CLINICAL STUDY PROTOCOL

AN ADAPTIVE PHASE I/II DOSE ESCALATION TRIAL OF STEREOTACTIC BODY RADIATION THERAPY IN COMBINATION WITH RADIOMODULATING AGENT GC4419 IN LOCALLY ADVANCED PANCREATIC ADENOCARCINOMA

Industry-supplied agent(s):	GC4419 (avasopasem manganese)
Sponsor:	Galera Therapeutics, Inc. 2 West Liberty Blvd, Suite 110 Malvern, PA 19355
IND Number:	136,778
Protocol ID:	GTI-4419-101
Protocol Version:	Amendment 07, 24January2020
Medical Monitor:	Jon T. Holmlund, MD, Galera Therapeutics, Inc.
Lead Study Investigator:	Cullen Taniguchi, MD, MD Anderson Cancer Center
ClinicalTrials.gov Identifier:	NCT03340974

PROTOCOL APPROVAL PAGE

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Sponsor	Galera Therapeutics, Inc. 2 West Liberty Boulevard, Suite 110 Malvern, PA 19355 USA Phone: 610 725 1500 • Fax 610 408 0321

Sponsor Representatives

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

Signature Date

Jon T. Holmlund 29 JAN 2020

Jon T. Holmlund, M.D.
Chief Medical Officer
Galera Therapeutics, Inc.

Principal Investigator

By signing below, I, the Investigator, approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections, electronic case report form (eCRF) and any protocol-related documents (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). I agree to comply with the ICH-GCP, World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations. 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, Inc. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, or by me, if it becomes necessary to protect the best interests of the study subjects.

Investigator Signature Date

Name Institution City, Country

SUMMARY SYNOPSIS

Name of Sponsor/Company:

Galera Therapeutics, Inc.

Name of Investigational Product:

GC4419 (avasopasem manganese)

Name of Active Ingredient:

GC4419 (avasopasem manganese) (Manganese, dichloro[(4aS,13aS,17aS,21aS)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-eicosahydro-11,7- nitrilo-7H-dibenzo[b,h][1,4,7,10] tetraazacycloheptadecine-κN5, κN13, κN18, κN21, κN22]-) is a water soluble, highly stable, low molecular weight manganese-containing macrocyclic ligand complex whose activity mimics that of naturally occurring SOD enzymes.

Title of Study:

AN ADAPTIVE PHASE I/II DOSE ESCALATION TRIAL OF STEREOTACTIC BODY RADIATION THERAPY IN COMBINATION WITH RADIOMODULATING AGENT GC4419 IN LOCALLY ADVANCED PANCREATIC ADENOCARCINOMA

Number of Study Center(s): Up to 7 (Lead Site: University of Texas, MD Anderson Cancer Center)

Estimated Enrollment Period: 30 months

Studied period (years):	**Phase of development:** 1/2
Estimated date first patient enrolled: Jan 2018 Estimated date last patient completed dose: Jun 2020	

Objectives:

Primary:

- To determine the Maximum Tolerated Dose (MTD) of Stereotactic Body Radiation Therapy (SBRT) when given in combination with placebo or GC4419

Secondary:

- To evaluate Progression-Free Survival (PFS) for patients treated with SBRT given in combination with placebo or GC4419
- To evaluate Overall Response Rate (ORR) including stable disease, partial/complete response for patients treated with SBRT given in combination with placebo or GC4419
- To compare acute toxicity rate at 90 days for patients treated at the SBRT MTD with SBRT in combination with placebo or GC4419
- To evaluate late (12 month) toxicity of SBRT in combination with placebo or GC4419

Number of patients (planned):

48 patients will be enrolled in both subgroups (SBRT alone and SBRT plus GC4419). Within each subgroup, 24 patients will be treated in 8 cohorts of size 3 each.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Cytologic or biopsy confirmed adenocarcinoma of the pancreatic head, body or tail
2. Disease that is appropriate for SBRT by virtue of being:
    a. Locally advanced and technicallyunresectable, as determined by a pancreaticobiliary surgeon as part of a multidisciplinary review at the investigative site, including multi-phasic CT demonstrating:
        i. Greater than 180 degree tumor involvement of the superior mesenteric artery
        ii. Greater than 180 degree tumor involvement of the celiac axis, including major branches of the celiac axis that render it unresectable (e.g. common hepatic artery).
        iii. Tumor involvement of the first branch of the SMA that is not surgically reconstructible
        iv. Long segment involvement of the superior mesenteric vein/portal vein or hepatic artery that is not surgically reconstructible
    b. Potentially resectable, but patient is judged not a candidate for surgery, after multidisciplinary review at the investigative site;
    c. Potentially resectable, but the patients refuses surgery and is considered an acceptable candidate for SBRT after multidisciplinary review at the investigative site;
    d. “Borderline” resectable, as determined by multidisciplinary review, including absence of distant lymphadenopathy and the primary tumor characterized by one of more of the following:
        i. A tumor-vessel interface (TVI) with the mesenteric vein (SMV) or portal vein (PV) measuring ≥180° of the circumference of either vein’s wall or short-segment occlusion of either vein with a normal vein above or below the obstruction amenable to reconstruction;
        ii. Any TVI with the common hepatic artery (CHA) with normal artery proximal and distal to the TVI amenable to reconstruction;
        iii. A TVI with the superior mesenteric artery (SMA) measuring <180° of the circumference of the vessel wall
3. Primary tumor size and limited bowel involvement by tumor must be judged acceptable for SBRT at the discretion of the treating investigator.
4. No evidence of distant metastasis either prior to or after induction chemotherapy.

5. Completion of medically indicated first-line chemotherapy, as determined by the treating investigator
6. Patient must have metal stent in place if duodenal stent is required. If patient has plastic stent, this must be replaced prior to radiation.
7. Ability to understand and follow the breathing instructions involved in the respiratory gating procedure or to tolerate compression sufficient to reduce fiducial motion to ≤ 5mm.
8. Age 18 years or older
9. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (0, 1 or 2)
10. Adequate hematologic function as indicated by
    a. Absolute neutrophil counts (ANC) ≥ 1,500/mm3
    b. Hemoglobin (Hgb) ≥ 8.0 g/dL
    c. Platelet count ≥ 75,000/mm3
11. Adequate liver function as indicated by:
    a. Total bilirubin ≤ 1.5 x upper-normal limit (ULN)
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
12. Properly obtained written informed consent

Exclusion Criteria:

1. Prior radiation therapy to the abdomen that would overlap with treatment field
2. Prior surgical resection of pancreatic tumor
3. Receiving any approved or investigational anti-cancer agent other than those required for this study
4. Uncontrolled or active gastric or duodenal ulcer disease within 30 days of dosing
5. Visible invasion of tumor into the lumen of the bowel or stomach on endoscopy (Note: Radiological infiltration into bowel is allowed, unless deemed clinically unsafe.)
6. Residual or ongoing ≥ Grade 3 non-hematologic toxicity from chemotherapy
7. Contraindication to IV contrast
8. Concurrent participation in another interventional clinical trial or use of another investigational agent within 30 days of study consent (Note: Patients who are participating in non-interventional clinical trials (E.g., QOL, imaging, observational, follow-up studies, etc) are eligible, regardless of timing of participation)
9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, renal failure, cardiac arrhythmia, stroke, or psychiatric illness that would limit compliance with treatment

10. Second primary malignancy within the last 5 years, unless treated definitively and/or low risk in the judgment of the treating investigator (e.g non-melanomotous skin cancers, low risk prostate cancer, etc)
11. Known history of HIV or active hepatitis B/C (patients who have been vaccinated for hepatitis B and do not have a history of infection are eligible)
12. Female patients who are pregnant or breastfeeding
13. Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control to avoid pregnancy for the entire study period and for 30 days after the last dose of GC4419. Acceptable methods include, but are not limited to, barrier methods, IUD, and birth control pills. This includes any woman who has experienced menarche but has not undergone successful surgical sterilization or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months, or women on hormone replacement therapy with serum FSH levels greater than 35 mIU/mL. A negative urine or serum pregnancy test must be obtained within 14 days prior to the start of study therapy in all women of child-bearing potential.
14. Male subjects who are unwilling or unable to use an acceptable method of birth control (barrier method) to avoid pregnancy for the entire study period and for up to 90 days after the last dose of GC4419/placebo are excluded.
15. 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.
16. Medical history that includes any condition, or requires the use of concomitant medications which, in the investigator's judgment, are associated with or create a risk of increased carotid sinus sensitivity, symptomatic bradycardia, or syncopal episodes.

Investigational product, dosage and mode of administration:

GC4419 is formulated as a clear solution at a concentration of 9 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. % saline for parenteral administration (drug product). GC4419 will be presented in single-use amber vials. Vials will be filled with 11 mL of GC4419, of which 10 mL be added into a 240 mL bag of normal saline, for daily IV administration over 60 minutes. GC4419 will be administered Monday through Friday on days when SBRT is administered. On days when fractions of SBRT are administered, the completion of infusion of GC4419 or placebo will be within 180 minutes prior to that day's SBRT.

Duration of treatment:

Five doses will be administered with 5 daily fractions of SBRT, given Monday through Friday whenever possible. On days when SBRT is administered, GC4419 will be administered before the SBRT fraction, with a goal of delivering the SBRT fraction within 180 minutes from the end of the GC4419 infusion.

Reference therapy, dosage and mode of administration:

Matching placebo will be prepared by respective investigational site's pharmacy, who will be unblinded; the rest of the clinic staff will be blinded. For those subjects randomized to the placebo arm, the treatment assignment will be prepared by the unblinded investigational pharmacy as 100% normal saline at 250mL, for IV administration over 60 minutes. Placebo will be administered

Monday through Friday on weeks when SBRT is administered. On days when fractions of SBRT are administered, placebo will be administered prior to that day's SBRT.

Assessment Criteria:

Toxicity:

- Unacceptable toxicity of SBRT will be defined as related, CTCAE grade 3 or 4 gastro-intestinal (GI) toxicity or death, occurring within 90 days from the start of therapy.

Efficacy:

- Radiographic stable disease (SD) or better based on modified RECIST criteria for the primary target, compared to baseline imaging of the same type, as evaluated at day 90 from the start of therapy.

Safety:

National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.03 up to 1 year post-SBRT Patient-Reported Outcomes:

- Linear Analogue Self Assessment (LASA)
- NCI Patient Reported Outcomes CTCAE (PRO-CTCAE) version 1.0

Safety Monitoring and Toxicity Management:

1. Adverse/Serious Adverse Event assessments per CTCAE version 4.03
2. Safety monitoring will be built into the model and ongoing LO-ET analysis using a pre-specified trade-off between efficacy and toxicity.
3. Toxicity requiring 25% GC4419 or PBO dose reduction:
    - Grade 2 or greater hypotension within 2 hours after the start of GC4419/placebo infusion
    - GC4419 Grade 3 or greater nausea or vomiting

Two dose reductions of GC4419/placebo for toxicity will be permitted per patient. Patients unable to tolerate GC4419/placebo after two dose reductions must discontinue treatment with the study drug GC4419 but may continue with SBRT at the discretion of the treating investigator.

For other toxicities (including those attributable to SBRT): management per institutional and ASCO guidelines and investigator judgment.

Concomitant Medications/Treatments:

Investigators may prescribe any concomitant medication or supportive therapy deemed necessary to provide adequate supportive care including antiemetics, systemic antibiotics, hydration to prevent renal damage, with the following exceptions:

- Other concurrent chemotherapy or investigational agent during the period when SBRT is being given
- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildanefil, 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 GC4419

- Pyridostigmine or other drugs that in the judgment of the treating investigator could create a risk of increased carotid sinus sensitivity, symptomatic bradycardia, or syncopal episodes.
- Other biologic response modifiers – except systemic hematopoietic growth factors for the management of anemia or myelosuppression
- Concurrent approved or investigational anti-cancer therapy (e.g., chemotherapy, immunotherapy, targeted therapy, hormone and biologic therapy) other than the Protocol regimen
- Other investigational agents

Anti-emetic and anti-diarrheal prophylaxis and hematopoietic growth factor use are permitted per ASCO guidelines.

Statistical methods:

A maximum of 2x24 = 48 patients will be randomized between two subgroups. Patients in Arm A will receive GC4419 in combination with their assigned RT dose, and patients in Arm B will receive their assigned RT dose and placebo. Randomization will be restricted so that the sample size within each subgroup is exactly 24 patients. The restricted randomization sequence will be constructed prior to trial initiation, and applied by the Statistical Analyst overseeing the trial treatment and RT dose assignments. An overall accrual rate of approximately 3-4 patients per month is anticipated, which will give approximately 1.5-2 patients per month in each subgroup. Simulations demonstrate a trial length of 6 months (early stopping criteria for excess toxicity) to 12-16 months (run to trial completion) with model stability. Full design operating characteristics are available in subsection 13.8. The same adaptive dose-finding design will be used in each of the two subgroups. Within each subgroup, up to 24 patients will be treated in 8 cohorts of size 3 each. The first cohort will be treated at dose level 1, all successive doses will be chosen by the LO-ET method to maximize the posterior Efficacy-Toxicity trade-off, and an untried dose level (dose level 2) may not be skipped when escalating initially.

The sponsor was unblinded to treatment assignment for overall study monitoring and safety review. One unblinded interim descriptive efficacy analysis will be performed for study design planning on the first 19 subjects. To facilitate future study design planning with investigators, interim efficacy results on those first 19 subjects will be provided to participating investigators. Subsequent to the single completed interim analysis by the sponsor, no unblinded efficacy analysis will be performed until the final statistical analysis. Investigators and supporting staff will remain blinded to randomized treatment assignments for patients 20-48, with only unblinded staff being site pharmacists, MDACC statisticians, and limited sponsor staff relative to study management and routine safety oversight.

TABLE OF CONTENTS

1.0 BACKGROUND

1.1 Background and Rationale

Pancreatic adenocarcinoma (PAC) remains the fourth leading cause of cancer-related death in the United States, with a 5-year overall survival in the range of 5%,[1] despite improvements in systemic chemotherapy, as well as advances in radiation and surgical techniques. Surgical resection remains the only reasonable option for cure, given inability to reach ablative doses to local tumor with radiation[2]. Locally advanced pancreatic cancers (LAPC) are particularly difficult to treat since they only exhibit a modest response to chemotherapy[3] and are, by definition, not immediately resectable. BRPC and LAPC account for approximately 30% of newly diagnosed PAC and, if not resected, a high proportion of patients experience local progression and/or die with a significant burden of local disease, and may experience significant amount of morbidity and mortality from local progression.[4-6] As systemic therapies advance, including the advent of nab-paclitaxel and FOLFIRINOX, the burden of local disease will only increase[3]. This pattern of regional failure in LAPC suggests that local control may be critical to reducing the symptomatic burden of this disease. Recent data have suggested that while modest doses of chemoradiation do not improve survival compared to chemotherapy alone, local control is significantly improved[7,8].

1.2 Rationale for SBRT and Dose Escalation

1.2.1 Rationale for SBRT

Pancreatic cancer remains a disease with a dismal 5-year survival rate of less than 5% and is the fourth leading cause of cancer death in the United States. In particular, locally advanced pancreatic cancer presents an even greater challenge, since these tumors cannot be surgically resected upfront and thus can only be treated with a combination of chemotherapy and radiation. Pancreatic cancer commonly occurs in the head of the pancreas, which abuts a portion of the small bowel called the duodenum. Progression of the primary tumor is a significant source of morbidity and mortality from pancreatic cancer[5], local control will be required for any curative treatments for localized disease. Pancreatic cancer can progress locally and/ or systemically. Therefore, the need for a combination of systemic and local treatments is essential in the management of this disease. Recent data has shown that up to 30% of pancreatic cancer patients die from progression of disease locally[5], supporting the need for more aggressive local treatment.

Definitive chemoradiation to tumors within the head of the pancreas can be technically and anatomically challenging due to the surrounding organs at risk, particularly the duodenum. Pancreatic cancer requires radiation doses in excess of 60 Gy to achieve local control, but the nearby duodenum can only tolerate a maximum of 50 Gy, which limits the dose that can be safely administered to an ineffective 50 Gy. Consequently, recent trials for conventionally fractionated and hypofractionated chemoradiation treatments have been shuttered due to poor accrual, and due in part to its perceived lack of efficacy, thanks to recently published trials demonstrating that conventional chemoradiation with 3D conformal therapy and capecitabine is no different than chemo alone, despite a statistically significant improvement in local control[9].

Compared to standard radiotherapy, SBRT can deliver higher, more conformal radiation doses to a smaller volume over a course of 1-5 treatments with the use of image guidance. A shorter

course of treatment allows for more patient convenience, better cost-effective treatment and also earlier resumption of systemic therapy. Studies have shown that patients receiving SBRT with gemcitabine-based chemotherapy have also reported better short-term pain control and quality of life[10,11]. In addition, a short course of SBRT has been shown to cause less immunosuppression and lymphopenia when compared to conventional radiation therapy given over 5-6 weeks[12]. SBRT coupled with immunotherapy has also been shown to potentiate both local and systemic responses in melanoma and renal cell carcinoma[13].

Intriguingly, SBRT may be able to elicit unique radiobiological responses from pancreatic tumors. A recent phase II multi-institutional study involving Hopkins, Memorial Sloan Kettering Cancer Center and Stanford[14] demonstrated efficacy and acceptable toxicity levels when adding SBRT (6.6 Gy x 5) to full-dose gemcitabine in patients with LAPC[15]. Emory University[16] recently published a dose escalation SBRT + FOLFIRINOX study, which increased dose to 12 Gy x 3 fractions with acceptable toxicity and efficacy. Unfortunately, at its current doses of 5-7 Gy x 5, only palliation can be achieved with no improvements in mean survival rate. Additional dose escalation has not been tried since initial studies using higher doses such as 25 Gy x 1 had resulted in unacceptable duodenal toxicity[2]. Currently, with adequate protection of the surrounding normal tissues, and/or selective radiosensitization of the pancreatic tumor, the therapeutic ratio of SBRT could be significantly improved.

The optimal sequencing and doses of chemotherapy and SBRT are not yet known. However, most patients with locally advanced disease will now receive newer and more powerful chemotherapy combinations that were extrapolated from the metastatic setting, such as FOLFIRINOX (5-fluorouracil, folinic acid, irinotecan, and oxaliplatin), or gemcitabine-abraxane, and may be even more effective at reducing tumor burden and improving resectability. If patients do not metastasize after induction chemotherapy, they could be considered for consolidative radiation treatments that would either convert them to a resectable state or maintain sufficient local control for a prolonged period of time. SBRT is effective and well-tolerated, but is not curative because its biologically effective dose is too low. Thus, the primary goal of this combined phase I/II study would be to determine the maximum tolerated dose (MTD) of SBRT in combination with GC4419, a dismutase mimetic (DM), and describe efficacy endpoints consistent or better than historical standards in preparation for a phase III trial.

1.2.2 Rationale for Dose Escalation with SBRT

Standard radiation has failed to produce an overall survival benefit in the LAPC patient population[7,8], but may provide modest local control and increase time off systemic chemotherapy. Standard dose radiation (SDR) for pancreatic cancer is often limited to 50.4Gy in 28 fractions, as the dose is constrained by radiosensitive organs in close proximity to the pancreas including the duodenum, jejunum and stomach. Radiation dose escalation through more conformal treatment techniques, such as intensity modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT) or proton therapy, has overcome this threshold to improve local control and overall survival in other tumor sites including cholangiocarcinoma,[17] prostate[18] and head and neck cancers.[19]

Evidence exists to suggest that achieving an ablative biologically equivalent doses (BED) may significantly improve both progression free survival (PFS) and overall survival (OS). At MDACC, BED doses up to twice as high as SDR have been delivered using intensity modulated

radiotherapy (IMRT) in a hypofractionated setting in an attempt to improve local control.[20,21] The results of this technique were recently reported by Krishnan et al,[21] demonstrating preliminary evidence that radiation dose escalation during consolidative chemoradiation therapy improves both overall survival and locoregional recurrence free survival in carefully selected patients. Toxicity data from Colbert et al [*In press*][68] suggests this approach has both long term and short term safety.

Although hypofractionated escalated dose IMRT (EDR) is appealing, it is still not ideal for a patient population in whom time off systemic therapy and patient convenience is of the essence. EDR is still delivered over 3-4 weeks, and is inconvenient for both patients and medical oncologists who wish to administer other systemic therapies. As the technical capabilities of radiation rapidly advance, stereotactic body radiation therapy (SBRT) has become increasingly popular due to its potential ability to deliver increasing BED with decreased toxicity over three or five days, allowing less time off systemic therapy. New techniques in advanced motion management, on board imaging and tumor visualization allow the potential for higher dose escalation than previously thought possible. Still, few institutions have tested the bounds of dose escalation in SBRT.

1.2.3 Rationale for SBRT Dose Escalation in Locally Advanced PAC

The recently closed LAP-07 randomized trial attempted to define the role of radiation therapy in LAPC by randomizing patients to chemotherapy alone versus chemoradiation with a standard 54 Gy after gemcitabine-based induction chemotherapy. Although the overall survival endpoint was not significantly different between the two arms, chemoradiotherapy was associated with increased chemotherapy-free interval, decreased local progression (32% vs 46%, P = .03) and no increase in grade 3 to 4 toxicity, except for nausea[7]. Local progression is a very significant endpoint in this patient population, given the heavy burden of local disease. Autopsy studies have shown that as high as 30% of PAC patients die of local disease alone[5], indicating local progression may also directly affect overall survival.

Still, despite a local control advantage and although we suspect an overall survival advantage would exist with higher BED radiation than the LAP-07 trial, clinicians are hard pressed to hold systemic therapy and ask patients to undergo five weeks of standard chemoradiation, given the lack of prospective data confirming its effectiveness. With advances in radiation delivery techniques, SBRT now offers an exciting opportunity to provide similarly ablative BED in a shorter one week timespan. Most previously studies conducted in earlier eras have used a BED that is known to be non-ablative, and similar to previous conventionally fractionated courses, given concerns about toxicity and lack of dose escalation evidence. A properly executed dose escalation study would set the stage for a potential prospective study in this patient population with an ablative dose of radiation.

1.2.4 Toxicity Rates in SBRT for PAC

Previous studies in SBRT for PAC demonstrate that SBRT has at least comparable efficacy to standard fractionated radiation (local control ranging from 75% to 90%[22,23]) with decreased toxicity[24]. The potential toxicities are similar to those potentially observed with standard fractionated radiation, and are related to proximity of tumor and dose to duodenum, stomach and other small bowel. The majority of the severe toxicities previously noted occurred using single fraction SBRT in the era before modern image guidance and tumor localization, but nevertheless instilled a fear of utilizing high dose SBRT[25]. Data for 3 fraction and 5 fraction SBRT demonstrates a favorable toxicity

profile. The largest available population of these BRPC and LAPC patients treated with SBRT comes from a recent meta analysis by Petrelli et al[22], which pooled 19 studies with a total of 1009 patients. In this study, pooled 1-year OS was 51.6%, local control rate was 72.3% and the occurrence of severe adverse events (grade 3-4 toxicity) exceeding 10% in only 3/19 studies, even for the highest doses studied and those studies performed without fiducials or image guidance. In all studies, the rate of late toxicity ranged from 0-11%, with a rate of 0% in 6/19 studies. Acute toxicities noted included anorexia, bleeding, duodenitis, gastritis, diarrhea, gastrointestinal ulcers, abdominal pain, nausea, and abdominal pain. Late toxicities included ulcer, fistula, hemorrhage and GI obstruction. BED in these studies ranged from 37.5 Gy to 112.5 Gy. The study which utilized 112.5 Gy[26] by Hoyer et al prescribed 15 Gy in 3 fractions. 66% (8/12) of patients improved in performance status at 90 day post treatment, exhibited decreased nausea and pain scores, and required less analgesic medications. Four patients suffered severe mucositis or ulceration of the stomach and duodenum and one patient had a non-fatal ulcer perforation of the stomach. This study exhibits a multitude of problems, including the fact that the prescription dose was given to the entire PTV volume, without consideration of nearby adjacent organs at risk (OAR's). Our novel treatment delivery technique (in section 1.2.5) delivers high dose radiation to the tumor, while respecting nearby OAR's. Additionally, we expect the delivery of this BED in 5 fractions to be safer than delivery in 3 fractions as it allows more margin of error for potential OAR shift between treatments.

1.2.5 Novel SBRT Planning Technique

Previous radiation therapy planning techniques for SBRT involved contouring a gross tumor volume (GTV) and creating a uniform PTV with an expansion ranging from 3mm-7mm. The dose was prescribed to the PTV, although more recent studies may include an escalated dose to the GTV simultaneously, in what is described as a simultaneous integrated boost technique (SIB). This allows a nested dose delivery, hypothetically protecting normal structures from a higher dose they may be unable to tolerate. Unfortunately, this technique does not take into consideration the location of the OAR that is to be avoided. Often, these plans are heterogeneous, and heterogeneity up to 10% in either direction is considered acceptable. The radiation oncologist upon evaluating the plan, can take into consideration whether these "hot spots" are in tumor or in OAR and adjust accordingly, but this discrimination is subjective and prone to error. The lead study site, MDACC, has developed a novel technique using multiple SIB volumes and a multiple OAR avoidance volumes with 3-5mm margins, known as planning risk volumes (PRV's). In this method, the PRV is subtracted from the PTV volumes, with planning algorithms designed to ensure that normal structures receive no high dose volume. OAR volumes receive only the dose level known to be safe. Using this technique, MDACC has treated >200 patients with BRPC, LAPC and cholangiocarcinoma safely and with minimal toxicity[17,20,21,27].

This novel MDACC technique has not been widely utilized in SBRT to our knowledge. Previous studies have provided an SIB to the tumor-vessel interface (TVI) where tumor meets SMA and the highest risk for a positive margin resection exists, and have provided SIB to the GTV. We proposed taking advantage of this technique to boost the TVI and center of tumor, while protecting OAR's better than previous studies have. We are currently performing dosimetric studies to better understand its potential uses and limitations in SBRT, but we feel it may increase safety by decreasing the subjective nature of plan evaluation and allowing better delineation of dose

contraints and PTV dose levels. Figure 1a illustrates a typical SBRT radiation delivery with two dose levels, GTV and a symmetric PTV expansion. Figure 1b demonstrates our novel planning technique adapted from institutional experience in escalated dose IMRT (EDR) demonstrating avoidance structures which take priority over target volumes, thus limiting OAR dose to safe volumes while allowing escalation to tumor and to TVI.

1.2.6 Selected SBRT Dose Levels

The dose levels selected for this study (table 1) were designed with previous SBRT studies and known dose limitations to OAR's in mind. The PTV1 dose level is identical for all three dose levels, 6.6 Gy x 5 fractions. At this dose, previous data demonstrates that duodenal toxicity is less than 2% and treatment is uniformly safe and well-tolerated. The PTV1 volume covers the tumor contour (iGTV) including the high risk of recurrence intravascular space (TVI) adapted to the 4D motion and a 3mm margin.The proposed PTV2 volume is PTV1 but with subtraction of the bowel contours with their 5mm motion margin (PRV) with the PRV given priority, ensuring that the PRV will receive none of this high dose volume. At the dose levels 2 and 3, the PTV2 is considered to be an ablative BED. Dose level 1 has been safely studied, even in a 3 fraction regimen[14,16].

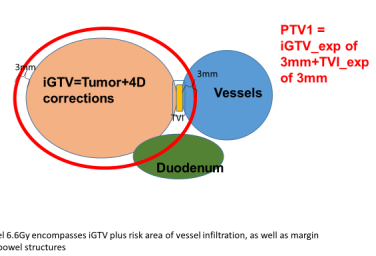

Figure 1a

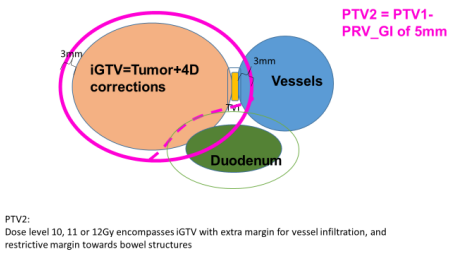

Figure 1b

Two SBRT dose escalation trials are currently underway, one at University of Colorado (NCT02873598) which started in November 2016 and the second from Memorial Sloan Kettering Cancer Center (NCT02643498), started in December 2015. Both trials are utilizing a standard 3+3 dose escalation design with evaluation at 90 days as part of a Phase I trial. For both trials, dose escalation starts with 9 Gy x 3 fractions and increases by 1 Gy per fraction at each dose level. Dose level 2 is 10 Gy x 3 fractions and dose level 3 is 11 Gy x 3 fractions. This BED of the highest dose level on these trials is still lower than our highest dose level target, and due to the basic design, will not provide any phase II data at its conclusion. Additionally, with the addition of a novel radioprotectant we anticipate improved toxicity and higher achievable dose levels than trials with radiation alone.

Table 1. Proposed dose levels according to PTV1 and PTV2 Doses

Dose Level	Total Dose	Per Fraction	Tumor BED (a/B = 10)
1			
PTV1	33 Gy	6.6 Gy	55 Gy
PTV2	50 Gy	10 Gy	100 Gy
2			
PTV1	33 Gy	6.6 Gy	55 Gy
PTV2	55 Gy	11 Gy	115.5 Gy
3			
PTV1	33 Gy	6.6 Gy	55 Gy
PTV2	60 Gy	12 Gy	132 Gy

1.2.7 GC4119 as a Radioprotectant Agent in PAC

GC4419 is a small-molecule mimetic of the human superoxide dismutase enzymes (SOD), or dismutase mimetic. GC4419 is being investigated in clinical trials for the reduction of the incidence and severity of severe oral mucositis (SOM) induced by radiation therapy (RT), with or without systemic therapy under United States Food and Drug Administration (FDA) IND 111,539.

In normal biology, superoxide ($O_2^{\bullet-}$) is generated at moderate levels as a by-product of mitochondrial cellular respiration. It is also produced by activation or uncoupling of a number of enzymes, including NADPH (nicotinamide adenine dinucleotide phosphate) oxidases. Particularly large amounts are also generated directly or indirectly by external environmental stresses such as radiation and chemical toxins, including some chemotherapies. In all studied species, $O_2^{\bullet-}$ levels are normally constrained to an acceptable level by SOD enzymes. These SODs are oxidoreductases that dismutate $O_2^{\bullet-}$ into molecular oxygen (O_2) and hydrogen peroxide (H_2O_2). There are three vertebrate SODs: cytoplasmic (“Cu/Zn SOD”), mitochondrial (“MnSOD2”), and extracellular (“EcSOD3”) responsible for dismutation of superoxide present in their respective compartments. Additional systems then further process the resulting H_2O_2, neutralizing it, or in the case of phagocytic activity using it to manage threats such as bacterial infection.

Since $O_2^{\bullet-}$ and certain daughter products are extremely reactive with biological molecules, excess $O_2^{\bullet-}$ can be quite toxic to normal cells. If $O_2^{\bullet-}$ production is excessive or if $O_2^{\bullet-}$ dismutation is compromised, the SOD enzymes may be insufficient and excess $O_2^{\bullet-}$ can overwhelm the body’s ability to eliminate it leading to a variety of superoxide-initiated or -mediated disease states.

Ionizing radiation, as used to treat cancer, attacks tumor cells both by direct DNA damage, but perhaps more importantly by transiently increasing certain reactive oxygen species (ROS), particularly hydroxyl radical ($HO^{\bullet}$). Radiation also significantly increases $O_2^{\bullet-}$, another ROS, via at least three mechanisms: (1) radiolytic hydrolysis coincident with irradiation, (2) mitochondrial dysfunction and direct activation of $O_2^{\bullet-}$ producing enzymes acutely after radiation, and (3) $O_2^{\bullet-}$ production by inflammatory cells migrating chronically to the site of tissue injury. Normal cells in the radiation field experience this burst of $O_2^{\bullet-}$, but counter its damaging effects via their intact redox

protective enzyme systems (SODs, catalase, glutathione peroxidase, etc.) and by the activation of DNA repair mechanisms. However, it appears that in radiation therapy, especially as radiation doses increase, these endogenous controls on $O_2^{\bullet-}$ are insufficient to fully protect normal cells, and effective cancer radiation therapy often carries major normal tissue toxicity. Galera's clinical and pre-clinical results with its dismutase mimetics suggest that the SODs are a limiting component in this normal tissue response, and that increasing SOD activity can protect against various radiation therapy toxicities *(unpublished data).*

Cancer cells, on the other hand, are more tolerant of significant elevations in $O_2^{\bullet-}$, and may in fact increase $O_2^{\bullet-}$ levels to support proliferative pathways and modify the tumor microenvironment. However, it has been known for decades that cancer cells in general are more sensitive to increases in H_2O_2 than normal cells, with high levels of H_2O_2 production triggering tumor cell apoptosis. Galera and its collaborators have shown that the shift from an excess of $O_2^{\bullet-}$ generated by radiation therapy to elevated H_2O_2 driven by dismutase mimetics increases the differential toxicity of tumor over normal tissue[28]. This difference in sensitivity to these two key ROS supports the hypothesis and Galera's experimental observations that dismutase mimetics can both protect normal cells from the toxicity of ionizing radiation while also increasing anti-tumor efficacy.

GC4419 (avasopasem manganese) (Manganese, dichloro[(4aS,13aS, 17aS,21aS) 1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-eicosahydro-11,7-nitrilo-7H-dibenzo[b,h][1,4,7,1O]tetraazacycloheptadecine-KN5,KN13,KN18,KN21, KN22]-) is a water soluble, highly stable, low molecular weight manganese-containing macrocyclic ligand complex whose activity mimics that of naturally occurring SOD enzymes. Unlike non-specific oxygen catalytic agents which may also dismutate $O_2^{\bullet-}$ as part of a generic catalysis of reactions of various oxygen species, GC4419 is unique in that it selectively removes $O_2^{\bullet-}$ anions, just as the native SODs do, without reacting with other reactive oxygen species, including H_2O_2, $HO^{\bullet}$, nitric oxide ($^{\bullet}NO$), and peroxynitrite ($ONOO^-$). Also, at physiologic conditions it acts at the extremely rapid catalytic rate approaching that of the SOD enzymes. In addition, unlike native SOD, GC4419 is not deactivated by reaction with ONOO nor product inhibited by H_2O_2.

Nonclinical data have identified Galera's dismutase mimetics, including the next generation candidate in this program, GC4419 as promising anti-cancer agents, particularly in combination with higher doses of radiation therapy.

In a prior Phase 1b/2a trial (see Figure 2), 46 head and neck cancer (HNC) patients received GC4419 administered intravenously over 60 minutes at doses up to 112 mg/day, M-F, for up to 7 weeks in combination with standard-fractionation RT plus concurrent cisplatin, with acceptable toxicity. A randomized, placebo-controlled, double blind Phase 2b trial compared 30 or 90 mg/day of GC4419, or placebo, plus single-agent cisplatin plus IMRT in 223 patients with locally advanced, non-metastatic squamous cell carcinoma of the oral cavity or oropharynx. One third of the patients on this study were randomized to receive 90 mg/d, M-F, for 7 weeks, concurrent with chemoradiotherapy. At that dose, the duration, incidence, and severity of severe OM were reduced compared to placebo (Anderson, et al, presentation at ASTRO 2018). Adverse events at the 90 mg dose were of similar frequency and severity as in the placebo arm, indicating that GC4419 did not appear to increase the toxicity of the underlying chemoradiotherapy regimen. Therefore, the 90 mg dose of GC4419 is expected to be sufficiently safe for administration M-F for 1 week in combination with SBRT, which follows a similar short course. Given the differences in RT schedule, and the

presence of cisplatin in the HNC studies (but not planned in SBRT studies described in this application), higher doses than 90 mg of GC4419 may also be safe and well-tolerated in combination with SBRT. Accordingly, the planned GC4419 dose of 90 mg for this study provides an expected margin of safety[67].

SEVERE ORAL MUCOSITIS (Grade 3 & 4)
Comparison of Key Efficacy Parameters

		Comparative Historical Control Data			GC4419 Phase Ib/2a Data	
		Matched Data Set	Partially Matched Data Phase 3 Control Arm		Partial Treatment	Full Treatment
		Sonis	Le	Henke	(3 wks)	(6-7 wks)
OM Endpoints	Number of Patients:	380	94	94	20	14
INCIDENCE	Incidence through 60 Gray Cumulative	60%	57%	62%	40%	29%
ONSET	Time to Onset Median #Days	≈28	35	32	>54	>50
DURATION	Median Duration Median #Days	26-30	26	22	4.5	2.5

Tumor Response	Historical Expectation	GC4419 Phase Ib/2a
1-Yr Loco-regional Control	80-90%	93%
1-Yr PFS	*60-75%*	84%
1-Yr OS	80-90%	93%

Figure 2. Phase 1b/2a Results versus Historical Comparators

1.2.8 Preclinical Data for GC4419 in improving tumor control of PAC in combination with SBRT

Curbing the harmful effects of radiation in normal tissues is thus a prime objective to achieve better therapeutic benefits in pancreatic cancer chemoradiation. Radiation therapy kills cells through both direct effects of DNA damage and through indirect effects of ionizing water and oxygen to create damaging radicals. The superoxide radical is perhaps the most potent damaging agent of radiation, and thus it has been proposed that reduction of this species could limit radiation-induced tissue damage[29]. Superoxide dismutase is an enzyme that catalyzes the reaction of superoxide to hydrogen peroxide, which can be easily disposed of through bioreductive pathways such as the glutathione system. Tumors, however, often do not express Glutathione (GSH) pathway and are thus particularly susceptible to cell kill by intracellular hydrogen peroxide. This differential effect on normal tissue versus tumor provides the rationale of using a superoxide dismutase mimetic. GC4419 is a novel, small-molecule SOD mimetic that selectively removes superoxide anions, and thus radiation-induced side effect predominantly in normal tissues. GC4419 has been shown to markedly reduce the severity of radiation-induced oral mucositis in patients with head and neck cancer, and is being tested in a Phase III study. The efficacy of GC4419 in the

abdomen is largely unknown. A previous study using the enantiomer of GC4419 demonstrated protection against GI death from whole body irradiation[30].

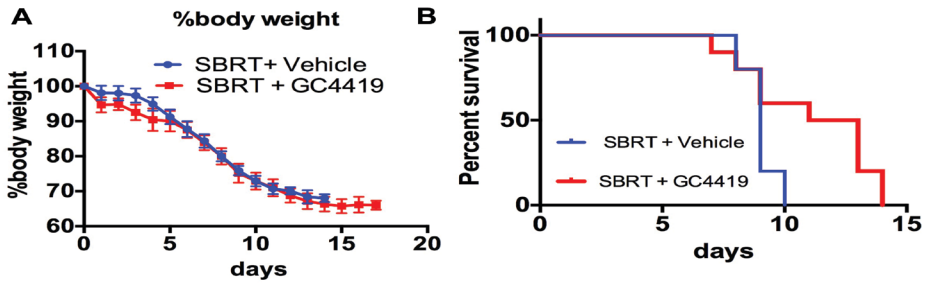

Figure 3. Mice treated with an SBRT regimen (8.5Gy x 5) to an upper abdominal field. A) No differences in body weight after SBRT with GC4419 B) Improved survival with addition of GC4419 (p=0.03)

To determine the role of GC4419 in protecting the gut in a clinically relevant SBRT model, C57BL/6 mice were treated with 10mm SBRT field with AP/PA technique targeted to the pancreas of C57BL/6 mice using cone beam CT on our X-RAD 225Cx machine. Liver, stomach, duodenum and jejunum were also in the treatment field as confirmed by cone beam CT. Mice were immobilized with an isoflurane anesthesia manifold. We treated these normal mice with 8.5Gyx5 fractions given daily (BED_{10}=78.6Gy). We found that there was no overt toxicity from GC4419 and that administration of the drug 30 minutes prior to each SBRT dose improved survival (p=0.03).

Prior data demonstrated dose-related protection of mice from lethal total body irradiation by an equipotent enantiomer of GC4419, GC4403[30]. As noted above, initial clinical data with GC4419 show an apparent marked reduction in severe oral mucositis induced by standard fractionation RT plus cisplatin given to patients with head and neck cancer, consistent with pre-clinical models of mucositis[31]. In animal studies, Galera's collaborator Dr. Michael Story (U. Texas/Southwestern [UTSW]) has also demonstrated that GC4419 both prevents (when administered before RT) and mitigates (when administered after RT, with prolonged treatment producing progressively greater mitigation) pulmonary fibrosis after a very large single focal dose (54 Gy) of radiation to normal mouse lung (*see* Figure 3), while others have demonstrated the ability of GC4419 and other analogs to protect liver[32], bone marrow and salivary gland from radiation toxicity.

Most relevant to combinations with SBRT, an enhancement of tumor response to radiotherapy has been demonstrated in multiple non-clinical models, most dramatically with higher fraction doses of radiotherapy. Further, GC4419 also shows single-agent tumor growth inhibition *in vitro* with an IC50 of approximately 10 micromolar (approximately the plasma C_{max} with a dose of 90 mg in clinical studies), and *in vivo* in susceptible tumors. This latter activity is likely linked to the significantly (5-10-fold) elevated innate $O_2^{\bullet-}$ levels measured by Galera and others *in vitro* with cancer cells under normal and hypoxic culture conditions, which the dismutase mimetic converts to increased H_2O_2 levels.

In separate studies done by Dr. Story and others, GC4419 sensitized lung and HNC cell lines to radiation and also enhanced the growth-inhibitory effects of cisplatin, gemcitabine and paclitaxel. *In vivo,* GC4419 did not inhibit, and may have slightly enhanced, tumor response to standard-fraction (2Gy per fraction) radiation. However, if the fraction size is increased, as in SBRT, progressively synergistic tumor response has been observed in multiple xenograft and syngeneic tumor models with the addition of GC4419 resulting in 100% complete response rates at the highest fraction doses (*see* Figure 4a).

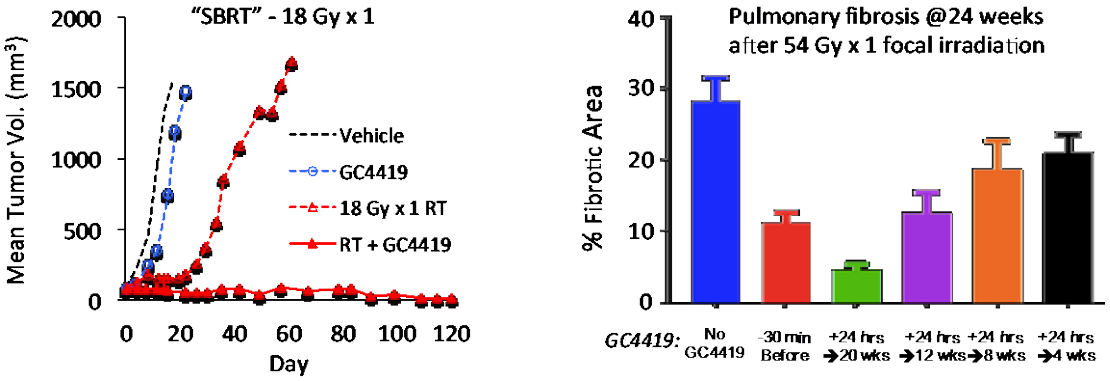

Figure 4. Increased Anti-Tumor Efficacy and Decreased Normal Tissue Toxicity in SBRT Models

As noted above, the major reason for this differential effect on cancer and normal cells is the differences in $O_2^{\bullet-}$ and H_2O_2 sensitivities between these cells. Elevated $O_2^{\bullet-}$ may actually benefit tumor growth and metastasis, while in normal tissues, $O_2^{\bullet-}$ may enhance radiation toxicity. This difference is because significant elevations in H_2O_2 are toxic to cancer cells but relatively benign to normal tissue. The addition of a dismutase mimetic (such as GC4419) more rapidly drives $O_2^{\bullet-}$ to H_2O_2, creating a burden that is markedly more toxic to tumor cells than normal cells. Increasing radiation fraction doses drive increased $O_2^{\bullet-}$ generation that the dismutase mimetic converts to increased H_2O_2. Thus, as supported by data with GC4419, the anti-tumor synergy with SBRT and dismutase mimetic increases with radiation fraction dose (*see* Figure 5).

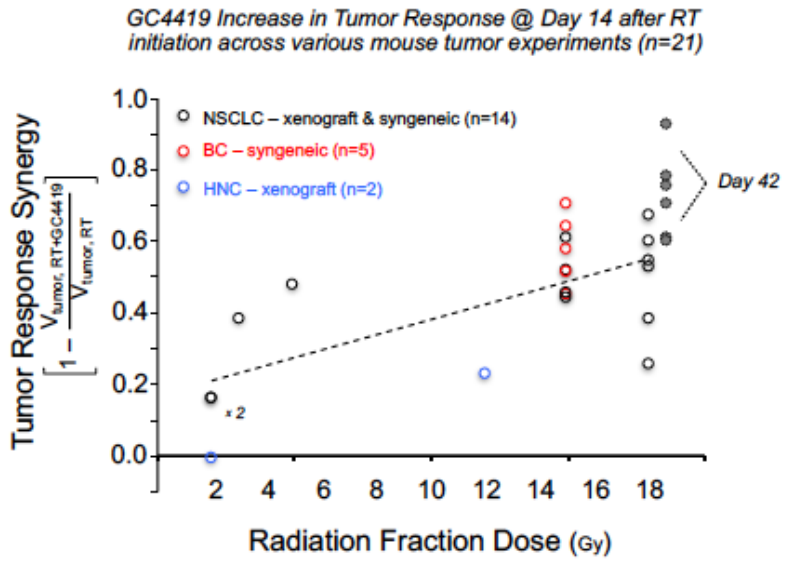

Figure 5. Potentiation of Anti-tumor Efficacy Increases with Fraction Dose Size (Source: Galera Therapeutics, Inc)

Antitumor efficacy of GC4419 in mouse SBRT models has been similar with 3, 10, or 24 mg/kg. This effective dose range overlaps with that seen with GC4419 in mouse and hamster models of normal tissue protection from radiation, such as those supporting the OM study above. Further, the GC4419 dosing schedules used in the mouse SBRT models experiments (daily x 5 after a single SBRT dose) suggest that clinical dosing of the dismutase mimetic on the 5 consecutive weekdays of planned SBRT (daily x 5) is appropriate.

1.2.9 Novel Adaptive Clinical Trial Design

Pancreatic adenocarcinoma is a relatively rare disease with a short overall survival and low probability of efficacy for any individual novel treatment. Standard phase I/II dose escalation trials may require upwards of 100 patients, and have a rare chance of demonstrating the statistically significant benefit for which they are powered at their completion. Unlike other disease sites, a novel treatment that provides disease stability with minimal toxicity could be considered a victory, although a standard phase I/II trial would be negative. Alternatively, a higher toxicity rate may be acceptable if a treatment provides a significant survival or disease response benefit, yet this dose would never be reached in a standard phase I/II trial due to a dichotomous toxicity outcome. The proposed LO-ET model has been used successfully in radiation studies with similar disease outcomes previously, including for diffuse intrinsic pontine glioma (DIPG) and lung adenocarcinoma. It allows for both of these outcomes to be considered, all while requiring often $^1/_3$ to ½ of the patients and time required for a standard trial design, allowing more rapid testing of novel therapies while maintaining patient safety.

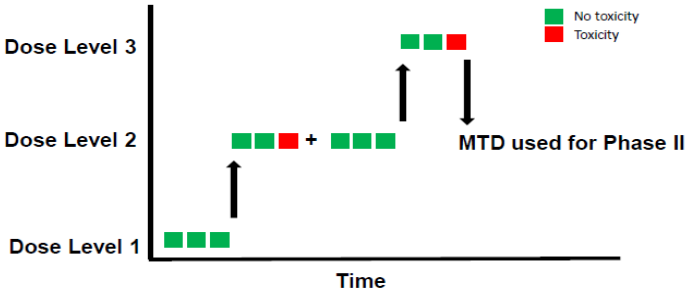

Figure 6. A standard 3 + 3 dose escalation design requires three patients treated at each dose level without toxicity in order to progress to next level, and evaluation of efficacy requires a separate phase II trial to be conducted.

Standard phase I dose escalation trials often utilize a “3 +3” design (figure 6), where 3 patients must be treated at the first dose level and followed until completion of the evaluation period without toxicity before a patient may be enrolled on the next dose level. If a patient has a toxicity at any dose level, 3 more patients must be treated at that dose level without toxicity before escalation is allowed. If any of these patients has toxicity, the trial is stopped and the maximum tolerated dose (MTD) has been reached. The phase II portion then serves as a preliminary exploration of efficacy utilizing the MTD calculated in the phase I portion, where generally two groups are compared and the study is powered to detect a minimal clinically relevant difference between the two groups. This design has several limitations, including the inability to assign patients to the next level until the follow up period has been completed for each of the three patients, leading to longer trials requiring more patients. Clinically, efficacy and toxicity are often a tradeoff, i.e. higher efficacy and higher toxicity may go hand-in-hand where clinicians may tolerate a toxicity rate of 20% if efficacy could be 50% higher than current standard of care, yet in this model toxicity is a dichotomous outcome with no consideration of efficacy. In this case, if toxicity occurs in one patient the calculated MTD may not be the most efficacious dose.

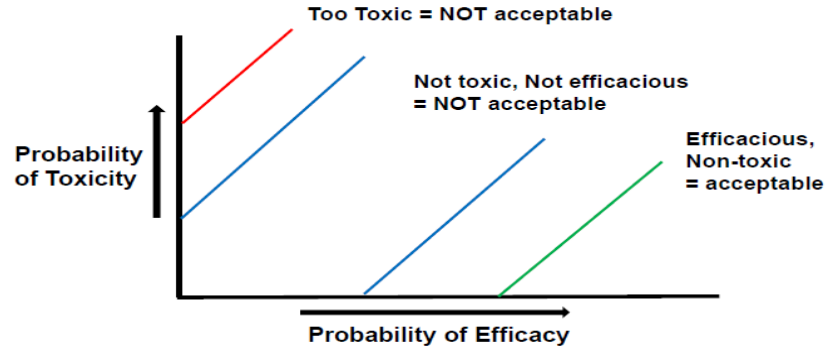

Figure 7. Efficacy/ Toxicity curve demonstrating efficacy and toxicity cutoffs defined by clinicians, where dose levels must meet maximum acceptable probability of toxicity (15%) and minimum acceptable probability of efficacy (75% stable or responsive disease) to continue accruing patients

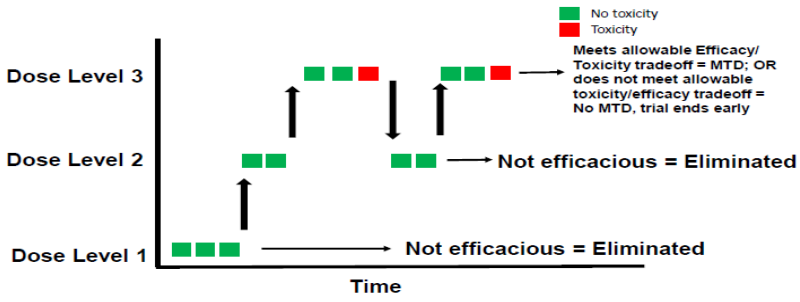

Figure 8. LO-ET Model using continual reassessment to assign dose levels; where dose levels are eliminated as probability of efficacy and toxicity is adjusted for available "person-time" for accrued patients. Each arm is eliminated if the probability of efficacy falls below pre-specified level or probability of toxicity is above prespecified level. Two possible outcomes include either the model assigning all patients to dose levels and therefore choosing a Maximum Tolerated Dose (MTD) when all other levels are eliminated, or all arms being deemed too toxic or inefficacious, thus ending the trial early and allowing patients to be diverted to other trials more quickly.

The LO-ET model (Thall et al, 2013; Thall et al, 2012) is rooted in the Bayesian continual reassessment method (CRM), where probabilities of responses for each dose level are continuously assessed as the trial progresses and each patient is enrolled. Instead of requiring all patients to be enrolled and assessment done at the completion of the trial, the "person-time" contributed by each patient for the time they have been enrolled is encompassed in the estimation of response, in addition to any prior data known about the treatment. For example, if two patients have been enrolled and completed a 90 day observational period without toxicity, this will increase the posterior probability of that dose level being "safe." The LO-ET model takes this model one step farther by utilizing a 2-dimensional continuous reassessment method. In this model, the ideal outcome is estimated as a tradeoff "curve" (Figure 7) between toxicity and efficacy dictated by clinicians, i.e. a 20% toxicity rate is allowable if 75% disease stability/response can be achieved. As dose levels are evaluated with accumulating "person-time," if at any point it appears the dose level is either too toxic or not efficacious, it is eliminated and no longer accrues patients. This continual reassessment (Figure 8) continues until either all dose levels are eliminated (all dose levels are either too toxic or not efficacious) or a clearly superior arm emerges that meets the prespecified efficacy and toxicity criteria.

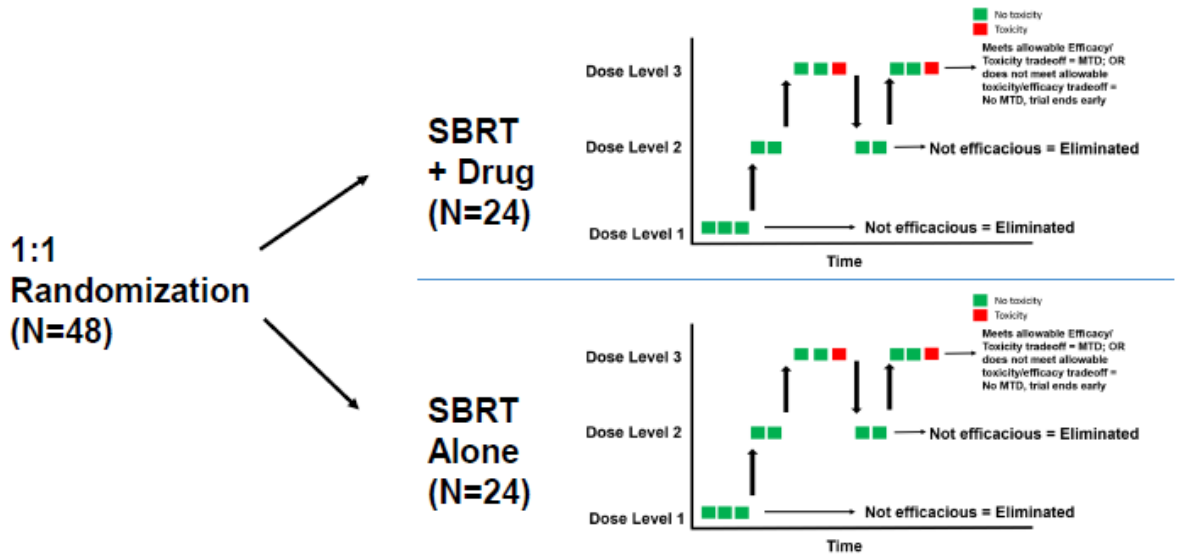

Figure 9. Schema for randomized LO-ET adaptive phase I/II dose escalation, with patients randomized up front, but arms running parallel dose escalation trials with independent dose selection

In this novel phase I/II adaptive dose escalation trial (Figure 9) we are addressing two primary questions: Determining the MTD of dose escalated SBRT with and without drug, and comparing efficacy and toxicity of SBRT with and without drug. Our trial design will enroll 48 patients and essentially run two parallel LO-ET models (24 patients per arm) to determine MTD nested within a randomized trial design. Patients are randomized to either “SBRT + Drug” or “SBRT” arms, after which the LO-ET models will run independently in each arm. The flexibility of this model will also allow the “SBRT + Drug” and “SBRT” arms to each continue to trial completion should all dose levels on either arm be eliminated, meaning the above mentioned potential outcomes of identifying an MTD or stopping the arm early due to excess toxicity or efficacy could occur in either the SBRT alone arm or the “Drug” arm. Efficacy threshold will be set at 75% minimum probability of radiographically stable disease or partial/complete response at 90 days. Maximum toxicity threshold will be set at 15% maximum probability of greater than grade 2 gastrointestinal toxicity at 90 days. Prior probabilities of efficacy and toxicity for each dose level are based on a review of all previous available SBRT literature as noted in section 1.2.2 and 1.2.3. Further statistical details are available in section 13.0.

1.2.10 Overall Impact of the Trial

This trial provides a unique opportunity to improve progression free survival and overall survival in BRPC and LAPC patients and change standard of care. Although other dose escalation trials are currently underway, the addition of this novel radiomodulator may allow further dose escalation than otherwise possible and increase the potential opportunity of long term survival in

this group of patients. Additionally, the novel design of this trial, if successful, will develop a platform for rapid early phase trial completion in PAC, decreasing time to discovery of novel and potentially successful treatment options. Once piloted, this trial design could be quickly repeated with other novel drugs and radiation techniques.

2.0 PRIMARY OBJECTIVES

2.1 Rationale for Primary Objective

The maximum tolerated dose (MTD) for SBRT using a technique that protects adjacent OAR's is unknown. If dose escalation could be achieved while protecting OAR's, we may be able to deliver ablative doses to the pancreatic tumor and increase local control rates and overall survival rates. Previous studies of radiation in LAPC and BRPC have failed due to inadequate radiation doses, but better prospective studies cannot be designed until the MTD is known. The novel radioprotectant agent, GC4419, may provide additional protection to the gastrointestinal mucosa and modulate the interaction of radiation with tumor tissues, thus resulting in an either higher or lower MTD when given in conjunction with SBRT over SBRT alone. This primary objective was designed to answer this question by allowing parallel MTD selection arms both with and without GC4419.

2.2 Primary Objective

- To determine the MTD of SBRT when given in combination with placebo or GC4419

2.3 Secondary Objectives

- To evaluate PFS for patients treated with SBRT given in combination with placebo or GC4419
- To evaluate ORR including stable disease and partial/complete response for patients treated with SBRT given in combination with placebo or GC4419
- To compare acute toxicity rate at 90 days for patients treated at the SBRT MTD in combination with placebo or GC4419
- To evaluate late (12 month) toxicity of SBRT in combination with placebo or GC4419

2.4 Exploratory and Correlative Science Objectives

- To evaluate tumor resectability rate after SBRT in combination with placebo or GC4419
- To evaluate the R0 Resection Rate and pCR for patients who eventually undergo surgical resection
- To evaluate patient reported outcomes for patients treated with SBRT in combination with placebo or GC441
- To compare genomic changes based on whole exome sequencing and transcriptome sequencing from pre and post SBRT core biopsy samples.
- To compare pathologic changes pre and post SBRT based on core biopsy samples
- To compare differences in immune infiltrate pre and post SBRT using IHC for immune activation, exhaustion and proliferation phenotypes, deep T cell sequencing from core biopsy specimens and multiparametric flow cytometry (MPFC) from cytology brushings
- To compare changes in circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and MPFC pre and post SBRT

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

This is a parallel arm adaptive design phase I/II dose-finding study to determine the optimal dose of fractionated SBRT, given either with the radiomodulating agent GC4419 or placebo for treatment of locally advanced pancreatic cancer. Dose-finding will be done using the sequentially adaptive phase I/II Late onset Efficacy-Toxicity (LO-ET) trade-off-based design [1-3].

3.2 Detailed Treatment Plan

Patients will be randomized to one of two arms in a prespecified randomization to ensure 24 patients per arm.

- Arm A: 90 mg GC4419 per day daily (60 min IV infusion), concurrent with daily fractions of SBRT to assigned dose level, administered Monday – Friday over one week.
- Arm B: Placebo daily (60 min IV infusion), concurrent with daily fractions of SBRT to assigned dose level, administered Monday – Friday over one week.

Planned radiation treatment fields will be according to guidelines in section 6.0.

GC4419/placebo will be given intravenously in a one hour infusion. SBRT must be initiated as soon as possible upon completion of the GC4419/placebo infusion but no later than 180 minutes following the end of the GC4419/placebo infusion.

GC4419/placebo will be given beginning on the first day of radiation and continuing daily, concurrent with each dose of SBRT.

If SBRT administration is not planned on any given day due to a treatment break or unforeseen circumstances, GC4419/placebo should not be administered on that day. If GC4419/placebo is given and SBRT is not given, GC4419/ placebo should still be administered on each day that SBRT is anticipated to be given. Breaks in SBRT will be determined by the patient's treating physician in accordance with standard of care. Patients should resume GC4419/placebo administration when SBRT resumes. On days when planned doses of both GC4419/placebo and SBRT are not administered (e.g., due to a holiday site closure, etc.), GC4419/placebo dosing may be extended along with SBRT to make up the missed dose(s).

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

3.3 Rationale for GC4419 Dose Selection

Previous data for selection of GC4419 dose is extrapolated from 3 human studies of GC4419 in prevention of oral mucositis in head and neck cancers. GC4419 does not appear to increase the toxicity of IMRT/cisplatin. The acute toxicity of GC4419 was acceptable at all doses tested, and consistent with prior expectations as described in the Investigator's Brochure[67]. A true (MTD) of GC4419 by the common definition used in oncology Phase 1 trials (>1/6 patients with DLT) was not reached in previous trials. Although dose-limiting toxicities were suggested in two patients receiving 112 mg/dose, the relationship of the events to GC4419 is questionable in each

case. However, the overall incidence of Grade 3 nausea at 112 mg was nominally greater than at lower doses. Even if not strictly dose-limiting, nausea is highly undesirable in this patient population given predilection to nausea with PAC. In addition, circumoral paresthesia, although mild, was dose-related. Therefore, to provide an additional margin of safety and reduce the possibility of adverse events that could increase the possibility of breaking study blinding, an upper dose of 90 mg of GC4419 was used in the now-completed randomized Phase 2b trial. Safety was acceptable at this dose when administered for 30 to 35 doses over six to seven weeks with concurrent IMRT and cisplatin, and the 90 mg dose is being studied in a Phase 3 trial to reduce severe OM in patients receiving chemoradiotherapy for head and neck cancer.

3.4 Randomization and Blinding

Forty eight patients will be randomized 1:1 to Arm A or Arm B. Patients in Arm A will receive GC4419 in combination with their assigned SBRT dose, and patients in Arm B will receive Placebo (PBO) with their assigned SBRT dose. The randomization will be restricted so that the sample size within each arm is exactly 24 patients. The restricted randomization sequence will be constructed prior to trial initiation, and applied by the Trial Statistical Analyst (YY, PT) overseeing the trial treatment and RT dose assignments. Each patient will randomized by the MDACC biostatistical analyst maintained for the duration of the study. Patients will be followed by their Patient ID (also known as a CORe Number), assigned by Galera prior to randomization. Operational and system details will be included in the Study Plan and Pharmacy Manual.

Investigators and patients will be blinded to GC4419 or PBO assignment, but not to SBRT dose level assignment. Treatment should remain blinded until the end of the study. Only in the case of an emergency, when knowledge of the investigational product is essential for the clinical management or welfare of the patient, may the investigator unblind a patient's treatment assignment prior to the end of the Post-active Phase. The investigator will, whenever possible, discuss options with the Medical Monitor, on-call physician, or appropriate Galera Therapeutics, Inc./CRO study personnel before unblinding. If the blind is broken for any reason and the investigator is unable to contact Galera Therapeutics, Inc. prior to unblinding, the investigator will notify Galera Therapeutics, Inc./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 patients remaining in the study. In addition, the investigator will record the date and reason for revealing the blinded treatment assignment for that subject in the appropriate section of the CRFs.

If a serious adverse event (SAE; as defined in section 9.0) is reported to Galera Therapeutics, Inc./CRO, Galera Therapeutics, Inc. staff may unblind the treatment assignment for the individual patient. If an expedited regulatory report to one or more regulatory agencies is required, the report will identify the patient's treatment assignment. When applicable, a copy of the regulatory report may be sent to investigators in accordance with relevant regulations, Galera Therapeutics, Inc. policy, or both.

Site pharmacies and MDACC statisticians responsible for the treatment assignment will remain unblinded throughout the study. Operational precautions will be taken to ensure that patients and participating investigators remain blinded to treatment assignments (GC4419/placebo). Personnel at Galera Therapeutics may be unblinded to the treatment assignment for purposes of safety monitoring. The sponsor was unblinded to treatment assignment

for overall study monitoring and safety review. One unblinded interim descriptive efficacy analysis will be performed for study design planning on the first 19 subjects. To facilitate future study design planning with investigators, interim efficacy results on those first 19 subjects will be provided to participating investigators. Subsequent to the single completed interim analysis by the sponsor, no unblinded efficacy analysis will be performed until the final statistical analysis. Investigators and supporting staff will remain blinded to randomized treatment assignments for patients 20-48, with only unblinded staff being site pharmacists, MDACC statisticians, and limited sponsor staff relative to study management and routine safety oversight.

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

1. Cytologic or biopsy confirmed adenocarcinoma of the pancreatic head, body or tail
2. Disease that is appropriate for SBRT by virtue of being:
    a. Locally advanced and technically unresectable, as determined by a pancreaticobiliary surgeon as part of a multidisciplinary review at the investigative site, including multi-phasic CT demonstrating:
        i. Greater than 180 degree tumor involvement of the superior mesenteric artery
        ii. Greater than 180 degree tumor involvement of the celiac axis, including major branches of the celiac axis that render it unresectable (e.g. common hepatic artery).
        iii. Tumor involvement of the first branch of the SMA that is not surgically reconstructible
        iv. Long segment involvement of the superior mesenteric vein/portal vein or hepatic artery that is not surgically reconstructible
    b. Potentially resectable, but patient is judged not a candidate for surgery, after multidisciplinary review at the investigative site;
    c. Potentially resectable, but the patients refuses surgery and is considered an acceptable candidate for SBRT after multidisciplinary review at the investigative site;
    d. “Borderline” resectable, as determined by multidisciplinary review, including absence of distant lymphadenopathy and the primary tumor characterized by one of more of the following:
        i. A tumor-vessel interface (TVI) with the mesenteric vein (SMV) or portal vein (PV) measuring ≥180° of the circumference of either vein’s wall or short-segment occlusion of either vein with a normal vein above or below the obstruction amenable to reconstruction;
        ii. Any TVI with the common hepatic artery (CHA) with normal artery proximal and distal to the TVI amenable to reconstruction;
        iii. A TVI with the superior mesenteric artery (SMA) measuring <180° of the circumference of the vessel wall
3. Primary tumor size and limited bowel involvement by tumor must be judged acceptable for SBRT at the discretion of the treating investigator.
4. No evidence of distant metastasis either prior to or after induction chemotherapy.
5. Completion of medically indicated first-line chemotherapy, as determined by the treating investigator
6. Patient must have metal stent in place if duodenal stent is required. If patient has plastic stent, this must be replaced prior to radiation.

7. Ability to understand and follow the breathing instructions involved in the respiratory gating procedure or to tolerate compression sufficient to reduce fiducial motion to ≤ 5mm.
8. Age 18 years or older
9. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (0, 1 or 2)
10. Adequate hematologic function as indicated by
    i. Absolute neutrophil counts (ANC) ≥ 1,500/mm3
    ii. Hemoglobin (Hgb) ≥ 8.0 g/dL
    iii. Platelet count ≥ 75,000/mm3
11. Adequate liver function as indicated by:
    i. Total bilirubin ≤ 1.5 x upper-normal limit (ULN)
    ii. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
12. Properly obtained written informed consent.

4.2 Exclusion Criteria:

1. Prior radiation therapy to the abdomen that would overlap with treatment field
2. Prior surgical resection of pancreatic tumor
3. Receiving any approved or investigational anti-cancer agent other than those provided for in this study
4. Uncontrolled or active gastric or duodenal ulcer disease within 30 days of dosing
5. Visible invasion of tumor into the lumen of the bowel or stomach on endoscopy (Note: Radiological infiltration into bowel is allowed, unless deemed clinically unsafe.)
6. Residual or ongoing ≥ Grade 3 non-hematologic toxicity from chemotherapy
7. Contraindication to IV contrast
8. Concurrent participation in another interventional clinical trial or use of another investigational agent within 30 days of study consent Note: Patients who are participating in non-interventional clinical trials (e.g., QOL, imaging, observational, follow-up studies, etc.) are eligible, regardless of the timing of participation.
9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, renal failure, cardiac arrhythmia, or psychiatric illness that would limit compliance with treatment
10. Second primary malignancy within the last 5 years, unless treated definitively and with low risk of recurrence in the judgment of the treating investigator
11. Known history of HIV or active hepatitis B/C (patients who have been vaccinated for hepatitis B and do not have a history of infection are eligible)

12. Female patients who are pregnant or breastfeeding
13. Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth cont avoid pregnancy for the entire study period and for 30 days after the last dose of GC4419. Acceptable methods include, but are not limited to, barrier methods, IUD, and birth control pills. This includes any woman who has experienced menarche but has not undergone successful surgical sterilization or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months, or women on hormone replacement therapy with serum FSH levels greater than 35 mIU/mL. A negative urine or serum pregnancy test must be obtained within 14 days prior to the start of study therapy in all women of child-bearing potential.
14. Male subjects who are unwilling or unable to use an acceptable method of birth control (barrier method) to avoid pregnancy for the entire study period and for up to 90 days after the last dose of GC4419 are excluded.
15. 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.
16. Medical history that includes any condition, or requires the use of concomitant medications which, in the investigator's judgment, are associated with or create a risk of increased carotid sinus sensitivity, symptomatic bradycardia, or syncopal episodes.

4.3 Screen Failure and Randomization Failure

A patient is considered to be a screen failure if the patient signs the informed consent form but withdraws consent or is deemed ineligible prior to receiving their first dose of SBRT and GC4419/placebo. A patient is considered to be a randomization failure if the patient signs the informed consent form and is randomized to a treatment arm but withdraws consent or is deemed ineligible prior to receiving their first dose of SBRT and GC4419/placebo. Basic demographic and disease history information will be collected for randomization failures, as well of the reason the patient was precluded from the clinical trial. All randomization failures will be listed on the Screening, Enrollment, and Discontinuation Log.

4.4 Withdrawal from Study Criteria

In accordance with the Declaration of Helsinki, a patient has the right to withdraw from the study at any time for any reason. The investigator may also, at his/her discretion, discontinue a patient from participating in this study at any time. Additionally, study treatment may be discontinued for any of the following reasons:

- Unacceptable Adverse Event
- Medical requirement to administer a contra-indicated medication
- Patient non-compliance
- Discontinuation of the study at the request of Galera Therapeutics, Inc.

- Inability to receive consensus-approved SBRT treatment plan after simulation due to organ at risk constraints or inability to tolerate simulation (see section 6.1)

The primary reason for ceasing treatment with the randomized therapy (GC4419 or placebo) will be clearly documented in the patient's medical record and recorded on the appropriate case report form (CRF) page. Once a patient discontinues, the patient will not be allowed to be retreated.

If a patient discontinues randomized therapy as a result of an adverse event (AE) or serious adverse event (SAE), every attempt should be made to keep the patient in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the patient or investigator, the patient may be withdrawn from the study.

Withdrawn subjects will not be replaced.

4.5 Treatment Compliance

Compliance with GC4419/placebo dosing, including administration details (e.g., volume, start, stop times, etc.) should be documented in the source documents and recorded on the CRF.

4.6 Central Review and Study Entry

4.6.1 Initial Eligibility Determination

Initial eligibility determination will be at the discretion of the treating institution. Galera and MDACC investigators will be available for discussion regarding eligibility criteria. Determination of resectability status will be at the discretion of the treating institution's multidisciplinary teams; however, MDACC radiologists will be available for second opinion review of imaging and consultation if requested. Central pathology review will not be required but will be allowed if clinically appropriate.

4.6.2 Patient Registration and Randomization

The treating site will notify Galera of new patient consent and submit a Registration Form for review following confirmation of eligibility. Galera will then enroll/registerthe patient and notify the MDACC biostatistics team. A Patient ID (previously known as a CORe number) will be assigned as a four digit number (two digit site – two digit subject number) and returned to the respective site on the Registration Form. Following simulation, the site will send a request for randomization to the MDACC biostatistics team who will then complete randomization of patient to GC4419/placebo. MDACC biostastistics team will provide the SBRT dose level assignment to treating institution and MDACC investigators for purposes of SBRT treatment planning. The unblinded site investigational pharmacy will access the CTC system for the treatment assignment (GC4419/placebo). Please reference the Pharmacy Manual and Study Plan for additional detail around safety unblinding and registration.

4.6.3 SBRT Treatment Planning

To ensure protocol compliance, the treatment plans for the first three patients treated at each site will be reviewed by the MDACC Study Investigators and Participating Site's PI. Radiation treatment plans will be reviewed to ensure a common understanding of the procedures listed in

sections 6.1 through 6.8 at each participating institution. This may be done during the trial periodically as needed.

All treatment plans will be reviewed for quality assurance according to the standard review process at each participating institution.

All plans will also be reviewed by the responsible physicist or his/her designee at each participating institution for compliance with the protocol and standard of practice at each institution.

When performed, plan reviews for patients from one institution by the staff of another institution will utilize the resources of MDACC, including WebEx; and/or other feasible resources that comply with HIPPA. The options for sharing the SBRT plans and communication flow will be outlined in a separate document.

4.7 Study Closure

Both the sponsor and the investigator reserve the right to terminate the study at any time. If all dose levels on a specific arm fail to meet prespecified toxicity/ efficacy criteria, that arm shall terminate and patients will continue to accrue on the remaining arm. Should all dose levels on the second arm also fail to meet prespecified toxicity/ efficacy criteria, the trial will terminate. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, Galera Therapeutics, Inc. and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or site staff, as appropriate:

- Return of all study data to Galera Therapeutics, Inc. (as applicable)
- Resolution of all data queries
- Accountability, reconciliation, and arrangements for all unused study drug
- Review of site study records for completeness
- Shipment of laboratory samples (as applicable)

In addition, Galera Therapeutics, Inc. reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If Galera Therapeutics, Inc. determines such action is needed, Galera Therapeutics, Inc. will discuss this with the investigators (including the reasons for taking such action) at that time. When feasible, Galera Therapeutics, Inc. will provide advance notification to the investigators of the impending action prior to it taking effect.

Galera Therapeutics, Inc. will promptly inform all investigators conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigators must inform the IRB/IEC/REB promptly and provide the reason for the suspension or termination. If the study is prematurely discontinued, all study data must be returned to Galera Therapeutics, Inc.

5.0 STUDY CALENDAR

The pre-study intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using best clinical judgment of the responsible attending physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients with PAC treated with SBRT. Registration is defined as the date the patient consents.

Pre-Randomization Testing

- To be completed ≤ 30 Days before randomization: All laboratory studies, history and physical.
- Minor changes to the assessment schedule may be made to accommodate holidays, administrative closures, etc, which if necessary, are not considered as significant deviations by the Sponsor. If possible, site should contact the Sponsor prospectively to address rescheduling protocol assessments and data handling.
- Standard of care evaluations may be utilized for screening, provided the assessments are clearly documented as standard of care in the source and meet protocol requirements and timelines.

Tests & Observations	**Screening/ Prior to Randomization***	**Baseline**	**Last Day of SBRT**	**4[B] weeks post SBRT (optional)**	**7[B] weeks post SBRT**	**12 weeks post SBRT[B]**	**Post Tx Follow- up****
	Within 30 days of randomization	Day -21 to 1 (pre-dose)	Day 5	Day 33	Day 54	Day 89	
			+/-2 days	+/-7 days	+/-7 days	+/-5 days	+/-28 days
Medical and Disease History (including disease status and pathology review)	X (1)	X (1)					
Physical, weight, ECOG PS (May be physician clinic visit at baseline visit)	X (1)	X (1)	X (1)		X (1)	X (1)	X (1)
Pulse, BP	X	X (1)	X (1)		X (1)	X (1)	X (1)
Height $	X						
Adverse Event Assessment†		X (1)	X (1)	X (1)	X (1)	X (1)	X (1)
PRO-CTCAE	X (2)	X(2)	X	X	X	X	X
Fatigue/QOL/Physical/Mental LASA Assessment	X (2)	X(2)	X	X	X	X	X
Endoscopy with Fiducial placement for CT guided on-line positioning (not necessary for MR-linac treatments), core biopsies, cytologic brushings	X*						
Endoscopy with duodenal evaluation, core biopsies if possible, cytologic brushings						X (5)	

Radiation Simulation (>5 business days prior to SBRT and following eligibility)***	X						
Laboratory Studies							
Electrocardiogram (ECG)	X						
CBC, Differential, Platelets	X	X	X	X	X	X	X
Chemistry (Serum Creatinine, Electrolytes, AST, ALT, Alk. Phos., Albumin, Total Bilirubin)	X	X	X	X	X	X	X
Pregnancy Test (#)	X						
Tumor marker (CA 19-9)	A	A	A	A	A	A	X
Blood and Tissue Collection for Correlatives		X (4)	X (4)	X (4)	X (4)	X (4)	X (4)
Evaluation for Resectability (7)	X				X		
Staging							
Pancreatic Protocol CT(3,6) (for resectability assessment)					X		
MRI abdomen w/ and w/o contrast (for assessment of small bowel toxicity), is possible.	X (3)					X (3)	
Restaging CT Scan of Chest/Abd/Pelvis	X (3)					X (3)	X(3)
Randomization****		x					

* Endoscopy for fiducial placement and biopsies may occur anytime between screening and radiation simulation

** After the 12 week visit, patients will continue in follow-up with physical examinations, labs, and staging scans every 3 months (+/- 28 days) post-SBRT until they have reached 36 months post-SBRT or until local progression. Thereafter, clinical status information is required every 6 months for 5 years post-SBRT, to include survival information and toxicity data. This information may be obtained via telephone call if patient is lost to clinic follow up. For patients who discontinue treatment for progressive disease or are removed from protocol treatment, survival information is required every 6 months for 5 years post-SBRT. Adverse events including radiation toxicity up to 1 year post-SBRT will be assessed during visits and phone calls, and recorded in the case report form (See section 9.3 for details).

*** Simulation should be within 30 days of SBRT. If simulation is done > 2 weeks prior to treatment start, a verification simulation should be performed in the week prior to treatment start.

**** Randomization will occur following completion of the radiation simulation. See Study Manual for details on the registration and randomization process.

1 Medical and Disease History, including pathology, collected within the Screening and Baseline Period will include information deemed medically-relevant by the Investigator (or designee). May be performed by physician, NP, or PA responsible for oncologic care of the patient. Vitals may be collected by RN or MA.

2 To be completed ONCE prior to treatment. The study files will contain examples and IRB approval of the assessments.

3 Chest scans must be CT or chest X-ray. Abdominal baseline and restaging scans can include either a pancreatic protocol CT or MRI, although pancreatic protocol CT is preferred. The CT must be acquired with at least a 5 mm or less slice thickness. Initial scans for determining eligibility and resectability status will be reviewed at the treating institution and central review will not be required except in cases of uncertainty. In case of contraindications (eg pacemaker, severe claustrophobia, etc) a high quality CT scan can be acquired.

4 Correlative blood collection will occur at Baseline, at day 2 (pre- treatment), day 5 (pre- treatment), week 7 and week 12. The blood draw at week 4 and all Follow Up time points will be optional. Tissue collection is required at Baseline and week 12. Please see Table 7 for sample collection timepoints.

5 Endoscopic evaluation approximately 12 weeks post radiation.

6 The resectability imaging will be done based on clinical necessity per the surgical oncologist.

7 Resectability will be assessed at respective institutions.

† AEs are to be collected starting at baseline and through 1 year post SBRT. Routine AEs are to be collected starting after randomization. See section 9.0 AE definition. See section 9.3 for expedited reporting of SAEs.

For women of age 18-55 without hysterectomy or tubal ligation. Must be done ≤ 14 days prior to study entry (dosing). Testing should be done per institutional standard.

$ A previous height may be utilized if within 6 months of consent

A Previously obtained CA19-9 may be used if within < 28 days prior to randomization. Subsequently, CA 19-9 may be performed +/- 14 days from the scheduled date. During treatment, CA 19-9 should be performed every 28 days. For patients who have normal CA 19-9 levels at baseline, continued testing of CA 19-9 is not required.

B Research coordinator or RN will call patient weekly up to the week 7 visit, and again at week 10 to confirm no adverse events between clinical visits. The week 4 visit is optional. If the patient is not seen in the clinic, the patient should be contacted by phone this week.

6.0 RADIATION DELIVERY

6.1 Radiotherapy Technical Factors

6.1.1 Eligibility criteria for SBRT

In order to ensure safety, patients must meet the following criteria in order to proceed with SBRT:

- Patients must have no evidence of active duodenal or gastric ulcers or direct tumor invasion of the bowel or stomach on pre-SBRT endoscopy Previous history of ulcers >30 days prior to treatment with no active bleeding or symptoms are eligible for treatment.
- Patients should not be treated with SBRT if SBRT-specific organ at risk (OAR) constraints (listed in section 6.3) cannot be met.
- Patients must be able to undergo 4D CT simulation to assess tumor motion with respiration and able to comply with breath hold for motion management.
- Patient must not have any contraindication to contrast administration at simulation, including contrast allergy refractory to premedication at the discretion of the treating physician.
- Patient must have a functioning metal stent in place if biliary or duodenal stent is required.

6.1.2 Technical Factors including Treatment Delivery and Fiducial Placement

- Only ≥6 MV photons are permitted for SBRT.
- Particle therapy is not permitted.
- Static IMRT or VMAT must be used; 3DCRT is not permissible. It is recommended that 6-12 co-planar static IMRT fields or 1-3 arc fields (VMAT/Rapid-Arc) be used in the radiation treatment plan. Flattening Filter Free (FFF) treatment is allowed.

- Both treatments with CT and MRI guidance for positioning are accepted, for CT guided positioning 1-5 (preferably ≥3) fiducial markers should be placed for targeting purposes. These markers will be placed directly at the tumor periphery and/or within 1 cm of the tumor (normal pancreas) under endoscopic ultrasound at any time prior to radiation simulation. Fiducials are optional for MR Linac based treatment.Simulation can follow fiducial marker placement on the same day in case of an uncomplicated positioning endoscopic procedure, however, some hours of delay are recommended to reduce the risk of post-positioning swelling. The simulation quality and timing is at the decretion of the treating physician.
  - Simulation should be done ≤ 30 days prior to first fraction of SBRT.
  - If simulation is done > 2 weeks prior to treatment start, a verification simulation should be performed in the week prior to treatment start.
  - Patients will be positioned supine, arms above the head, in a custom immobilization device.
  - Administration of IV and oral contrast is required for target and normal tissue delineation unless patient has a contrast allergy refractory to premedication or at the discretion of the treating physician. A pretreatment renal scan to assess kidney differential will be performed prior to initiation of treatment if clinically appropriate per the treating physician.

- A 4D CT scan may be performed to assess respiratory motion. If > 5 mm of tumor motion in any direction is noted, then the use of breath-hold (BH) technique is required. If BH is utilized, 3-5 BH scans will be performed for reproducibility. If there is < 5 mm tumor motion on 4DCT and patient cannot tolerate BH, treatment planning may be done in free breathing using 4D CT.
- MRI or PET simulation may be optionally performed in the treatment position and later fused to the CT simulation scan to assist in target volume delineation, but this is not required.
- Patients will be treated on CT- or MRI guided linacs, for all daily imaging is required for position verification (CBCT, daily KV withch fiducial tracking or MRI positioning.
- Deformable adaptive repositioning and planning is accepted done on-line or off-line, while well documented as e.g. adapted plan1…6
- If not clinically contraindicated, patient will be placed on proton pump inhibitor for duration of treatment and 90 days post treatment.

6.2 Target Delineation

6.2.1 Required Structures

- GTV: Primary pancreatic tumor as delineated on all available pre-treatment imaging and CT simulation
- iGTV: GTV expanded to encompass tumor in all phases of 4DCT or all BH scans obtained during simulation.
- iGTV_Exp = iGTV + 3mm (uniform expansion)
- TVI: The segment of portal vein, SMV, SMA, and/or celiac artery that is in direct contact with tumor. TVI structures will be contoured to include entire radial extent of any vessel that contacts tumor. For example, the SMA TVI will include the entire 360-degree extent of SMA even if there is only 90-degree involvement of the SMA by tumor. This radial contour should extend superiorly and inferiorly on each axial slice where there is GTV contoured.
- TVI_Exp: TVI + 3mm (uniform expansion)
- Fiducials: Fiducials and/or clips should be contoured separately starting superiorly and moving inferiorly in numeric order.
- Fiducials_Exp: Fiducials + 3mm (uniform expansion)
- iDuodenum: Duodenum contoured to encompass tumor in all treatment phases of 4DCT or all BH scans obtained during simulation.
- PRV_Duo: iDuodenum + 5mm (uniform expansion)
- iStomach: Stomach contoured to encompass tumor in all treatment phases of 4DCT or all BH scans obtained during simulation.
- PRV_Stom: iStomach + 5mm (uniform expansion)
- iBowel: Any other small bowel in the treatment area, contoured to encompass tumor in all treatment phases of 4DCT or all BH scans obtained during simulation.
- PRV_Bowel: iBowel + 5mm (uniform expansion)

- PRV_GI = PRV_Duo + PRV_Stom + PRV+Bowel
- Bilateral kidneys, liver, spinal cord and spleen contoured per institutional guidelines. No PRV structures are required.
- Prescription Dose will be prescribed to different PTV volumes according to the dose level (figure 10):
- PTV 1 = iGTV_Exp + TVI_Exp. Prescription dose to this structure is 6.6Gy in 5 fractions at all dose levels to the 95% isodose line.
- PTV 2 = PTV1 – PRV_GI. Prescription dose to this structure will be according to PTV2 dose for assigned dose level to the 95% isodose line.

Safety Note: SBRT feasibility is judged by the treating physician.

- Tumor volume is not a restrictive criteria, however, the PTV2 needs to be sufficiently covered at least 60% of the prescribed dose, while still meeting the normal tissue constraints
- Radiological or endoscopic signs of tumor infiltration in bowel structures need to be well described before SBRT. Aside from bulging tumor masses in the bowel lumen, tumor infiltration in itself it is not an exclusion criteria but informs judgement of the physician to perform SBRT. All suspect areas need to be included in the PTV1 and sufficiently covered for at least 60% of the (6.6Gy) prescribed dose while still meeting the normal tissue constraints

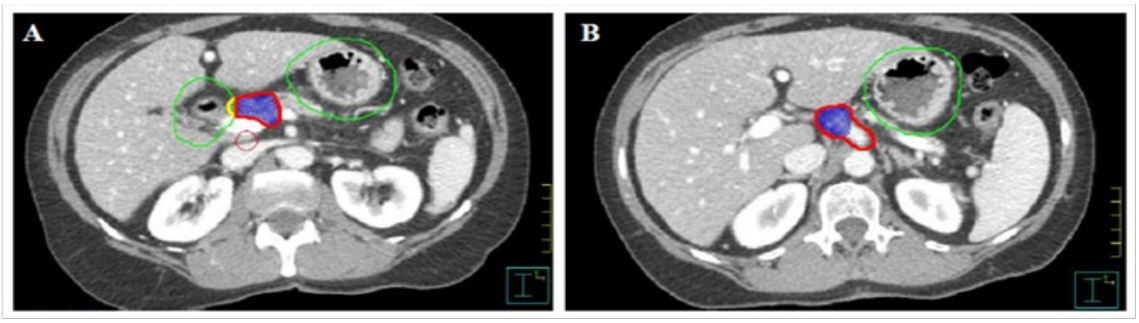

Figure **10**. Representative slices in a patient with LAPC due to complete celiac axis encasement of tumor. Representative slices are of PTV_1 (yellow), PTV_2 (red) and PRV_GI (green). A) PTV_2 is equal to PTV_1 with PRV_GI subtracted. B) PTV_1 and PTV_2 cover TVI where celiac touches tumor directly.

6.3 Treatment Planning Guidelines and Dose Constraints

Prescription dose to PTV_1 must cover 95% of the target volume. There are no formal coverage constraints on PTV_2, but they should be maximized while maintaining OAR constraints at the treating physician's discretion. Recommended and mandatory dose constraints are outlined in Table 2.

Table 2. Dose Constraints Recommended for Treatment Planning

Description	**Planning System Name**	**Constraints**
PTV_1	PTV_1	***V33 > 95%****
OAR		**Constraints**
Duodenum	iDuodenum	
		V30<3cc*
		V35<1cc*
		V40<0.5cc*
Small Bowel	iBowel	
		V30<1cc*
		V35<0.1cc*
		V40<0.5cc*
Stomach	iStomach	
		V30<2cc*
		V35<1cc*
		V40<0.5cc*
Liver	Liver	***V12 <50%****
Combined Kidneys	Kidneys	***V12 <75%****
Spinal Cord	Spinal_Cord	***V20 <1cc****
Spleen	Spleen	Mean < 2 Gy (optional)

* Notation indicates required mandatory constraints to be met in order to proceed with SBRT; Other constraints are recommended as reasonably achievable.

6.4 Treatment Schedule

All patients will begin SBRT within 30 days of the simulation scan. If possible, treatment will begin on a Monday and complete on a Friday, unless a holiday or other treatment interruption occurs. In this case, treatments may occur on different days, but all 5 treatments must occur within an 8 day window.

6.5 Treatment Delivery

- Patients may be treated on any image-guided (IGRT)-enabled machine (including MRI linac).
- (on-line) adaptive planning may be done at the discretion of the treating physician if being well documented.

- Initial patient positioning will be based on MRI, CBCT, volumetric kV or CTOR imaging with shifts to referenced anatomy at the level of the tumor as appropriate.
- In case Orthogonal kV/MV, kV/kV projection, or CTOR imaging will be used to verify the location of the fiducials prior to delivery of the first treatment beama secondary shift based on the location of fiducials should be utilized, as indicated by the position of the fiducials.
- In case MRI imaging is used for position verification, at least 2 contours need to be matched (e.g. PTV and duodenum), on-line re-contouring and planning is accepted, while well documented as serial plans given
- Documentation of active monitoring of treatment delivery accuracy will be asked using CBCT, MRI images or kV and/or MV projection imaging, either immediately before or during all (or a subset of) treatment fields.

6.6 Compliance Criteria

6.6.1 Dose Uniformity

- Variation Acceptable: Minimum dose within the PTV_1 is less than 97% of the prescribed dose, but does not fall below 93% of this dose or Maximum dose within the PTV_1 is greater than 107% of the prescribed dose, but does not exceed 110% of this dose.
- Deviation Unacceptable: Minimum dose within the PTV_1 is less than 93% of the prescribed dose or Maximum dose is greater than 110% of the prescribed dose.

6.6.2 Volumes

- Deviation Unacceptable:
  1. Incomplete contouring of the entire GTV or PTV;
  2. Use of different margins than specified for the PTV1;
  3. Over-contouring of the GTV by > 30 cc (15 cc if it results in inclusion of extra duodenum, small intestine or stomach);
  4. Incorrect contouring of the duodenum, stomach or small intestine that results in > 15 cc overlap of the PTV with the OAR.

6.6.3 Treatment Interruptions

- Per protocol: All treatments occur within 8 calendar days
- Acceptable variation: All treatments occur with 8 to 16 calendar days
- Unacceptable variation: Treatments take greater than 16 days to complete

6.7 Definitions of Radiation related Adverse Events

The criteria used for the grading of toxicities encountered in this study are Common Toxicity Criteria (CTC) version 4.0.3

<u>Very likely (80-90%)</u>:

- Fatigue (which generally goes away after the radiation therapy is completed)

- Skin irritation, redness, itchiness, discomfort
- Temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms

Less likely (30%):

- Nausea, vomiting (during therapy) – more common if stomach or gastrointestinal track irradiated
- Chest wall pain, rib fracture (< 10%)

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 patients with large tumors and in patients with 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.

6.8 Rapid Review and Radiation Therapy Quality Assurance

Radiation plans for all MDACC-treated patients will be reviewed at MDACC prior to treatment start during weekly gastrointestinal radiation therapy quality assurance (QA) rounds by a minimum of two gastrointestinal radiation oncology specific attending physicians who are not investigators on the trial and will also be reviewed by both radiation oncology study investigators.

To ensure protocol compliance, the treatment plans for the first three patients treated at each participating non-MDACC site will be reviewed by a MDACC Study Lead Investigator and the respective site PI. Radiation treatment plans will be reviewed to ensure a common understanding of the procedures listed in sections 6.1 through 6.8 at the respective institution. This may be done during the trial periodically as needed.

All treatment plans will be reviewed for quality assurance according to the standard review process at each participating institution.

All plans will also be reviewed by the responsible physicist or his/her designee at each participating institution for compliance with the protocol and standard of practice at each institution.

When performed, plan reviews for patients from one institution by the staff of another institution will utilize the resources of MDACC, including WebEx; and/or other feasible resources that comply with HIPPA.

7.0 STUDY DRUG MATERIALS

7.1 Description of Study Drug GC4419

GC4419(avasopasem manganese) manganese,dichloro[(4aS,13aS,17aS,21aS)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21a-eicosahydro-11,7-nitilo-7H-dibenzo[b,h][1,2,7,10]tetraazacylcoheptadecine-κN5,κN13,κN18,κN21,κN22]-) is a water soluble, highly stable, low molecular weight manganese-containing macrocyclic ligand complex whose activity mimics that of naturally occurring SOD enzymes.

GC4419 Administration: 90 mg GC4419, 9 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. % saline for parenteral administration. There are no other excipients. GC4419 is packaged as an 11 mL ± 0.1mL aliquot in a 10 mL amber glass vial with an S-127 4432/50 gray stopper and a 20 mm red flip-off seal.

Placebo Administration: Matching placebo will be prepared at the unblinded investigational site pharmacy with 100% normal saline at 250 mL, for IV administration over 60 minutes.

7.2 Clinical Safety Data with GC4419

In the completed Phase 1b/2a trial of GC4419 plus IMRT/cisplatin to reduce oral mucositis experience by patients with head and neck cancer, the most common adverse events observed were nausea, fatigue, dysgeusia, oropharyngeal pain, decreased white blood cell count, constipation, dry mouth, anemia, vomiting, diarrhea, decreased lymphocyte count, and decreased appetite. These and other adverse events observed are characteristic of the cisplatin/IMRT regimen in this patient population.

The following mild to moderate adverse events were reported as possibly related to GC4419 for >10% of patients in the GT-001 study: nausea, vomiting, dry mouth, diarrhea, fatigue, dyspepsia, gastroesophageal reflux disease, dizziness, dysgeusia, weight loss, decreased appetite, headache, paresthesia, and hiccups.

The following more severe adverse events were reported by treating investigators as possibly related to GC4419 in the GT-001 study: anemia, nausea, vomiting, gastroenteritis, low white blood cell count, low neutrophil count, weight loss, decreased appetite, arthritis, and reduced range of motion.

Potentially mechanism-related facial tingling or paresthesia, possibly due to nitric oxide potentiation, was reported for several patients in the GT-001 study and appears related to GC4419 dose, occurring in 11/19 (58%) patients receiving 112 mg per dose, 5/9 (55%) patients receiving 90 mg/dose, but only 2/18 (11%) at lower doses. This facial tingling/paresthesia was mild to moderate, and when it occurred it did so during GC4419 infusion with resolution shortly after the end of the infusion. It was neither treatment-limiting nor troublesome to patients, and does not pose a meaningful safety risk.

Twenty-three (50%) patients experienced at least 1 serious adverse event (SAE). SAEs reported for > 1 patient included pyrexia and vomiting (each 11%), febrile neutropenia (9%), nausea (7%), and dehydration (4%). Of the 3 patients with nausea reported as an SAE, nausea was

accompanied by vomiting in all 3 cases. Two patients, both at the 112 mg/dose level, experienced at least 1 SAE that was considered by the Investigator to be GC4419-related, including Grade 3 gastroenteritis in 1 patient and Grade 3 nausea, vomiting, and hyponatremia in other patients; these events also were considered DLTs. All other SAEs reported were considered by the Investigator to be unrelated to GC4419.

In the randomized, double-blind, placebo-controlled Phase 2b trial, GT-201, the safety profile of GC4419 was similar to that of placebo, indicating that GC4419 did not appear to add significant risk to the known toxicity of the underlying chemoradiotherapy regimen used for patients with HNC in that trial.

7.3 Study Drug Packaging and Labeling

GC4419 will be presented as individual single-use vials, which represent daily doses to be administered IV concurrent with SBRT. Details regarding labeling can be found within the Pharmacy Manual.

7.4 GC4419

GC4419 is packaged as an 11 mL ± 0.1mL aliquot in a 10 mL amber glass vial with a S-127 4432/50 gray stopper and a 20 mm red flip-off seal. Each bottle will be labeled with the appropriate language, including the required regulatory text.

7.5 Placebo

Placebo vials will not be provided by the Sponsor. The Site will be responsible for preparing placebo IV infusion bags with 250 mL of 100% normal saline per the Pharmacy Manual.

7.6 Study Drug Storage

GC4419 solutions must be stored at 2°C to 8°C at all times until use. GC4419 solutions must not be frozen at any time. Temperature excursions above freezing and up to 25°C or down to 0.1°C for four hours are acceptable; however, Galera Therapeutics, Inc. or its designee must be notified immediately of the temperature excursion to ensure proper oversight.

Once prepared, the IV bags containing GC4419/saline mixtures must also be stored at 2°C to 8°C until use, and must be administered to patients within 24 hours of preparation. GC4419 dosing solutions must not be frozen at any time. If freezing of the material is evident, that supply must be quarantined per institutional guidelines and Galera Therapeutics, Inc. or its designee must be notified immediately.

7.7 Study Drug Preparation GC4419 and Placebo

GC4419 will be provided to the study site in single use, sterile, pyrogen-free vials ready for dose preparation. Proper mixing with normal saline is required. Standard aseptic techniques will be used to maintain sterility.

Assignment of treatment arm will be randomized with respect to treatment arms A (90mg GC4419) and B (placebo). GC4419 will be presented in single-use vials.

To prepare daily IV solutions of GC4419, investigational pharmacists will extract 10 mL from a single vial and add to 240 mL normal saline. Note that there is no extraction of saline (i.e., the infusion solution volume will be 240 mL saline + 10mL volume of GC4419/placebo). No additional modifications or adjustments are to be made to the infusion solution.

The GC4419 solution may appear clear or have a slight yellowish tint. Although solutions should be free of particulates, it is possible that some vials may have some fine visible particulates. Infusions should be prepared using a sterile 0.2 micron syringe filter prior to introduction into the infusion bag. The prepared admixture should be inspected visually for any particulate matter prior to administration, and prepared solutions still containing any visible particles after filtration should not be used. Filtration does not influence dosage calculations.

To prepare daily IV solutions of placebo, investigational pharmacists will use 250 mL of 100% normal saline.

Further information and preparation details will be provided in a separate Pharmacy Manual.

Note: Investigational staff who prepare infusion solutions will be unblinded and cannot be discussed with the clinical team.

7.8 Study Drug Administration

GC4419 and Placebo: GC4419 or Placebo/saline mixture will be administered intravenously at an infusion rate that totals 60 min (± 6 min to account for saline overfill) for the total dose assigned. Infusions of GC4419/placebo must be administered using an infusion pump (i.e., not by drip rate). Infusion pump models are not specified and may be per institutional preference/standard.

To facilitate administration of GC4419 according to the study schedule, an indwelling venous access device may be used, at the discretion of the treating investigator. If an indwelling venous access device is placed to facilitate administration of GC4419, this fact will be recorded with the study data, as will information about the date of placement, type of device, and subsequent complications or adverse events related to the use of the device.

SBRT must be initiated as soon as possible upon completion of the GC4419/placebo infusion, but no later than 180 minutes following the end of the GC4419/placebo infusion.

GC4419/placebo will be given beginning on the first day of radiation and continuing daily, concurrently M-F throughout the administration of SBRT

If SBRT is not administered on any given day due to a treatment break or unforeseen circumstances, GC4419/placebo should not be administered on that day. Breaks in SBRT will be determined by the patient's treating physician in accordance with standard of care. Patients should resume GC4419/placebo administration when SBRT resumes. On days when planned doses of both GC4419/placebo and SBRT are not administered (e.g., due to a holiday site closure), GC4419/placebo dosing may be extended along with SBRT to make up the missed dose(s).

7.9 Study Drug Accountability

The investigator is responsible for ensuring adequate accountability of all used and unused GC4419. This includes acknowledgment of receipt of each shipment of GC4419 (quantity and condition), patient dispensing records, and quantity of GC4419/placebo returned or destroyed. Dispensing records will document quantities received from Galera Therapeutics, Inc. and quantities dispensed to patients, including container number or lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication. Any GC4419 that is prepared but not used must also be recorded in the dispensing records. Further accountability instructions can be found in the Pharmacy Manual.

All GC4419 supplies and associated documentation will be reviewed and verified by the study monitor. Copies of all forms, documenting drug receipt at the study site, drug transportation to satellite sites, and drug return to Galera Therapeutics, Inc., together with drug accountability records, will be retained according to the regulations governing record retention.

The investigator will not allow GC4419/placebo to be given to any patient not included in the study or any unauthorized person.

7.10 Study Drug Handling and Disposal

GC4419: After completion of the study, all unused study drug will be inventoried by the study monitor and if possible, destroyed locally at the site after complete accountability by the Sponsor and/or its representatives. GC4419 should not be returned directly to Galera Therapeutics, Inc. unless specifically requested by Galera Therapeutics, Inc. The study monitor will instruct the site in the disposal and/or destruction of all used and unused GC4419 supplies. Destruction of any GC4419 should be documented appropriately.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary therapy, concomitant medications and supportive care

Necessary supportive measures for optimal medical care will be given throughout the study. Supportive care medications may be administered at the investigator's discretion and recorded in the CRF (including administration of prophylactic antiemetic and antidiarrheal medication if deemed appropriate by the investigator). Concomitant medications will be recorded in the eCRF up to Week 12 for AEs and until resolution of SAEs. However, medications are subject to the following exclusions:

- Other concurrent chemotherapy or investigational agent during the week of SBRT
- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildanefil, 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 GC4419
- Pyridostigmine or other drugs that in the judgment of the treating investigator could create a risk of increased carotid sinus sensitivity, symptomatic bradycardia, or syncopal episodes.
- Other biologic response modifiers – except systemic hematopoietic growth factors for the management of anemia or myelosuppression
- Concurrent approved or investigational anti-cancer therapy (e.g., chemotherapy, immunotherapy, targeted therapy, hormone and biologic therapy) other than the Protocol regimen
- Other investigational agents

8.2 Dose Delays and Dose Modifications

The following toxicities require a 25% dose reduction in GC4419/placebo:

- Grade 2 or greater hypotension within two hours after the start of GC4419/placebo infusion
- Grade 3 or 4 vomiting, or Grade 3 nausea

Two dose reductions for toxicity will be permitted per patient. After the first event, the patient will be re-challenged at 75% of the original dose (7.5 mL GC4419/placebo in normal saline for a total volume of 250 mL). After the second event, the patient will be re-challenged at 50% of the original dose (5.0 mL GC4419/placebo in normal saline for a total volume of 250 mL). Patients who are unable to tolerate GC4419/placebo infusions following two dose reductions must be discontinued from the study treatment but may continue with SBRT at the discretion of the treating investigator.

For other toxicities (including those attributable to SBRT), management will be per institutional and ASCO guidelines and investigator judgment.

Any radiation related toxicities ≥ grade 4 will necessitate removal of patient from further SBRT.

9.0 ADVERSE EVENTS

9.1 Definitions

The treating physician and investigator team are responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (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 GC4419/placebo, SBRT or other cause. To avoid confusion, the AE should be recorded in standard medical terminology.

The following definitions of terms are guided by the International Conference on Harmonization and the US Code of Federal Regulations and are included here verbatim.

Adverse Event (AE):

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which may or may not 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.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity (grade) of the condition.
- New conditions detected or diagnosed after investigational product administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae associated with a suspected interaction of the investigational product with a concomitant medication.
- Signs, symptoms, or the clinical sequelae associated with a suspected overdose of either investigational product or a concurrent medication.

Serious Adverse Event (SAE):

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening – NOTE: The term ‘life-threatening’ in the definition of ‘serious’ refers to any adverse drug experience [adverse event] that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death. [emphasis added]
- Requires inpatient hospitalization or prolongation of hospitalization – NOTE: In general, hospitalization signifies that the patient or subject 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 or significant disability/incapacity – NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

OR

- Is a congenital abnormality/birth defect.
- Other Important Medical Event

9.2 Serious Adverse Event Reporting

All events meeting the criteria for Serious Adverse Events (listed in section 9.1) must be reported to the Sponsor by investigational sites within 24-hours of becoming aware of the event. In order to determine the sponsor's timeline for notifying regulatory authorities and investigators per Federal Regulations, an event term, serious criteria, and causality is required at the time of the initial report. Specific SAE reporting instructions are provided in a separate manual.

The investigator will also notify your local IRB in writing of serious events per the IRB reporing policy.

9.3 Routine Adverse Event Reporting

Any adverse medical condition or laboratory abnormality with an onset date before the date of randomization is considered to be pre-existing in nature, and part of a patient's medical history. Adverse medical conditions that begin on or after date of randomization will be considered an adverse event. Increases in toxicity grade of pre-existing conditions that occur on or after the date of randomization are also considered an adverse event. AEs and SAEs occurring up to 1 year after SBRT will be recorded in the electronic data capture system. All SAEs will be followed to resolution; i.e., until they no longer meet criteria for seriousness. Non-serious AEs will be followed to resolution to the extent possible for up to one year post-SBRT. The frequency of routine AE assessments will be as indicated in the schedule of events.

All adverse events must be recorded in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to randomized therapy.

Gastrointestinal toxicity will be carefully assessed for causality because GI toxicity will used in the primary endpoint. Disease progression or death due to disease progression will not be reported as an AE as it is captured as a study endpoint in the CRF. Progressive disease found by scan or on clinical evaluation should be captured on the applicable CRF pages and not on the AE page.

9.4 Grading and Cause Assignment of Adverse Events

The severity of adverse events will be designated as mild, moderate, severe, life threatening, or fatal per NCI CTCAE version 4.03. If not specifically addressed in NCI CTCAE version 4.03, use table 3 below. Cause assignment of adverse events will be made in accordance

with table 4 below. The Investigator should consult the Investigator Brochure and/or product information in the determination of his/her assessment.

Table 3. Grading of Adverse Events

Grade	**Criteria**[1]
Mild – Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate – Grade 2	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[2]
Severe – Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[3]
Life Threatening – Grade 4	Life-threatening consequences; urgent intervention indicated
Death – Grade 5	Death related to adverse event

Table 4. Cause Attribution of AE's

Attribution	**Definition**
Related	It is likely that GC4419/placebo caused or contributed to the cause of the adverse event or laboratory abnormality, when the temporal sequence from the time of GC4419/placebo or SBRT administration, the known consequences of the patient's clinical/state condition or study procedures, the effects of discontinuing or reintroducing GC4419/placebo on the adverse event, and other medically relevant factors are considered.
Possibly Related	There is a reasonable possibility that the adverse event or laboratory abnormality was caused by GC4419/placebo or SBRT, when the temporal sequence from the time of GC4419/placebo administration, the known consequences of the patient's clinical state/condition or study procedures, and other medically relevant factors are considered.
Unrelated	The investigator has a high level of certainty that the patient's clinical state/condition, study procedures, or other medically relevant factors other than treatment with GC4419/placebo or SBRT caused the adverse event or laboratory abnormality. This relationship category should only be used when a clear precipitating cause exists and it is not reasonably possible that the event is caused by treatment with GC4419/placebo or SBRT.

10.0 ASSESSMENTS

10.1 Schedule of Evaluations

See Study Calendar in section 5.0.

10.2 Safety Assessments

General safety will be assessed during radiation, weekly (see visits on the basis of treatment-emergent AEs, physical examination findings, clinical laboratory tests, and vital sign measurements).

10.3 Clinical Assessments

Clinical assessment will consist of standard history and physical examination by a physician, nurse-practitioner or physician assistant responsible for the oncologic care of the patient.

Long-term follow-up may include telephone calls by study staff where clinic follow up is not feasible.

10.4 Laboratory Assessments

All protocol required laboratory assessments in the study calendar section 5.0 will be performed at a local laboratory.

10.5 Endoscopic Assessment

The endoscopic evaluation (including EUS) will take place at approximately 12 weeks post radiation. The endoscopist will be blinded to receipt of drug versus placebo. The following scale will be used for assessment where a score of 0=no toxicity, 1-2 indicates mild toxicity, 3-4 indicates moderate toxicity and 5 or more indicates severe toxicity:

- Erythema: (0=none, 1=mild (looks pink), 2=moderate/severe (red)
- Edema: (0=none, 1=mild, 2=moderate/severe)
- Ulcers: (0= none, 1= single, 2= 2 or more ulcers)
    - If ulcers are present, the endoscopist will measure cumulative surface area to normalize for ulcer size.
    - Note will also be made of whether ulcer has a clean base, active bleeding or stigmata of recent bleeding
- Stricture: (0-none 1= mild, 2=moderate/severe)

The endoscopist will also record the location of the tumor using anatomic coordinates including stomach (antrum, lesser and greater curvature, anterior and posterior wall) and duodenal bulb (medial or lateral wall), second portion of the duodenum (medial or lateral wall).

10.6 Radiographic Assessments and Definition of Radiographic Treatment Response

Staging imaging will be performed according to the study calendar in section 5.0 at baseline, one month post SBRT (clinical exam), 7 weeks (+/-1wk) post SBRT (clinical exam, triphasic CT for purpose of evaluating resectability) and 12 weeks (+/-5days) post SBRT (clinical exam, CT and endoscopy), in addition to regular q3 month follow up visits. Progression of disease will be evaluated at each time point. Radiographic response will be measured according to a modified Response Evaluation Criteria in Solid Tumors (RECIST) as described in section 10.6.3 and 10.6.4 below. Only response assessment of the primary target will be considered for biostatistical purposes of the primary analysis, since these targets are affected by radiation. Overall Response will be considered per RECIST 1.1 for PFS calculations (secondary endpoint), but not used for the primary endpoint of determining the MTD. All imaging will be interepreted by an MDACC-affiliated radiologist. All participating sites will submit scans to MDACC for review per the Study Manual. The same method of cross-sectional imaging used at baseline must be used at each follow up evaluation for treatment response.

10.6.1 Measurable Lesion

The measurable lesion must measure ≥ 1cm in the longest dimension utilizing CT scan thickness < 5 mm.

10.6.2 Non-measurable Lesions

Non-measurable disease will include all lesions < 10cm in longest dimension, in addition to truly non-measurable disease including leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal mass/organomegaly that cannot be confirmed on imaging.

10.6.3 Target Lesion

The target lesion will be the primary pancreatic tumor classified as measurable disease. The response within the target lesion will be used for statistical consideration. Non-target lesions will also be tracked and measured, but will be considered only for the purpose of determining progression-free survival. The primary target lesion will be considered in evaluating local control.

10.6.4 Response Criteria Definitions

Complete Response (CR): Disappearance of the target lesion. Any pathologic lymph nodes (target or non-target) must have reduction in short axis to <10mm

Partial Response (PR): At least a 30% decrease in the diameter of the target lesions, utilizing baseline measurements as reference.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Local Progressive Disease (LPD).

Local Progressive Disease (LPD): At least a 20% increase in the the longest diameter of the target lesion, utilizing baseline measurement (scan) as reference. The meansurement must also demonstrate an absolute increase of at least 5mm. If the study in which LPD is noted at the 6-8 week post-SBRT scan, LPD must be confirmed in the subsequent scan (at the 12 week post SBRT

scan) to rule out post-radiation inflammation from SBRT. If a repeat scan is indeterminate, additional imaging modalities including MRI or PET/CT can be utilized. Progression will be retroactively dated to the initial scan on which the LPD was suspected.

Distant Progressive Disease (DPD): The appearance of new unequivocal metastatic lesions on follow up imaging will denote distant progression. The finding of a new lesion must not be attributable to differences in imaging technique, change of imaging modality, or findings thought to represent something other than tumor, especially if primary target lesions shows partial or complete response. If a new lesion is equivocal but suspicious for DPD, continued follow up should be done until it becomes unequivocal. Progression will be retroactively dated to the initial scan on which the DPD was suspected.

Biochemical Response (BR): Elevated CA19-9 level will not be used to determine disease progression, but will be used to measure biochemical progression free survival (bPFS). A CA 19-9 level that decreases by 50% from pre-treatment value will be considered a biochemical response.

Biochemical Failure (BF): If the CA 19-9 level increases by 50% on 2 successive measures from the lowest recorded on study value, it will be considered biochemical failure.

10.7 Surgical and Pathologic Determination of Treatment Response

10.7.1 Evaluation of Resectability

Determination of locally advanced disease/ technically unresectable disease will be determined at diagnosis and at 6 to 8 weeks post treatment by surgical collaborators in the multidisciplinary setting. This will be generally according to the following criteria at the surgeon's discretion:

- Greater than 180 degree tumor involvement of the superior mesenteric artery
- Greater than 180 degree tumor involvement of the celiac axis, including major branches of the celiac axis that render it unresectable (e.g. common hepatic artery).
- Tumor involvement of the first branch of the SMA that is not surgically reconstructible
- Long segment involvement of the superior mesenteric vein/portal vein or hepatic artery that is not surgically reconstructible

10.7.2 Histologic Response

Should the patient undergo surgical resection, pathologic review will be performed locally to determine histologic response according to the following criteria:

- **Pathologic Complete Response (pCR)**: 0% residual tumor cells in specimen
- **Near Pathologic Complete Response (pNR)**: 1 to < 5% residual tumor cells in the specimen
- **Partial Pathologic Response (pPR)**: ≥ 5% to 30% residual tumor cells in the specimen

10.7.3 Margin Status at Resection

Margins will be assessed according to location (common bile duct, SMA or pancreatic neck) according to the following criteria:

- **R0:** Macroscopically complete tumor removal with negative microscopic surgical margins.
- **R1:** Macroscopically complete tumor removal with positive microscopic margins (any or all).
- **R2:** Macroscopically incomplete tumor removal with known or suspected residual gross disease.

10.8 Patient Reported Outcomes using PRO-CTCAE and LASA

The PRO-CTCAE and LASA items will be used to determine QOL and patient reported disease and treatment related symptoms.

We do not anticipate major differences in physical function between the two arms and various dose levels; however, the various domains of the PRO-CTCAE will help elucidate differences in short term effects of SBRT and GC4419 on patients' well-being. Higher doses of radiation may be more effective in alleviating patients' abdominal pain, nausea and obstructive symptoms.

The IRB-approved questionnaires within the protocol can be provided to patients for completion. Please include patient identifiers on all pages. At visits in which the questionaires are to be completed, the questionaires should be given to the patient before any discussion of the patient's health status or test results.

The single item linear self-assessment or LASA items for overall QOL, fatigue, mental, and physical quality of life will be used to assess the quality of life of patients randomized to each treatment arm. These single items have been demonstrated to be prognostic for survival in general cancer populations and in pancreatic cancers. These LASA items will be assessed at screening/baseline and at specified follow up visits. Overall QOL, fatigue, mental and physical quality of life will be assessed at post treatment follow-up.

Potential treatment-related symptomatic adverse events will be measured using the Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE). To improve precision and patient-centeredness in the capture of symptomatic AEs, NCI funded a team of investigators led by Dr. Basch to develop a library of patient-reported outcome (PRO) items to supplement the CTCAE, called the PRO-CTCAE. Of the 790 AEs in the CTCAE, 78 were identified as amenable to patient self-report. For each of these AEs, PRO items were created reflecting the attributes of frequency (with response options of "never", "rarely", "occasionally", "frequently", or "almost constantly"), severity ("none", "mild", "moderate", "severe", or "very severe"), interference with usual or daily activities ("not at all", "a little bit", "somewhat", "quite a bit", or "very much"), amount ("not at all", "a little bit", "somewhat", "quite a bit", or "very much"), or presence ("no" or "yes"). One to three attributes were selected for any given AE depending on the content of the CTCAE criteria for that AE and the nature of that particular AE. In total, 124 individual items represent the 78 symptomatic AEs currently in the PRO-CTCAE item library. Each item includes a plain language term for the AE, the attribute of interest, and the standard recall period of "the past 7 days." Cognitive interviews previously determined a high level of patient understanding and meaningfulness of the items and a national multi-site validation study showed that items were valid, reliable, and sensitive to change. For this study, the following symptomatic AEs selected were based on the known symptomatic toxicities occurring in >10% of patients treated with SBRT. Specifically, at the selected time points, patients will complete 15 PRO-CTCAE items measuring: Fatigue, nausea, vomiting, diarrhea,

neuropathy, abdominal discomfort, abdominal bloating, pain, heartburn, decreased appetite, dry mouth, taste changes, itching (pruritis), depression, anxiety. The recall period will be 2 weeks. AEs will be measured at baseline, end of SBRT and at follow up visits. Reporting will occur using table based technology or paper booklets, as available.

The final survey contains only 4 LASA items plus 15 PRO-CTCAE items it is anticipated that the questionnaire will take approximately 10 minutes for the patient to complete at each administration time point. We anticipate having questionnaires available in English and Spanish. Patients may decline to complete a questionnaire at any time. The primary reason for each missed questionnaire will be collected on a case report form.

11.0 END OF TREATMENT/INTERVENTION

11.1 Duration of Treatment

The treatment period will begin the first day of SBRT and GC4419/placebo treatment and end the final day of SBRT and GC4419/placebo treatment.

Patients may *not* receive additional anti-cancer therapy during the 90 day follow up period, except in the instance of progression of disease. After 90 days, patients may receive therapy at the treating physician's discretion. Any anti-cancer therapy should be recorded in the case report form.

11.2 Managing ineligible patients and registered patients who never receive protocol intervention

Patients who are randomized but later deemed ineligible for SBRT or voluntarily withdraw from the study will still be eligible for follow up imaging and correlative studies, in addition to PRO data, should they so choose. These patients will not be considered in the n=48 patients to be randomized, and will not be considered in the final analyses for primary and secondary endpoints. The reason for not receiving protocol intervention must be documented.

11.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on the case report forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Primary Endpoint

For the purposes of dose finding the following definitions will be used in determining MTD:

- **Toxicity:** CTCAE grade 3 or 4 related gastro-intestinal (GI) toxicity or death, occurring within 90 days from the start of therapy.
- **Efficacy**: Radiographic stable disease (SD) or better based on modified RECIST criteria, (section 10.6.4), compared to baseline imaging of the same type, as evaluated at day 90 from the start of therapy.
    - If a patient dies or has local progressive disease (LPD) at some time t* prior to day 90, then Efficacy will be scored at the time t* as not occurring for that patient.
    - If a patient undergoes resection at some time t* prior to day 90, then Efficacy will be scored as occurring at t* and Toxicity will be scored as not occurring within 90 days for that patient.

Prior to determination of final MTD, 12 month toxicity will also be evaluated. If any dose level demonstrates >20% grade 4 or 5 gastrointestinal toxicity related to radiation, the preceding dose level will be used as the final MTD.

12.2 Prior Probabilities

An adaptive design requires prior mean probabilities of efficacy and toxicity at each dose level. These estimates were determined in collaboration by all study investigators based on all available SBRT dose escalation studies, as discussed in section 1.2.5, with particular weight placed on more modern studies using modern radiation techniques. Table 5 outlines the prior mean probabilities for each dose level.

Table 5. Prior mean probabilities of efficacy and toxicity for each dose level of interest.

Dose Level	PTV2 BED[a] (a/B = 10)	Prior mean efficacy probability	Prior mean toxicity probability
1	100 Gy	75%	2%
2	115.5 Gy	85%	7%
3	132 Gy	95%	10%

12.3 Randomization and Sample Size

A maximum of 2x24 = 48 patients will be randomized between two subgroups. Patients in subgroup 1 will receive GC4419 in combination with their assigned RT dose, and patients in subgroup 0 will receive their assigned RT dose and placebo (no GC4419). The randomization will be restricted so that the sample size within each subgroup is exactly 24 patients. The restricted randomization sequence will be constructed prior to trial initiation, and applied by the Statistical

Analyst overseeing the trial treatment and RT dose assignments. An overall accrual rate of approximately 3 patients per month is anticipated, which will give approximately 1.5 patients per month in each subgroup.

12.4 Phase I-II Dose Finding Design

Dose-finding will be done using the sequentially adaptive phase I-II Late onset Efficacy-Toxicity (LO-ET) trade-off-based design[33-35]. For the purpose of dose-finding, as stated in section 12.1:

- **Toxicity** is defined as a grade 3 or 4 gastro-intestinal (GI) toxicity, or death, occurring within 90 days from the start of therapy. For the purpose of dose-finding
- **Efficacy** is defined as stable disease (SD) or better, compared to baseline, as evaluated at day 90 from the start of therapy (section 10.6.4).

12.5 Maximum Sub-sample Size and Cohort Size

The same adaptive dose-finding design will be used in each of the two subgroups. Within each subgroup, up to 24 patients will be treated in 8 cohorts of size 3 each. The first cohort will be treated at dose level 1, all successive doses will be chosen by the LO-ET method to maximize the posterior Efficacy-Toxicity trade-off, and an untried dose level (dose level 2) may not be skipped when escalating initially.

12.6 Dose Acceptability

For the two LO-ET dose acceptability rules, the upper limit on the probability of Toxicity is 0.15, the minimum probability of Efficacy 0.75, and the decision cut-offs 0.10 will be used or both stopping probability criteria. If the lowest dose level is found to be unacceptable in terms of high toxicity, or if the highest dose level is found to be unacceptable in terms of low efficacy, the trial will be terminated and no dose level will be selected. Accrual will only be paused before proceeding to the highest dose level. Dose level 1 has been safely used previously so there will be no pause in accrual.

12.7 Efficacy-Toxicity Trade-Off Contours and Priors

The three equivalent trade-off (pE, pT) probability pairs used for computing the trade-off contours are (0.60, 0), (0.75, 0.15), (1, 0.40). The prior hyper-parameters were computed based on the assumed prior means Prob(Efficacy | dose) = 0.75, 0.85, 0.95 and Prob(Toxicity | dose) = 0.02, 0.07, 0.10, respectively, at the three RT dose levels. The prior effective sample size = 1 for the toxicity parameter prior and 1 for the efficacy parameter prior. This is illustrated in Figure 11.

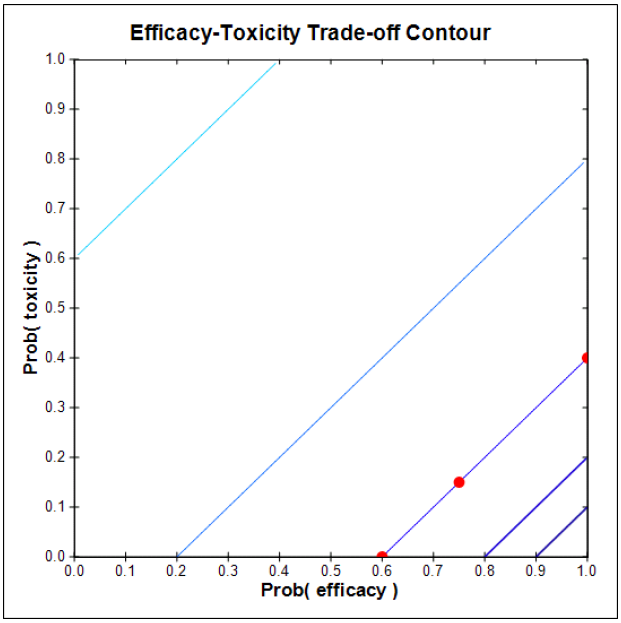

Figure **11**. Efficacy-Toxicity Trade-Off Contours for the Current Study based on assumed prior means Prob(Efficacy | dose) = 0.75, 0.85, 0.95 and Prob(Toxicity | dose) = 0.02, 0.07, 0.10, respectively, at the three RT dose levels.

12.8 Design Operating Characteristics

Operating characteristics of the design, as conducted within each subgroup, are summarized in table 6 below, based on simulations with 1000 replications per scenario. In the simulations, it is assumed that the times to toxicity and efficacy follow Weibull distributions, the percentage of toxicity (or efficacy) events occurring in the later half of each evaluation interval is 50%, and the accrual rate is 1.5 patients per month. The maximum sample size is 24, with up to 8 cohorts of size 3.

Table 6. Design Operating Characteristics of the current study with 24 patients per arm, 3 dose levels, and accrual rate of 1.5 patients per month, based on simulations with 1000 replications per scenario, assuming toxicity and efficacy follow Weibull distributions.

Scenario		**SBRT Dose level**		
		1	2	3
1	True toxicity probability	005	0.06	**0.07**
	True Response probability	0.50	0.70	**0.85**
	Selection percentage	0.20	18.5	**74.9**
	Average number of patients	4.7	8.3	**10.1**
2	True toxicity probability	0.02	**0.08**	0.30
	True response probability	0.60	**0.80**	0.90
	Selection percentage	2.3	**67.0**	24.6
	Average number of patients	5.9	**12.2**	5.4
3	True toxicity probability	**0.10**	0.30	0.46
	True response probability	**0.90**	0.92	0.94
	Selection percentage	**80.9**	9.3	0.2
	Average number of patients	**15.1**	4.5	0.8
4	True toxicity probability	0.02	0.04	0.05
(poor efficacy)	True response probability	0.20	0.30	0.40
	Selection percentage	0	0.1	3.4
	Average number of patients	3.5	3.7	8.9
5	True toxicity probability	0.35	0.45	0.60
(excessive toxicity)	True response probability	0.50	0.70	0.85
	Selection percentage	0.1	0.4	0.1
	Average number of patients	4.9	3.5	1.1

Based on these simulations, should all dose levels in any treatment arm demonstrate > 15% probability of grade 3 or higher toxicity based on prior probabilities and enrolled patients, the study arm will terminate in approximately 6 months with 5, 4 and 1 patients assigned to dose levels 1,2 and 3, respectively. Should all dose levels in any treatment arm demonstrate < 75 % probability of

stable/responsive disease, the study arm will terminate in approximately 12 months with 4, 4 and 9 patients assigned to dose levels 1,2 and 3, respectively. Should dose level 3 be the MTD, the study will accrue to completion (approximately 16 months) with 5, 8 and 10 patients assigned to dose levels 1, 2, and 3, respectively. Should dose level 2 be the MTD, the study will accrue to completion (approximately 16 months) with 6, 12 and 5 patients assigned to dose levels 1, 2 and 3 respectively. In this scenario, dose limiting toxicity (DLT) would have to occur in a minimum of 2/5 patients treated at dose level 3. Should dose level 1 be the MTD, the study will accrue to completion (approximately 16 months) with 15, 5 and 1 patients assigned to dose levels 1, 2 and 3 respectively. Again, in this scenario, DLT would have to occur in a minimum of 2/5 patients treated at dose level 2.

12.9 Implementation

12.9.1 LO-ET Trial Implementation

The Late-Onset Efficacy-Toxicity (LO-ET) design will be implemented using the specialized computer program developed by Jin et al.[35] During trial conduct, application of the statistical design will be carried by Rebecca Slack, a Statistical Analyst in the Department of Biostatistics. This will include (1) randomization of each patient at entry between the two arms, RT+ GC4419 versus RT only, and (2) adaptive dose assignment within each arm using the LO-ET method. Outcome-adaptive dose-finding will be done by inputing the current trial data and running the specialized computer program that implements the LO-ET method. This process will require close interaction between Ms. Slack and personnel in the clinic, including repeatedly providing Ms. Slack with all dose-outcome data from all previously enrolled patients, including each previous patient's time of Toxicity occurrence or current follow up time without Toxicity, up to the defined 90-day observation interval, and whether efficacy occurred at day 90. Critical variable data (provided within your Study Manual) should be entered into the electronic data capture clinical database in a timely fashion to ensure data is included in the ongoing analysis for SBRT dose level assignments. Xuemi Wang, a Senior Statistical in the Department of Biostatistics, will serve as a backup for Ms. Slack in the process of trial conduct. Additional statistical support or input will be provided as required by Drs. Peter Thall and Ying Yuan[33,34,36,37]. Details and procedures related to the various safety, efficacy, and correlative analyses will be provided in a formal Statistical Analysis Plan.

12.9.2 Secondary Endpoints and Analysis

Secondary outcomes will include progression-free survival (PFS) time and overall response rate in addition to rate of long-term toxicity, surgical resection and rates of R0 and pathologic complete response at resection. Unadjusted distributions of the time-to-event outcomes PFS and OS will be estimated using the method of Kaplan and Meier and their relationship to prognostic covariates and RT cell dose level will be evaluated by Bayesian piecewise exponential survival regression.

Resectability will be assessed at the seven week time point. If a patient goes on to resection, he or she will be categorized as acceptable efficacy. If the patient is deemed unresectable, efficacy will be reassessed at 12 weeks. Toxicity will also be assessed at the 12 week timepoint and descriptive statistics will be generated. If endoscopy exhibits severe toxicity, the patient will be deemed as unacceptable toxicity.

12.9.3 Interim Analysis

The sponsor was unblinded to treatment assignment for overall study monitoring and safety review. One unblinded interim descriptive efficacy analysis will be performed for study design planning on the first 19 subjects. To facilitate future study design planning with investigators, interim efficacy results on those first 19 subjects will be provided to participating investigators. Subsequent to the single completed interim analysis by the sponsor, no unblinded efficacy analysis will be performed until the final statistical analysis. Investigators and supporting staff will remain blinded to randomized treatment assignments for patients 20-48, with only unblinded staff being site pharmacists, MDACC statisticians, and limited sponsor staff relative to study management and routine safety oversight.

13.0 CORRELATIVE STUDIES

13.1 Imaging Correlative Studies

In addition to CT based imaging, patients may also undergo baseline and follow up MRI scans in order to better assess toxicity and tumor response. With improved technology, MRI based techniques are increasingly used in the inflammatory bowel setting for improved evaluation and monitoring of the mucosa[38]. The small bowel is particularly a challenging organ for MRI imaging due to mobility, distention and contrast. Biphasic oral contrast agents have been shown to help us better evaluate the mucosal lining in IBD[38]. They allow for the mucosal enhancement on T1 and T2 weighted images leading to a drastic contrast between the wall and the lumen allowing for more detailed evaluation of the fold and wall thickness for inflammation following SBRT. In addition to oral contrast agents, iv gadolinium and fat suppression can further help highlight tissue edema on T2 weighted imaging[38].

There is an abundance of literature highlighting the benefits of MR imaging in the evaluation of bowel mucosal inflammation and edema in IBD[38,39]. We aim to use similar MR techniques in order to evaluate toxicity and efficacy from SBRT. Patients may undergo baseline MRI post-induction chemotherapy and prior to initiation of SBRT. They may then undergo MRI abdomen/pelvis approximately 12 weeks following completion of SBRT. MRI characteristics will be associated with efficacy findings at 12 weeks. In case of contraindications (eg pacemaker, severe claustrophobia, etc) a high quality CT scan can be acquired.

13.2 Pathologic and Biomarker Correlative Studies

13.2.1 Background and Rationale

While targeted therapies and immunotherapies have provided significant advances in other cancer types with poor prognoses, including non-small cell lung cancer and melanoma, none of these therapies have provided significant advances in LAPC. There are a multitude of reasons for this, but primarily we have inadequate data regarding the genomics, proteomics, immune microenvironment, and tumor microenvironment surrounding these tumors. Although patients who undergo surgical resection (20% of all patients with PAC), analyses have been limited in patients with LAPC and metastatic pancreatic cancer (MPC) by the fact that the majority of these patients undergo only a fine needle aspiration (FNA) at time of diagnostic endoscopy. FNA samples exhibit cellular paucity in the range of <100 cells per sample, in addition to the fact that they are often contaminated with normal cells from duodenum and stomach in addition to tumor cells due to the endoscopic technique, making any type of high throughput sequencing a logistic challenge. Although technologies have advanced to allow sequencing with smaller volumes of extracted DNA[40,41], the question of tumor purity from these samples for sequencing purposes remains without any adequate studies with paired FNA and core needle biopsy (CNB) samples.

The second limitation of development of targeted therapies in LAPC is the fact that PAC remains one of the most heterogeneous cancer types currently understood, and it exhibits rapid changes in its genomic structure. Although common mutations exist, such as in KRAS and BRAF, PAC also exhibits a high frequency of alterations in a multitude of other pathways, including Wnt signaling, chromatin remodeling, Hedgehog signaling, DNA repair and cell cycle maintenance[42-46].

Metastatic lesions demonstrate even further genetic heterogeneity, with indications that metastatic lesions develop late in the genetic progression, despite the fact that 30% of patients present initially with MPC,[47,48] making targeted therapies less likely to work. Additionally, PAC is unique in that tumors exhibit a high stromal component made up of dense fibrotic tissue, immune cells and vascular structures, which limits drug delivery to the tumor and appears to interact with the tumor and both encourage and discourage growth through pathways which are not yet clearly understood[49]. While some models demonstrate that removal of the stroma leads to poor prognosis, aggressive tumor survival and decreased overall survival[50,51], others demonstrate that removal of the stroma may increase drug delivery and treatment response[52]. Despite strong evidence that immune environment plays a strong role in PAC carcinogenesis and phenotype in both clinical and pre-clinical data[53-56] PAC has overall demonstrated disappointing response to vaccine and immunotherapy. This may in part be due to pancreatic stromal microenvironment, although the mechanism is unclear.

Currently, one of the unclear clinical questions in the management of both LAPC patients and resected PAC patients is whether these patients benefit from radiation therapy. Although prospective studies in the modern era have failed to show a benefit of chemoradiation over chemotherapy alone in either setting, there are clearly patients who benefit from the local control of tumor provided by radiation, and patients who go on to develop local progression in the absence of metastatic disease. Previous studies show that as high as 30% of PAC patients may die from local disease progression alone in the absence of metastatic disease[4-6]. The development of biomarkers that could help identify these patients with an isolated local failure phenotype versus a propensity for development of metastatic disease would be a clinical game-changer in the setting of BRPC and LAPC, helping clinicians to select patients who would benefit from aggressive local therapy, including high dose, focused radiation therapy, potentially with a radiomodulator drug, versus those who would benefit from intensive systemic or targeted therapy to control risk of metastatic disease. Additionally, in the unique setting of a prospective radiation therapy study, evaluating biomarkers for likelihood of response to high dose radiation may help identify those more likely to respond and thus benefit from high dose radiation therapy.

Table 7. Study Calendar for Collection of Correlative Samples

Timepoint	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Day of Treatment*	Pre-SBRT	Day 1	Day 2	Day 3	Day 4	Day 5	4 weeks Post SBRT	7 weeks Post SBRT	Resection	12 weeks Post SBRT
Blood (1)	X		X			X	X(2)	X	X (6)	X
FNA	X									X
Core Biopsy (CNB)	X									X
Cytology	X									X
Imaging (4)	X							X		X
Resection Specimen (RS)									X (6)	

* The same study windows will apply as noted in the Study Calendar, section 5.0

1 If blood is being taken at the time of infusion of GC4419 or placebo, samples should be collected prior to dosing at the time of intravenous access. Otherwise, there is no restriction on when blood can be drawn as long as it is within the indicated window of time.

2 Optional blood draws at week 4 and follow-up

3 FNA and Core biopsy will not be taken at 3 month endoscopy if any sign of radiation damage is visualized

4 Fresh and FFPE Core needle biopsy specimens

5 Imaging consists of baseline MRI and/or triphasic CT

6 If patient undergoes resection, fresh and frozen tissue collected at time of resection in addition to standard histopathology for evaluation of treatment response

13.2.2 Sample Collection Calendar

Longitudinal patient samples will be collected at each participating center, according to the calendar in Table 7. Participating centers will send samples to UTMDACC Zayed as outlined in the Correlative Laboratory Manual. These samples will be maintained through the UTMDACC Zayed Pancreas Center or the Adaptive Patient-Oriented Longitudinal Learning and Optimization (APOLLO) platform and analyzed in-house. Patients reserve the right to refuse sample or blood collection at any time point and will remain enrolled on the protocol for treatment outcome analysis.

13.2.3 Pathologic Biomarker Correlates

This section includes FNA samples collected at time point 1 and 10, Core biopsy specimens collected at time point 1 and 10, and potential tissue collected at time point 9.

13.2.3.1 Collection, Storage and Maintenance of Samples

See tables 8-9 for collection methodology of each sample.

Table 8. Collection, Storage and Maintenance of Tissue Correlate Samples

Source	Collection	MDACC Storage and Maintenance	Other Institutions	Purpose
FNA	Aspiration using 25-guage needle, placed immediately into 1.5ml microcentrifuge tube in 1ml of normal saline and kept on ice for transport	Fresh to be processed for DNA extraction within 30 minutes, FFPE stored for future microdissection	Snap frozen and stored at -80; Shipped to MDACC en batch after coordination with MDACC Lead Study Investigator	Sequencing correlations to CNB
CNB	A minimum of two CNB's will be obtained during fiducial placement using an 18-guage Tru-Cut biopsy needle; Fresh to be kept on ice for transport, FFPE for storage	Fresh to be processed for DNA extraction and organoid development within 30 minutes, FFPE stored for future studies	Snap frozen and stored at -80; Shipped to MDACC en batch after coordination with MDACC Lead Study Investigator	Organoid development, Whole exome/ transcriptome, Immune profiling
RS	Intraoperative specimen collection will be performed of Fresh/ frozen tissue. FFPE tissue will be obtained after pathologic assessment	Fresh to be processed for DNA extraction within 30 minutes, FFPE stored for future	If available after pathologic assessment, FFPE will be shipped to MDACC after coordination with MDACC Lead Study Investigator	Sequencing, immune correlates

13.2.3.2 Planned/ Potential Analyses

- Organoid development
- Whole exome sequencing
- Whole transcriptome sequencing

13.2.4 Serum Biomarker Correlates

This section includes all blood samples collected at time points 1, 3, 6, 7, 8, 9 and 10.

Table 9. Collection, Storage and Maintenance of Correlate Samples

Timepoint	Collection	MDACC Storage and Maintenance	Other Institutions	Purpose
Plasma	One 5-10mL EDTA (Lavender top) tube at each time point	Centrifuged at 3,500 rpm for 15 minutes at 4°C within 3 hours of blood draw, stored at -80°C until use	Blood samples will be processed for plasma according to institutional standards and frozen at -80°C; Shipped to MDACC en batch after coordination with MDACC Lead Study InvestigatorI	ctDNA, exosomal DNA
Whole Blood	Two 5-10mL EDTA (Lavender top) tube at each time point	One tube to be maintained as fresh and stored cold to isolate PBMC's within 12 hours Second tube to be stored for future studies		Immune profiling, Whole exome sequencing

13.2.4.1 Planned/ Potential Analyses

Circulating tumor DNA/ Cell free (including exosomes) DNA: Peitrasz et al recently demonstrated that plasma circulating tumor DNA (ctDNA, or cell free DNA) may play a role as a prognostic marker in PAC. In this study, 48% of patients with locally advanced PAC demonstrated detectable ctDNA with a median mutation allelic frequency (MAF) of 6.1%. The presence of ctDNA was strongly correlated with overall survival, as was the MAF for individual patients57. In this study, we will have the opportunity to exploratorily examine the effect of SBRT on ctDNA levels and the potential utility of ctDNA as a prognostic factor for conversion to surgical resection and overall survival of patients undergoing SBRT for BRPC and LAPC.

13.2.5 Immune Correlates

In addition to the CNB and FNA samples collected during endoscopy, endoscopic brushings will be collected of the pancreatic tumor. These brushings will be analyzed using multiparametric flow cytometry (MPFC) for markers of immune proliferation, activation and exhaustion phenotypes.

Changes in the immune microenvironment with SBRT for pancreatic cancer have not been studied, nor has the interaction of the immune microenvironment on response of PAC to radiation therapy. These exploratory analyses will provide pilot data regarding the best methodology to assess immune environment in PAC.

13.2.5.1 Planned/ Potential Analyses

- T cell receptor profiling: Deep T-cell receptor β sequencing (TCR) has been used to predict response to immunotherapy and vaccine therapy in other tumor types, including melanoma, lung cancer, prostate and breast cancer[58-61]. We have been successfully using this technology to analyze cervical and anal cancers using DNA extracted from a non-invasive swab biopsy technique, and the ability to reliably detect T cell profiles using minimum DNA would allow new insight into predictors of the generation of a robust anti-tumor immune response stimulated by radiation in LAPC that may not be present with traditional fractionated radiation. TCR will be used to detect clonal amplification and density of intratumoral T-cells.

- Immunohistochemistry immune profiling
- Multiparametric flow cytometry (MPFC): Using cytology brushings, our group has previously used MPFC to characterize changes in immune profiles using cytobrush swabs of cervical and anal cancers. Cells collected from cytobrushes were stained with antibodies to CD3, CD4, CD8, ICOS, CTLA-4, Ki67, PD-1, FoxP3 and Fixable Aqua Dead Cell stain and analyzed by flow cytometry. Comprehensive analysis of TIL by flow cytometry will allow assessment of effector T cell ratios relative to Treg and MDSC, as well as phenotypic and functional analysis of multiple T, NK, and myeloid cell subsets.
- Peripheral Immune profiling: Static immune profiling in other tumor types demonstrates the presence of changes in immune markers, but it is unclear whether these changes are reflective of radiation induced generation of tumor specific immune response or a response to radiation induced direct cell killing. The only way to determine this is through the use of longitudinal immune assays through the course of radiation. Moreover, recent hypotheses suggest that the immune response of radiation may be optimized through a one week “package time” and that longer course of radiation may lead to adverse effects on immunogenic cell death (ICD) from radiation, in addition to a suggestion that larger single fraction sizes may increase ICD[62-65]. If this is true, we may see increased immune activation with SBRT, and this effect may change with increased doses. Performing exploratory peripheral immune profiling using deep TCR and MPFC will allow us to better characterize these fluid immune changes**.**

13.2.6 Specimen Storage for Future Studies

All remaining specimens will be maintained with the MDACC lead study investigator for use in future correlative and biomarker analyses.

14.0 GENERAL REGULATORY CONSIDERATIONS

14.1 Institutional Regulatory Approval

The study must be approved by the participating center's Institutional Review Board (IRB) and any research committee as require per institutional policy. The trial will be conducted according to all institutional IRB and if applicable, any local research committee guidelines. All modifications or amendments to the protocol will go through IRB review.

14.2 Informed Consent

Subjects, after having the study explained to them and an opportunity to have their questions answered sufficiently, will give voluntary and written informed consent (in compliance with ICH E6, 4.8 and 21 CFR Parts 50 and 312) before participating in any study-related procedures.

In addition to obtaining informed consent/assent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent/assent process shall be recorded in source documents. Signed copies of the informed consent and/or assent will be given to the Subject and originals will be placed in the Investigator study files.

14.3 Publication

All publication or presentation rights for the findings of the clinical study shall be governed by the appropriate terms of the Clinical Research Agreement between the investigational site and Galera Therapeutics Inc. in collaboration with the lead investigator site (UTMDACC)

14.4 Data Analysis

All data will be maintained within an electronic data capture system at Galera and UTMDACC throughout the duration of the study, and all analysis will be performed by Galera or UTMDACC statisticians. The data will be available to UTMDACC researchers for any future correlative or collaborative studies and publications.

14.5 Study Monitoring

The study will be monitored and managed in accordance with ICH GCP E6. Galera Therapeutics, Inc. or its representatives will monitor each Investigator site for study progress and to verify that standards of GCP were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms and other study related documents are readily available for review.

Galera Quality Assurance or its representatives and Regulatory agencies may conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

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16.0 SUMMARY OF CHANGES

The GTI-4419-101 Protocol Amendment 06, dated 26November2019, is replaced by this Protocol Amendment 07, dated 24January2020.

Listed below are a summary of substantive changes incorporated into Amendment 07. Administrative changes, such as cross-linking and typographical/grammatical corrections have also been made, which may not be summarized. (Note: The page numbers in the final version may not match exactly the page numbers in the redline version due to the listing of previous and new text).

Section Number(s)	Section Title(s)	Description of Change (s)	Rationale
Synopsis and 4.6.2	Synopsis and Patient Registration and Randomization	Registration process updated.	Streamline process for multi-center study.
Section 3.4 and 12.9.3	Randomization and Blinding	Language added to support interim analysis as follows: The sponsor was unblinded to treatment assignment for overall study monitoring and safety review. One unblinded interim descriptive efficacy analysis will be performed for study design planning on the first 19 subjects. To facilitate future study design planning with investigators, interim efficacy results on those first 19 subjects will be provided to participating investigators. Subsequent to the single completed interim analysis by the sponsor, no unblinded efficacy analysis will be performed until the final statistical analysis. Investigators and supporting staff will remain blinded to randomized treatment assignments for patients 20-48, with only unblinded staff being site pharmacists, MDACC statisticians, and limited sponsor staff relative to study management and routine safety oversight.	An Interim Analysis is now included to support future study design planning for the next phase of development.

Synopsis and Section 4.1	Inclusion Criteria	Criteria #5 modified to allow prior chemotherapy regimen requirements as judged by the treating physician	
Synopsis and Section 4.1	Inclusion Criteria	Criteria #11 modified to streamline the laboratory requirements for patient evaluation for eligibility with regard to liver function, which aligns with standard practice.	• Many patients experience moderate organ/bone marrow dysfunction following induction chemotherapy. • Alkaline phosphatase is not a standard or reliable indicator of liver function. • There has been no evidence to date of hepatotoxicity of GC4419. • Relevant conditions that would be reflected in an increased alkaline phosphatase would also be indicated by increased bilirubin, for which an exclusion criterion is retained.
Section 5.0	Study Calendar	Administrative clarifications made to footnotes 1 and †	Clarifications to requirements for scan and toxicity follow-up.
Section 6.1.2	Technical Factors including Treatment Delivery and Fiducial Placement	Lanugage updated to allow fiduals and simulation on the same day	Ease burden on patient and allow same day procedures. Delay is not always necessary and imaging on the same day is feasible and does not change the outcome.
Section 10.6.4	Response Criteria Definition	LPD language updated to clarify timepoints for scans required in the case of potential pseduprogression at 6-8 weeks.	Language provides more detail with regard to timepoints and how to categorize possible PD at 6-8 weeks.

17.0 Appendix 1: PRO and LASA

1. LASA – English and Spanish

2017-0606

APPENDIX I: REGISTRATION QOL/MENTAL WELL-BEING/FATIGUE AND PRO-CTCAE MEASURES

Registration QOL/Mental Well-being/Physical Well-being/Fatigue

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

1. your overall qualify of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

2. your overall mental (intellectual) well being in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

3. your overall physical well being in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

4. your level of fatigue, on average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No fatigue										Fatigue as bad as it can be

99

Version Date: 10/13/2017 Update #01

APÉNDICE I: MEDIDAS DE QOL/BIENESTAR MENTAL/FATIGA Y PRO-CTCAE AL REGISTRARSE

QOL/bienestar mental/bienestar físico/fatiga al registrarse

Durante el registro de pacientes, este formulario debe ser entregado por una enfermera o asistente de investigación clínica (CRA), completado por el paciente e ingresado en una base de datos de REDCap.

Si es necesario, este Apéndice puede adaptarse para ser utilizado como documento fuente.
No existe ningún folleto que contenga esta evaluación. Por favor no lo solicite.

¿Cómo describiría…

1. su calidad de vida general durante la última semana, incluido el día de hoy?

0 1 2 3 4 5 6 7 8 9 10

Muy mala Muy buena

2. su bienestar mental (intelectual) general durante la última semana, incluido el día de hoy?

0 1 2 3 4 5 6 7 8 9 10

Muy mala Muy buena

3. su bienestar físico general durante la última semana, incluido el día de hoy?

0 1 2 3 4 5 6 7 8 9 10

Muy mala Muy buena

4. su nivel de fatiga, en promedio, durante la última semana, incluido el día de hoy?

0 1 2 3 4 5 6 7 8 9 10

Sin fatiga Muchísima fatiga

2. NCI PRO-CTCAE Items – English and Spanish

NCI PRO-CTCAE™ Items - English
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As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
4.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
6.	In the last 7 days, how OFTEN did you have HEARTBURN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

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7.	In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

8.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

9.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ Never	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

11.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

12.	In the last 7 days, how OFTEN did you have PAIN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	○ Never	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ Items - English
Item Library Version 1.0

13.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

14.	In the last 7 days, how OFTEN did you feel ANXIETY?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

15.	In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTEFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ Items - English
Item Library Version 1.0

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

NCI PRO-CTCAETM Items - Spanish
Item Library Version 1.0

Los pacientes que reciben tratamiento para el cáncer a menudo presentan ciertos síntomas y efectos secundarios. Para cada pregunta, haga una marca o escriba una en la casilla que mejor describe sus experiencias en los últimos siete días…

1.	En los últimos 7 días, ¿cuál fue la INTENSIDAD de la SEQUEDAD EN LA BOCA en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
2.	En los últimos 7 días, ¿cuál fue la INTENSIDAD de los PROBLEMAS PARA NOTAR EL SABOR DE LAS COMIDAS O LAS BEBIDAS en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
3.	En los últimos 7 días, ¿cuál fue la INTENSIDAD de la DISMINUCIÓN DEL APETITO en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
	En los últimos 7 días, ¿cuánto INTERFIRIÓ la DISMINUCIÓN DEL APETITO en sus actividades habituales o diarias?				
	○ Nada	○ Un poco	○ Algo	○ Muco	○ Muchísimo
4.	En los últimos 7 días, ¿con qué FRECUENCIA tuvo NÁUSEAS?				
	○ Nunca	○ Rara vez	○ A veces	○ A menudo	○ Casi siempre
	En los últimos 7 días, ¿cuál fue la INTENSIDAD de las NÁUSEAS en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
5.	En los últimos 7 días, ¿con qué FRECUENCIA tuvo VÓMITOS?				
	○ Nunca	○ Rara vez	○ A veces	○ A menudo	○ Casi siempre
	En los últimos 7 días, ¿cuál fue la INTENSIDAD de los VÓMITOS en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
6.	En los últimos 7 días, ¿con qué FRECUENCIA tuvo ACIDEZ ESTOMACAL?				
	○ Nunca	○ Rara vez	○ A veces	○ A menudo	○ Casi siempre
	En los últimos 7 días, ¿cuál fue la INTENSIDAD de la ACIDEZ ESTOMACAL en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa

NCI PRO-CTCAETM Items - Spanish
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7.	En los últimos 7 días, ¿con qué FRECUENCIA tuvo HINCHAZÓN DEL ABDOMEN (EN EL VIENTRE)?				
	○ Nunca	○ Rara vez	○ A veces	○ A menudo	○ Casi siempre
	En los últimos 7 días, ¿cuál fue la INTENSIDAD de la HINCHAZÓN DEL ABDOMEN (EN EL VIENTRE) en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa

8.	En los últimos 7 días, ¿con qué FRECUENCIA tuvo HECES O EXCREMENTOS SUELTOS O LÍQUIDOS (DIARREA)?				
	○ Nunca	○ Rara vez	○ A veces	○ A menudo	○ Casi siempre

9.	En los últimos 7 días, ¿con qué FRECUENCIA tuvo DOLOR EN EL ABDOMEN (EL VIENTRE)?				
	○ Nunca	○ Rara vez	○ A veces	○ A menudo	○ Casi siempre
	En los últimos 7 días, ¿cuál fue la INTENSIDAD del DOLOR EN EL ABDOMEN (EL VIENTRE) en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
	En los últimos 7 días, ¿cuánto INTERFIRIÓ el DOLOR EN EL ABDOMEN (EL VIENTRE) en sus actividades habituales o diarias?				
	○ Nada	○ Un poco	○ Algo	○ Muco	○ Muchísimo

10.	En los últimos 7 días, ¿cuál fue la INTENSIDAD de la PICAZÓN (COMEZÓN) EN LA PIEL en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa

11.	En los últimos 7 días, ¿cuál fue la INTENSIDAD del ADORMECIMIENTO O DEL HORMIGUEO EN LAS MANOS O EN LOS PIES en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
	En los últimos 7 días, ¿cuánto INTERFIRIERON el ADORMECIMIENTO O EL HORMIGUEO EN LAS MANOS O EN LOS PIES en sus actividades habituales o diarias?				
	○ Nada	○ Un poco	○ Algo	○ Muco	○ Muchísimo

NCI PRO-CTCAETM Items - Spanish
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12.	En los últimos 7 días, ¿con qué FRECUENCIA tuvo DOLOR?				
	○ Nunca	○ Rara vez	○ A veces	○ A menudo	○ Casi siempre
	En los últimos 7 días, ¿cuál fue la INTENSIDAD del DOLOR en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
	En los últimos 7 días, ¿cuánto INTERFIRIÓ el DOLOR en sus actividades habituales o diarias?				
	○ Nada	○ Un poco	○ Algo	○ Muco	○ Muchísimo

13.	En los últimos 7 días, ¿cuál fue la INTENSIDAD del AGOTAMIENTO, EL CANSANCIO O LA FALTA DE ENERGÍA en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
	En los últimos 7 días, ¿cuánto INTERFIRIERON EL AGOTAMIENTO, EL CANSANCIO O LA FALTA DE ENERGÍA en sus actividades habituales o diarias?				
	○ Nada	○ Un poco	○ Algo	○ Muco	○ Muchísimo

14.	En los últimos 7 días, ¿con qué FRECUENCIA SINTIÓ ANSIEDAD?				
	○ Nunca	○ Rara vez	○ A veces	○ A menudo	○ Casi siempre
	En los últimos 7 días, ¿cuál fue la INTENSIDAD de la ANSIEDAD en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
	En los últimos 7 días, ¿cuánto INTERFIRIÓ la ANSIEDAD en sus actividades habituales o diarias?				
	○ Nada	○ Un poco	○ Algo	○ Muco	○ Muchísimo

15.	En los últimos 7 días, ¿con qué FRECUENCIA tuvo SENTIMIENTOS DE TRISTEZA O DE NO ESTAR FELIZ?				
	○ Nunca	○ Rara vez	○ A veces	○ A menudo	○ Casi siempre
	En los últimos 7 días, ¿cuál fue la INTENSIDAD de los SENTIMIENTOS DE TRISTEZA O DE NO ESTAR FELIZ en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
	En los últimos 7 días, ¿cuánto INTERFIRIERON los SENTIMIENTOS DE TRISTEZA O DE NO ESTAR FELIZ en sus actividades habituales o diarias?				
	○ Nada	○ Un poco	○ Algo	○ Muco	○ Muchísimo

NCI PRO-CTCAETM Items - Spanish
Item Library Version 1.0

¿Presenta otros síntomas de los que desea informar?	
○ Sí	○ No

Haga una lista de cualquier otro síntoma:

1.	En los últimos 7 días, ¿cuál fue la INTENSIDAD de este síntoma en su PEOR momento?				
	○ Ninguna	○ Leve	○ Moderada	○ Intensa	○ Muy intensa
2.	En los últimos 7 días, ¿cuál fue la INTENSIDAD de este síntoma en su PEOR momento?				
	○ Ninguna	○ Ninguna	○ Ninguna	○ Ninguna	○ Ninguna
3.	En los últimos 7 días, ¿cuál fue la INTENSIDAD de este síntoma en su PEOR momento?				
	○ Ninguna	○ Ninguna	○ Ninguna	○ Ninguna	○ Ninguna
4.	En los últimos 7 días, ¿cuál fue la INTENSIDAD de este síntoma en su PEOR momento?				
	○ Ninguna	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	En los últimos 7 días, ¿cuál fue la INTENSIDAD de este síntoma en su PEOR momento?				
	○ Ninguna	○ Ninguna	○ Ninguna	○ Ninguna	○ Ninguna