6.1 Collection of Concomitant Medications

Investigators may prescribe concomitant medication or supportive care deemed necessary. All medications taken from 30 days prior to dosing through 90 days post discontinuation of SBRT should be documented in source records and in the CRF.

After 3 months post-SBRT, only medications used to treat respiratory disease or late radiation toxicities should be recorded through 12 Months post SBRT, including inhalers, steroids, oxygen supply, etc.

Additionally, any new anti-cancer therapy given in follow-up should be recorded in the CRF through 24-months post-SBRT or until disease progression.

Supportive care includes anti-emetic prophylaxis, hematopoietic growth factor used as ASCO guidelines, systemic antibiotics, hydration to prevent renal damage etc., consistent with local standard of practice.

6.2 Drug Interactions

In vitro, GC4711 is an inhibitor of CYP2D6. A clinical study of the potential of GC4711 to increase the concentration of drugs that are CYP2D6 substrates has not yet been conducted. Concomitant use of GC4711 may increase the concentration of drugs that are CYP2D6 substrates, which may increase the risk of toxicities of these drugs. Avoid concomitant use of GC4711 with CYP2D6 substrates where minimal increases in concentration of the CYP2D6 substrate may lead to serious or life-threatening toxicities (substrates with a narrow therapeutic range).

Such CYP2D6 substrates (see list below) include certain beta blockers antidepressants, antipsychotics and antiarrhythmics.

In addition, concomitant use of GC4711 may decrease the concentration of active metabolites of prodrugs that require CYP2D6 for activation. Concomitant use of GC4711 with CYP2D6 prodrug substrates requiring functional CYP2D6 activity for their clinical benefit (e.g., codeine, tramadol, tamoxifen) may decrease their effectiveness.

Concomitant administration of a CYP2D6-substrate drug concurrent with administration of GC4711 should be limited to cases in which the treating investigator has determined that the use of the specific CYP2D6-substrate drug is medically necessary. In such cases, the patient should be carefully observed for clinical adverse events of the CYP2D6-substrate drug, the dose of which may require reduction.

Table 4 below provides some examples of CYP2D6-substrate drugs. See the GC4711 Investigator's Brochure for additional information.

Table 4 CYP2D6-substrate drugs

Beta Blockers:	Antidepressants:	Antipsychotics:	Others:
carvedilol S-metoprolol propafenone timolol	amitriptyline clomipramine desipramine duloxetine fluoxetine imipramine paroxetine	haloperidol risperidone thioridazine	aripiprazole atomoxetine codeine dextromethorphan doxepine flecainide mexiletine ondansetron oxycodone

			risperidone tamoxifen tramadol venlafaxine

6.3 Prohibited Medications

GC4711 may cause mechanism-related, transient hypotension, or lightheadedness. Because of the potential for such mechanism-related toxicities, the following drugs that could precipitate drops in blood pressure, should not be taken by patients while receiving GC4711/placebo:

- Nitrates (sublingual, oral or transdermal nitroglycerin; oral isosorbide mono- or dintitrate)
- Phosphodiesterase type 5 (PDE 5) inhibitors (sildenafil, tadalafil, vardenafil, avanafil).
- Alpha adrenergic blocking agents prescribed for hypertension, benign prostatic hypertrophy, prostate cancer treatment effects, and peripheral artery disease (doxazosin, prazosin, terazosin, tamsulosin, alfuzosin, silodosin, phenoxybenzamine, phentolamine).
- Other drugs that in the judgment of the treating investigator could create a risk of a precipitous decrease in blood pressure are prohibited until at least 24 hours after the last dose of GC4711 or placebo.
- Approved or investigational anti-cancer therapy (e.g., chemotherapy, immunotherapy, targeted therapy, hormone therapy, and biologic therapy) given before disease progression other than the protocol regimen without documentation of disease progression
- Any other investigational therapy not previously approved by the Sponsor

6.4 Toxicity Management and Infusion Modification

Anticipated toxicities of GC4711

Per the Investigator's Brochure, the following individual adverse events observed in healthy volunteer studies are listed and considered "expected" after GC4711 infusions:

- lightheadedness, faintness, or mild decrease in blood pressure
- mild facial tingling
- nausea
- headache
- pain, bruising, or redness at the spot where GC4711 was being given by IV
- pain or discomfort in the arm into which GC4711 was being given by IV
- fatigue

Toxicity Management/Infusion Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Schedule of Assessments (Table 1). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Toxicities that will require infusion modification of the GC4711 or placebo administration include the following:

- Grade 2 or greater hypotension occurring within 1 hour of the end of GC4711 or placebo infusion
- Other Grade 3 or greater AEs judged by the investigator to be possibly attributable to the study infusion.

The dose of GC4711/placebo should not be reduced.

Patients who experience a toxicity noted above during or shortly after the infusion of GC4711/placebo should have their infusion times increased to 30 minutes.

If the toxicity recurs, the infusion time should be increased to 45 minutes, and may be increased to 60 minutes if hypotension occurs with a 45-minute infusion.

If toxicity occurs with a 60-minute infusion, the patient should be discontinued from further treatment with GC4711/placebo but should remain on study for all other protocol interventions (SBRT) /assessments.

Anticipated toxicities of SBRT

Explaining the risk of local high dose RT delivery is important for each individual subject. The following anticipated toxicities are used in the informed consent form based on Common Toxicity Criteria (CTCAE) version 5 (Table).

Very likely (80-90%):

- Fatigue (which generally goes away after the radiation therapy is completed)
- Abdominal pain, discomfort
- Nausea, loss of appetite

Less likely (30%):

- Temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms
- vomiting (during therapy)
- diarrhea
- ulcers
- Skin irritation, redness, itchiness, discomfort
- Pain
- Breathing discomfort, hick-ups

Less likely, but serious (<20%):

- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction, or changes in motility following therapy (may require medications or surgery, < 10% permanent changes)
- Radiation-induced liver disease (RILD, <5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver
- Non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in subjects with large tumors and/ pre-existing liver disease.
- Permanent thrombocytopenia (<1%); this may lead to bleeding
- Kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.
- Spinal cord injury

Risk of rare but serious events is more prominent in subjects who did experience toxicities during chemotherapy or using co-medications for co-morbidity. Early signs of pain, obstruction and anemia need to be closely monitored and ulcers/bleeding treated with proton inhibitors or surgically if needed.

Table 5 Expected acute and late SBRT toxicities summarized

Acute:	**Late:**
• Abdominal pain • Nausea, vomiting • Diarrhea • Gastric/duodenal ulcers • Loss of appetite • Fatigue • Skin changes • Pain • Recurrent hick-ups • Renal/Liver dysfunction • Anemia, thrombopenia, neutropenia	• Liver failure • Kidney failure • Abdominal bleeding • Bowel stenosis, obstruction, or perforation • Persisting thrombopenia, anemia • Spinal cord injury

7 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Assessments.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

7.1 Efficacy Assessments

Tumor Assessment (RECIST)

Staging imaging will be performed by CT scan according to the SoA. Tumor Response will be evaluated at each time point. Radiographic response will be measured according to RECIST 1.1 (Eisenhauer 2009). All imaging will be interpreted locally by the investigational site radiologist. The same method of imaging used at baseline must be used at each follow up evaluation for treatment response.

The number of subjects exhibiting PR, CR and PR+CR will be reported at Months 6, 12, 18 and 24.

RECIST 1.1 Tumor Response Evaluation Definitions of the criteria used to determine objective tumor response for target lesions (Eisenhauer, 2009)	
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.

Definitions for Response Evaluation

Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the date of registration (Phase 1) or randomization (Phase 2), to first occurrence of local and/or regional NSCLC progression, distant metastases from NSCLC, second primary tumor, or death due to any cause, whichever occurs first. Patients without progression and who did not die are censored at their last evaluable tumor response assessment.

Local and Regional Control

Local and regional control is defined as the time from registration (Phase 1) or randomization (Phase 2), to any local and regional recurrence or progression of NSCLC. Local enlargement, marginal failures, involved lobe failure, or local relapse will be considered failure events for local control. Regional failure with nodal progression (new lesions) in the mediastinum will be a failure event for regional control. Distant metastases from the index lung cancer or a second primary tumor are not considered local progression. Patients who die with lung cancer, but who do not have documented local progression will be considered non-failures for local progression and will be censored on the day of their death. Patients who die without progressive lung disease and have no documented local progression will be considered non-failures for local progression and will be censored on the day of death.

Overall Survival

Overall survival (OS) is defined as the time from registration (Phase 1) or randomization (Phase 2), to death due to any cause. Survival status should be assessed every 6 months following progression through 24 months. All subjects who are in the Survival Follow-up Phase and not known to have died prior to sponsor requests for additional survival status timepoints may be contacted at that time to confirm survival status. Patients who have not died are censored at the date last known to be alive.

Distant Metastasis Rate

Distant metastasis rate refers to cancer that has spread from the original (primary) tumor to distant organs or distant lymph nodes (outside mediastinum).

7.1 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (Table 1).

Physical Examinations

A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Temperature and weight will also be measured and recorded. Height should only be recorded at Screening (Visit 1). The physical examination should be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations.

Vital Signs

Vital sign measurements prior to each infusion will include pulse rate, respiratory rate, systolic and diastolic blood pressure. Pulse and blood pressure readings will be taken after the subject has been at rest for 2 minutes before each infusion and after infusion prior to SBRT. Respiratory rate does not need to be repeated.

Electrocardiograms

A 12-lead ECG recording will be conducted using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. The recordings should be as close as possible to corresponding PK sampling (+/- 10 minutes from the PK draw) per the SOA. The pre- and post-dose ECG should be done in triplicate.

Pneumonitis Assessment

The following will be completed for the pneumonitis assessment:

- NCI-CTCAE scale (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
- CT of chest with IV contrast, unless contrast is medically contraindicated; evaluate for presence of the descriptive items listed in Appendix 4
- Spirometry including pulse oximetry [SpO2], forced vital capacity [FVC], first expiratory volume in the first second [FEV1], and diffusing capacity of the lungs for carbon monoxide (DLCO).
- Medications will be recorded, including inhalers and steroids
- Hemoglobin (Hb) monitoring (interference if Hb lower than 7 grams per deciliter needs repetition of spirometry assessment after Hb correction, e.g., transfusion)
- Any additional testing should be recorded in the CRF as unscheduled

Lung function

Clinically, radiation induced pulmonary injury can manifest within weeks to months following radiotherapy. However, most cases are reported within the first 8 months. The classic triad of symptoms includes dyspnea on exertion, non-productive cough, and hypoxemia, though low-grade fevers are also common. Physical exam findings can include pleural friction rub, moist rales as well as signs of consolidation. These manifestations may be complicated by the presence of pre-existing lung disease such as COPD or emphysema. The incidence of symptomatic pneumonitis has dropped with introduction of motion management and other modern RT techniques (Jain 2018). The most used grading system is the Common Terminology Criteria for Adverse Events (CTCAE) published by the National Cancer Institute: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

Objectively, the effect of pneumonitis on lung function can be assessed using pulmonary function tests (PFTs), a clinical gold standard. Borst, et al. (2005) reported a decrease in first expiratory volume in 1 s (FEV1) as early as three months post RT; however, most were observed at 6 months. Diffusion capacity of lungs (DLCO) is described as the most prominent PFT

parameter predictive of and impacted by radiation pneumonitis (Stone 2015, Jain 2018). Our primary efficacy measurement of lung function will be prevention of significant falls in DLCO by standard pulmonary function testing. DLCO can be affected by different factors, including alveolar volume and hematologic assessment, as well as smoking, pre-existent chronic obstructive lung disease (COPD), age and medication, including inhalers, oxygen supply and steroids.

In the follow-up portion of this trial, in addition to lung function, hemoglobin will be measured, and medication given for respiratory disease and radiation toxicities (See section 7.4), new anti-cancer treatments will be recorded through 24 months post SBRT completion, as well as smoking and COPD will be monitored throughout 12 months.

PFTs are not part of standard clinical routine follow-up of radiation therapy but can add significant information to radiological and clinical scoring of radiation induced lung injuries. In our study, we measure PFTs every six months in parallel to the radiological assessments (Videtic 2013, Takeda 2013, Ferrero 2015, Vansteenkiste 2014).

Declines in DLCO from baseline will be scored using the Radiation Therapy Oncology Group (RTOG) scale, in which:

- Grade 0 is <10% decline from baseline;
- Grade 1 is 10-25% decline from baseline;
- Grade 2 is >25%-50% decline from baseline;
- Grade 3 is >50%-75% decline from baseline;
- Grade 4 is >75% decline from baseline;
- Grade 5 is death.

7.2 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in

Appendix 3. The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. Throughout the study, AEs will be recorded in the source documents and on the appropriate pages of the CRF regardless of whether the AEs are considered related to GC4711/Placebo or SBRT. To avoid confusion, the AE should be recorded in standard medical terminology.

Adverse event(s) will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention/study (see Section 5.4).

Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

All adverse events will be collected from the Day 1 dosing through 90 days post-SBRT completion to ensure collection of acute toxicities and up to 12 months for late radiation toxicities. Please see Section 7.4 for the definition of late radiation toxicities.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in

Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Specific SAE reporting instructions are provided in a separate manual.

Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in

Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is discontinued from the study. Further information on follow-up procedures is given in

Appendix 3.

Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

Treatment of Overdose, Misuse, Abuse

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated per protocol for a given subject.

Any study drug overdose during the study should be noted on the study medication eCRF.

All AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 7.2. Reporting of Serious Adverse Events. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Galera Therapeutics Clinical Trial Report Form for SAEs and in an expedited manner but should be noted as non-serious on the form and the Adverse Event eCRF.

There is currently no specific treatment in the event of an overdose of GC4711. The investigator will use clinical judgment and standard supportive care to treat any overdose.

Adverse events associated with misuse or abuse will be appropriately reported as AEs or SAEs and monitored per Section 7.2.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

7.3 Pregnancy

The risks of treatment with GC4711 during pregnancy have not been evaluated. Male subjects and female subjects of childbearing potential who engage in sexual intercourse should use a barrier method of contraception throughout the study and for 30 days (females) or 90 days

(males) following the last dose of GC4711/Placebo. If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

7.4 Late Radiotherapy Toxicities

Late radiotherapy toxicities will be collected as per the Schedule of Assessments. Related, late radiation toxicities (Kang 2015) will be collected up to 12 months post SBRT and defined using NCI Common Terminology Criteria for Adverse Events (version 5.0).:

- Grade 1-5 Respiratory, thoracic and mediastinal disorders, including rib fractures
- Grade 1-5 esophagus, and
- Grade 3-5 cardiac events
- Grade 3-5 spinal cord/brachial plexopathy and vascular events

7.5 Phase 1 Dose-limiting Toxicities

Safety will be confirmed by the occurrence of dose limiting toxicities (DLTs), which are defined (using the NCI-CTC grading scale) as Grade 3-5 AEs occurring from Day 1 to 30 days post SBRT, and *excluding* the following:

- AEs clearly related to disease progression or intercurrent illness
- Grade 3 fatigue for 7 days or less,
- Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
- Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
- Hematological grade 3-4 toxicities except for the following:
    - Grade 4 neutropenia lasting >7 days.
    - Grade 3 thrombocytopenia with clinically significant bleeding.
    - Grade 4 anemia and grade 4 thrombocytopenia

Safety will be considered unacceptable in the Phase 1 portion of the study, if a DLT occurs in 2 or more of the first 5 subjects.

In the event of an occurrence of a DLT, the SRC will meet and determine what action should be taken with treatment.

Opening enrollment in the Phase 2 is dependent on the safety outcome (DLT occurrence) in Phase 1.

7.6 Pharmacokinetics (PK) and ECG

PK sampling will be sought from all patients for GC4711 and its two metabolites, GC4752 and GC4757. Blood sampling will be performed along with the ECGs on the days and times indicated in the Schedule of Assessments) and outlined below.

PK Draw	PK draw window	ECG
Pre-dose	- 1 hour from start of infusion	+/- 10 minutes of PK draw (triplicate)
End of Infusion	+ 10 minutes from EOI	+/- 10 minutes of PK draw (triplicate)
24-hour Post dose (Phase 1 only)	Prior to dosing if delivered on next sequential day	+/- 10 minutes of PK draw (single)

A separate PK Manual will be provided.

8 STATISTICAL CONSIDERATIONS

8.1 Sample size

In Phase 1 of the study, 5 patients will be treated with GC4711 in combination with SBRT. Dose limiting toxicity (DLT) is defined in Section 7.5. Safety is considered acceptable and confirmed in the Phase 1 portion of the study, if DLT occurs in no more than one of the first five DLT-evaluable patients.

If acceptable safety in Phase 1 is confirmed, Phase 2 will proceed. Approximately sixty-six (66) participants, randomized 1:1 to GC4711 or placebo, will be recruited for the Phase 2 portion to achieve 60 evaluable subjects, assuming an approximate 9% drop out rate prior to the 90-day timepoint evaluation.

The primary objective in Phase 2 is to estimate the difference in in-field tumor response between GC4711 and placebo through Month 6 following SBRT. Sample size in Phase 2 is selected to provide a reasonably precise estimate of the treatment effect as measured by the width of a two-sided 90% confidence interval around the difference in in-field tumor response as well as to provide other efficacy data that can used in planning future studies. With 30 patients/arm the half-width of the 90% confidence interval for the difference will be at most 21.2% % based on the large sample confidence interval with limits $\pm$ Z.05 $\sqrt{}$[(p1*(1-p1)/n + p2(1-p2)/m] of the point estimate where p1 and p2 are the response rates and n and m the corresponding number of patients in each arm.

8.2 Randomization/Blinding

Phase 1:

The Phase 1 part of the study will be conducted as an open-label investigation.

Phase 2:

In the Phase 2 of the study, all subjects, investigators, clinical study site personnel and the blinded study monitor will be blinded to patient treatment assignment.

The dispensing Site Pharmacists are unblinded. An unblinded Study Monitor will be assigned to the study for confirming drug accountability and monitoring at the site's pharmacy. The Unblinded Pharmacist should take every precaution to prepare the study treatment in a blinded fashion and out of site from the Blinded site clinical staff. The Blinded Clinical Staff should be mindful of the steps in place to maintain the blind.

Treatment assignment for Phase 2 subjects should remain blinded to subjects, investigators, and clinical site staff until analyses of the primary and secondary safety and efficacy results of the study have been performed on the final, locked data through the end of post-SBRT follow-up for all subjects.

Only in the case of an emergency, when knowledge of the investigational product is essential for the clinical management or welfare of the subject, may the Investigator unblind an individual subject's treatment assignment prior to the completion of the primary and secondary safety and efficacy analyses. The Investigator will, whenever possible, discuss options with the Medical Monitor or appropriate Sponsor/CRO study personnel before unblinding. If the blind is broken for any reason and the Investigator is unable to contact the Sponsor prior to unblinding, the Investigator must notify the Sponsor/CRO as soon as possible following the unblinding incident without revealing the subject's study treatment assignment, unless the information is important to the safety of subjects remaining in the study.

Randomization codes are generated and assigned using a Randomization and Trial Supply Management (RTSM) system. Electronic access to the randomization codes will be granted for unblinded pharmacy team members and unblinded CRAs.

8.3 Populations for Analyses

The Phase 1 population will include all subjects who receive at least one dose of GC4711. The DLT evaluable population includes all patients in the Phase 1 population who have received all five GC4711 doses, are followed for 30 days post SBRT and were DLT free or experienced a DLT. The Phase 2 intent-to-treat population includes all subjects randomized and is used in disposition. Safety and efficacy analyses for Phase 2 will be performed on a modified intent-to-treat population that includes all randomized subjects who receive at least one dose of GC4711 or placebo.

8.4 Subject Disposition

The number of subjects included in each study population will be summarized by treatment group. Subjects excluded from the intent-to-treat population will be listed by randomized treatment group.

The number and percentage of subjects who complete or who prematurely discontinue during the treatment periods will be presented. Screen failures (i.e., screened but not randomized subjects) and the associated failure reasons will be tabulated overall. Reasons for premature discontinuation from the treatment period as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment group for all randomized/registered subjects.

8.5 Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and will include a more detailed description of the statistical analyses described in this section. Should the statistical analysis plan and the protocol differ with respect to analytic conventions, the statistical analysis plan supersedes the protocol. Given the study has not been powered for formal hypotheses testing, all P-values should be considered descriptive in nature. As such no alpha adjustment for multiple testing is planned.

All time to event endpoints will be measured from date registration (Phase 1) or randomization (Phase 2).

Primary Endpoints:

Phase 1: DLT defined in Section 7.5.

Phase 2: The difference in in-field tumor response between GC4711 and placebo through Month 6 following SBRT will be estimated, and a two-sided 90% confidence interval constructed around the difference using the large sample confidence interval with limits ± Z.05 √[(p1*(1-p1)/n + p2(1-p2)/m] of the point estimate where p1 and p2 are the response rates and n and m the corresponding number of patients in each arm. In addition, a Fisher's Exact test will be performed but should be considered descriptive in nature. Phase 2: Percent reduction of in-field tumor response at Month 6 compared to baseline.

Secondary Efficacy Endpoints:

Phase 1: All Phase 1 efficacy endpoints will be summarized descriptively.

Phase 2: Response rate (PR+CR at any time during the study) per RECIST 1.1 will be compared using the same methodology as the primary endpoint.

In-field tumor response at Months 6, 12, 18 and 24 will be compared for the two treatment arms using a t-test at each timepoint and corresponding two-sided 90% confidence intervals constructed about the difference. The maximum reduction for each patient observed at any time will be analyzed similarly.

Progression-free survival (PFS) will be compared using a hazard ratio along with the associated 2-sided 90% confidence interval, using an un-stratified Cox's proportional hazard model and further characterized by Kaplan-Meir curves as well as the median and survival probability at

representative times (e.g. at 2, 4, 6, 4 etc. months). A log-rank test comparing treatment arms based on the score statistic from the Cox regression will also be provided. Patients who have not progressed of died will be censored at their last evaluable response assessment.

Overall Survival (OS) as well as duration of local and regional control will be analyzed using the same approach as PFS. For OS, patients who have not died as of the time of analysis will be censored the date last known to be alive. For duration of local and regional control, local enlargement, marginal failures, involved lobe failure, or local relapse will be considered failure events for local control. Regional failure with nodal progression (new lesions) in the mediastinum will be a failure event for regional control. Distant metastases from the index lung cancer or a second primary tumor are not considered local progression. Patients who die with lung cancer, but who do not have documented local progression will be considered non-failures for local progression and will be censored on the day of their death. Patients who die without progressive lung disease and have no documented local progression will be considered non-failures for local progression and will be censored on the day of death.

Distant-metastases rate will be summarized descriptively.

Exploratory Endpoints

All safety endpoints will be summarized descriptively including mean and mean change from baseline for continuous endpoints and n and percent for categorical endpoints.

8.6 Safety Review Committee (SRC)

In the Phase 1 portion of the study, safety will be reviewed by a Safety Review Committee (SRC) consisting of the Medical Monitor, the Principal Investigators, and additional designees by the Sponsor or the site Principal Investigators. After Phase 1, safety will be reviewed by the safety review committee (SRC) before proceeding to Phase 2.

In Phase 2, the Sponsor will perform routine reviews of the safety data at an interval no less than quarterly and after the 20th randomized subject reaches the 30-day follow up timepoint, whichever occurs first.

8.7 Interim Analysis

During the Phase 2 portion of the study, an unblinded interim analysis will be performed after 6- month follow-up data are available for the first 20 randomized subjects (i.e., roughly 30 percent of the planned enrollment of 66 subjects in Phase 2), for the purposes of assessing preliminary efficacy.

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for/Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g, participant recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information, as requested, to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

In accordance with regulatory and local IRB/IEC/REB requirements, before study procedures are performed, subjects will be informed about the study and required to sign the IRB/IEC/REB approved ICF. This form will be signed after adequate explanation of the aims, methods, objective and potential hazards of the study and prior to undertaking any study-related procedures. The Sponsor or its designee will provide an ICF template to the investigator. The Sponsor or its designee must approve changes to the ICF template prior to submission to the IRB/IEC/REB. Informed consent will be obtained according to the applicable IRB/IEC/REB requirements. No patient is to be screened or treated until an ICF, written in a language in which the patient is fluent, has been obtained. The signed ICF will be retained with the study records. Each patient will also be given a copy of his/her signed ICF.

Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is

being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator will promptly inform the subject and must ensure appropriate subject therapy and/or follow-up

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 2: Clinical Laboratory Tests

The tests detailed in Table will be performed by the local laboratory per the SoA. Abnormal clinically significant local laboratory results collected outside of the protocol should be captured as Adverse Events.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Assessments

Hematology/CBC	Biochemistry	Other
ANC Hemoglobin Hematocrit Red blood cell (RBC) Count White blood cell (WBC) count Platelet Count WBC Differential	Blood urea nitrogen (BUN) Creatinine Creatinine clearance Glucose Potassium Sodium Calcium Chloride CO_2 Inorganic phosphate Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT) Gamma-glutamyl transferase (GGT) Total bilirubin (direct bilirubin reflex if elevated) Albumin Alkaline phosphatase (ALP) Uric acid	INR/PTT (SCRN only)

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Event

AE Definition
An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. -

Events Meeting the AE Definition
- Any abnormal laboratory test results (such as hematology, clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). - Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. - Any new condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. - Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction, including investigational product with a concomitant mediation. - Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. - For situations when an AE or SAE is due to NSCLC report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (e.g., metastatic NSCLC). Note: The term “disease progression” should not be used to describe the DRE or AE.

Events NOT Meeting the AE Definition
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
• **Results in death**
• **Immediately life threatening** The term 'life threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
• **Requires inpatient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
• **Results in persistent disability/incapacity** - The term disability means a substantial disruption of a person's ability to conduct normal life functions. - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• **Is a congenital anomaly/birth defect**
• **Other medically important serious event:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Galera Therapeutics in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Galera Therapeutics. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Galera Therapeutics.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- The investigator must assign the following AE attributes:
  - AE diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to GC4711, SBRT; and
  - Action taken.

Severity/Grading of Adverse Events

The investigator will make an assessment of intensity for each AE and SAE reported during the study using NCI CTCAE grading scale, Version 5.0.

Assessment of Causality
- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. - A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out. - The investigator will use clinical judgment to determine the relationship. - Alternative causes, such as underlying disease(s), concomitant therapy/treatments, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. - The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. - For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. - There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Galera Therapeutics. However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Galera Therapeutics.** - The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. - The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Galera Therapeutics to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. - New or updated information will be recorded in the originally completed CRF. - The investigator will submit any updated SAE data to Galera Therapeutics within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to IQVIA Safety
All SAEs should be submitted in compliance with the reporting requirements and timelines per the SAE Report Form Completion Guidelines.

Appendix 4: Relationship Between National Cancer Institute – Common Terminology Criteria for Adverse Events, Version 5.0 and Radiographic Pneumonitis/Fibrosis Criteria (Kimura IJROB 2006)

Subjects will be evaluated radiographically for presence of the descripted items listed in the table below. The Grade and p-value columns are included only as a reference to the relationship between CTCAE grading of pneumonitis and the presence of the descriptors and do not need to be considered when collecting subject data.

	Grade 1*	Grade 2*	Grade 3*	Total	p value††
Acute radiation pneumonitis					
Diffuse consolidation	3	11	2	16	0.000675
Patchy consolidation and GGO	6	2	0	8	0.175
Diffuse GGO	4	2	0	6	0.479
Patchy GGO	0	1	0	1	0.286
No evidence of increased density	12	3	1	16	0.0314
Radiation fibrosis					
Modified conventional pattern	12	14	1	27	0.0394
Mass-like pattern	4	3	2	9	0.559
Scar-like pattern	9	2	0	11	0.0297
Total	25	19	3	47	

Abbreviation: GGO = ground-glass opacity.

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive GC4711.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be

reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant/breastfeed

The investigator will collect pregnancy information on any female participant who becomes pregnant or breastfeeds during treatment and 30 days after GC4711/placebo. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

Appendix 6: Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BED	biologically equivalent (total) dose
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulation
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COPD	chronic obstructive pulmonary disease
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DLCO	diffusion capacity of lung for carbon monoxide
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG PS	eastern cooperative oncology group performance status
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
PET/CT	Positron emission tomography combined with CT scan
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
Hgb	hemoglobin

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IEC	Independent Ethics Committees
IRB	Institutional Review Boards
IV	intravenous
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
PK	Pharmacokinetic(s)
PTV	planning treatment volume
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors
RT	radiation therapy
RTOG	radiation therapy oncology group
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SABR	stereotactic ablative body radiation therapy
SBRT	stereotactic body radiation therapy
SOA	schedule of activities
SOD	superoxide dismutase
SOM	severe oral mucositis
SRC	safety review committee
SUSAR	suspected unexpected serious adverse reactions
ULN	upper normal limit
WBC	white blood cell
WOCBP	woman of childbearing potential

Appendix 7: References

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