CLINICAL STUDY PROTOCOL

Protocol Title:		GRECO-2: A Randomized, Phase 2b Study of Stereotactic Body Radiation Therapy (SBRT) in combination with GC4711 in the Treatment of Unresectable or Borderline Resectable, Nonmetastatic Pancreatic Cancer	
Protocol Number:		GTI-4711-201	
Compound:		GC4711	
Sponsor	**Sponsor Name:**	Galera Therapeutics Inc.	
	Legal Registered Address:	45 Liberty Blvd, Suite 230, Malvern, PA 19355	
Regulatory Agency Identifier Number(s)		152586	
Protocol Date:		**Document Version**	**Date**
		Amendment 6.0	08 OCT 2023

CONFIDENTIALITY NOTICE

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Study Acknowledgement

GRECO-2: A Randomized, Phase 2b Study of Stereotactic Body Radiation Therapy (SBRT) in combination with GC4711 in the Treatment of Unresectable or Borderline Resectable, Nonmetastatic Pancreatic Cancer

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

_____

J. Mel Sorensen, MD
Chief Executive Officer
Galera Therapeutics, Inc.

Investigator Statement

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

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

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

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

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

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

_____ _____

Signature of Principal Investigator Date (DD MMM YYYY)

_____

Printed Name of Principal Investigator

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1 CLINICAL STUDY SYNOPSIS

Title of Study:

GRECO-2: A Randomized, Phase 2b Study of Stereotactic Body Radiation Therapy (SBRT) in combination with GC4711 in the Treatment of Unresectable or Borderline Resectable Nonmetastatic Pancreatic Cancer

Name of Investigational Product:

GC4711

Name of Sponsor/Company:

Galera Therapeutics, Inc.

Number of Study Centers: Approximately 40 in the United States, Canada, EU and UK

Estimated Enrollment Period: Approximately 36 months

Studied period:	**Phase of development:** 2b
Estimated date first subject enrolled, Q1 2021 Estimated date last subject completed, Q1 2027	

Objectives:

Primary: To determine the effect on overall survival (OS) of adding GC4711 to SBRT compared to placebo in subjects with locally advanced or borderline resectable nonmetastatic pancreatic cancer (PC)

Secondary: To determine the effect of adding GC4711 to SBRT on:

- Progression-free survival (PFS), locoregional control (LRC), and time to distant metastases (TDM).
- Surgical resection outcomes: proportion of subjects in whom R0 or R1 resection is achieved; pathological response in resected specimens.
- Overall response and in-field local response
- Acute and late toxicity observed after SBRT

Exploratory:

- To evaluate patterns of change in CA19-9 with GC4711 + SBRT
- To evaluate the effect of GC4711 + SBRT on patient-reported symptoms
- To assess pharmacokinetics of GC4711 in the study population

Rationale:

While systemic treatment of PC has improved, surgical resection rates are low, and patients with borderline or unresectable nonmetastatic PC still have poor outcomes. Both toxicity and

disease progression during induction chemotherapy limit the number of potential candidates for surgery (Maggino 2019, Lambert 2019). Different neo-adjuvant approaches, including multi-agent chemotherapy and radiotherapy (RT), are evolving (Balaban 2016, Palta 2019); however, timing and dose are under continuous debate. Reports on neoadjuvant (chemo)radiation with a biological equivalent dose (BED) lower than 100 Gy have cited improved local control but not OS (Krishnan 2016, Hammel 2013, Polistina 2010, Chin 2018). With introduction of SBRT (also known as stereotactic ablative radiotherapy or SABR), motion -management tools, and overall more precise delivery techniques, RT has shifted to higher dose delivery (Petrelli 2017, Colbert 2018) with the goal of improving surgical intervention rates and overall outcomes for PC patients (Mellon 2015, Jung 2019). Use of SBRT regimens that employ 3-5 fractions have been reported to show an acceptable toxicity profile (Reyngold 2019, Palta 2019, Suker 2019, Mellon 2015, Herman 2015) and exhibited superior cell killing compared to conventionally fractionated RT (Zhong 2017). Online imaging and adaptive workflow (CT-on-rails or MRI-linac) have rendered SBRT delivery of BED >100 Gy for pancreatic lesions feasible and a 5 × 10 Gy regimen has demonstrated acceptable safety, while normal tissue constraints are preserved (Hassanzadeh 2020, Elhammali 2015, Reyngold 2019, Jung 2019).

GC4711 is a novel, water-soluble, low-molecular weight, manganese-containing macrocyclic ligand complex that is being developed as a 15-minute intravenously (IV) administered treatment to be given in combination with SBRT to potentially improve efficacy and reduce normal tissue damage of high dose per fraction radiation delivery in local treatment of PC.

GC4711 is a selective mimetic of superoxide dismutase (SOD) enzymes—a "dismutase mimetic." It converts superoxide to hydrogen peroxide, and in so doing is a potential radiation response-modifier that may increase both the clinical efficacy and safety of SBRT. In nonclinical models, the addition of selective dismutase mimetics such as GC4711 to SBRT regimens enhanced antitumor activity in different tumor types, including PC experimental xenograft mouse models (Sishc 2019, 2020).

In a pilot Phase 1 trial (GTI-4419-101), subjects with locally advanced PC were randomized to receive SBRT plus either, the GC4711 analogue, GC4419, or placebo. This trial has demonstrated acceptable safety with SBRT (5 × 10-11 Gy), as well as apparent improvements in locoregional control, and time to distant metastases, PFS, and OS. GC4419 was chosen for the pilot study because it has the same mechanism of action as GC4711, and at the time that study was initiated, had already successfully completed Phase 2 trials for reduction of severe oral mucositis associated with Intensity-modulated radiation therapy (IMRT) (Anderson 2018, 2019).

Healthy human volunteer studies have demonstrated that the safety and plasma exposure to GC4711 and GC4419 are similar at equimolar doses administered via the same route and schedule. These studies further confirmed acceptable safety of repeated doses of GC4711 at an approximately equimolar dose as GC4419 used in the pilot trial.

Altogether, these data support the hypothesis that GC4711 may improve the benefit-risk ratio of 5-fraction SBRT delivering a BED >100 Gy by improving SBRT efficacy without increasing toxicity to healthy surrounding tissue (e.g., bowel toxicity).

Methodology:

GTI-4711-201 is designed as a Phase 2b, multicenter, randomized, double-blind, placebo-controlled study to determine the effect on the OS of adding GC4711 to SBRT following chemotherapy in subjects with unresectable or borderline resectable nonmetastatic PC. Approximately 220 subjects will be enrolled (Figure 1: Study Design). Subjects must have nonmetastatic unresectable, borderline resectable PC, or refuse or be medically unfit for surgery for PC.

All newly diagnosed subjects will receive at least 6 weeks of chemotherapy consisting of FOLFIRINOX, mFOLFIRINOX, and/or a gemcitabine-based doublet regimen (e.g., gemcitabine combined with nab-paclitaxel, cisplatin, capecitabine) prior to SBRT. There is no upper limit on the number of pre-SBRT chemotherapy cycles that a subject may receive as long as there is no evidence of metastatic spread during treatment with the initial chemotherapy regimen. Subjects may change chemotherapy regimens prior to starting SBRT (but still limited to FOLFIRINOX, mFOLFIRINOX or a gemcitabine-doublet regimen) for issues of toxicity or intolerance per institutional practice/SOC/NCCN guidelines. Subjects with local progression may be included as long as they remain non-metastatic at screening. Subjects who commence chemotherapy with single-agent gemcitabine but who are then able to tolerate either a gemcitabine doublet, FOLFIRINOX or mFOLFIRINOX may also be included in the trial as long as they fulfill the requirements for at least 6 weeks of pre-SBRT combination chemotherapy with these regimens as outlined above. Other variations such as FOLFOX or FOLFIRI are also acceptable; any other variations must be discussed with the Medical Monitor prior to randomization. After at least 6 weeks of chemotherapy, subjects will be evaluated by computed tomography (CT) and magnetic resonance imaging (MRI) for SBRT feasibility and for distant disease progression; those without metastases will be considered for enrollment. Eligible subjects will be stratified at randomization based on disease status at diagnosis: borderline resectable vs unresectable (radiographically or medically inoperable), as determined by the site's institutional multidisciplinary review following the NCCN definition v1.2020 (see Appendix 5).

Eligible subjects will be randomized in a 1:1 ratio to receive either GC4711 100 mg or placebo given via IV over 15 minutes (+ 5 minutes) before each fraction of SBRT (total of 5 doses).

Due to the risk of a radio-sensitizing effect of fluorouracil and gemcitabine, SBRT should not be started until at least one week following the end of the last chemotherapy cycle. SBRT should start no later than 42 days following the end of the last chemotherapy cycle. Following SBRT (and surgery, if possible), patients may receive additional adjuvant chemotherapy at the discretion of the investigator, and according to standard of care, institutional practice, and NCCN guidelines, as applicable.

Full details of protocol requirements for SBRT can be found in the Radiation Therapy Quality Assurance (RTQA) Manual. The RTQA Manual will establish requirements and expectations

for radiation therapy planning (including required contours, contouring guidelines and dosimetric criteria) and radiation therapy delivery (including simulation, motion assessment, motion management and image guidance). SBRT will be delivered as 5 fractions of 10 Gy prescribed to the residual gross tumor volume (GTV) including perineural and vascular invasion and 3mm margin to the clinical target volume (CTV) to at least 30 Gy, while respecting normal tissue constraints; no elective nodal fields will be given, only macroscopic areas will be treated. SBRT fractions should be given with MR or CT-image guidance, matching both target and avoidance structures, confirming respect of constraints.

Each participating center should provide SBRT certification. Additional training will be provided by the designated Radiotherapy Quality Assurance Group, and all radiation treatment plans will be centrally reviewed (see RTQA Manual). The first two radiotherapy planning case submissions from each site will be reviewed and approved prior to treatment. Subsequent radiotherapy plans will be submitted and reviewed retrospectively. All SBRT treatments will be reviewed to evaluate compliance with treatment guidelines and sites will receive case review reports that document case review results, findings and recommendations.

SBRT fractions will be given sequentially, and within 180 minutes from the end of the GC4711 or placebo infusion. Between fractions, a minimum of 18 hours and a maximum of 72 hours are permitted. Additionally, an occasional 96-hour window is acceptable (i.e. in case of a holiday or machine breakdown). All 5 fractions should be given within 10 calendar days. If a subject is unable to receive their treatment within 10 days, the Medical Monitor and Galera study team should be notified.

After SBRT, subjects judged by the site's institutional multidisciplinary review to be technically unresectable on CT/MRI (Appendix 5) or medically inoperable may receive additional chemotherapy at the discretion of the investigator, and according to standard of care, institutional practice, and NCCN guidelines, as applicable. All chemotherapy treatment should be documented in the source and electronic case report forms.

Those subjects judged by the site's institutional multidisciplinary review or medical team to be technically and medically operable after SBRT will be surgically explored within 8 weeks following SBRT, and outcomes of margins and pathology will be collected. Following surgery, additional chemotherapy may be administered at the discretion of the investigator, and according to standard of care, institutional practice, and NCCN guidelines, as applicable. All chemotherapy treatment should be documented in the source and electronic case report forms.

All subjects will be followed for survival and efficacy every 3 months from the completion of SBRT for 2 years and every 6 months after, for a total of 3 years. Late toxicity will be followed for the first year or until distant disease progression. In the event of documented progressive distant disease, subjects will move to survival follow-up only.

For efficacy end points (PFS, LRC, TDM), CT-imaging will be used and centrally reviewed retrospectively.

Surgical exploration and excision rates, as well as margin status and pathological response will be recorded for all subjects judged resectable.

MRI will be used for SBRT eligibility (1), as well as judgement of post-SBRT technical resectability (2), validation by the site's institutional multidisciplinary review will be documented. When MRI is contraindicated, a CT scan is acceptable if fiducials have been placed.

CA19.9 values will be collected for exploratory analysis at diagnosis, screening, 4 weeks after SBRT and every 3 months until 1 year follow up or until local or distant documented progression. Patient reported outcomes will be collected through 13 months after the completion of SBRT.

Blood samples will be obtained for pharmacokinetic (PK) analyses on Day 1 prior to GC4711 or placebo, immediately after the infusion and 24 hours after the Day 1 infusion but prior to the following infusion. PK blood samples will also be obtained on Day 4 of SBRT prior to GC4711 or placebo, immediately after the infusion and 24 hours after the infusion on Day 4 but prior to the following infusion. 12-lead ECGs will be performed at the same timepoints.

An independent unblinded Data Monitoring Committee (DMC) will be convened to periodically review safety data as outlined in the DMC charter. After 20 subjects have been randomized, the will review unblinded safety data through the 4 week visit after SBRT. At this analysis, the DMC will review all safety data and, if necessary, will consider a recommendation to temporarily suspend trial enrollment and treatment, and consider revisions of the study for safety, in the case where more than 4 subjects encounter a significant toxicity in the experimental arm than in the control per arm. Adverse events (AEs), as well as treatment delay in SBRT fractions, surgical exploration and chemotherapy retake will be monitored independently given the blinded design.

All imaging for tumor assessment will undergo retrospective, independent central review (following RECIST 1:1). Local imaging assessments will be used for study eligibility and treatment decisions.

Number of Subjects (planned): approximately 220 subjects (110 per arm)

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Histological or biopsy proven adenocarcinoma of the pancreas. Cytology is acceptable if histology cannot be obtained.
2. Newly diagnosed non-metastatic PC judged by site multidisciplinary review to be feasible for SBRT, as well as having measurable disease as defined by RECIST

1.1 (see Appendix 2) and classified following NCCN guidelines v1.2020 (see Appendix 5):
a. Locally advanced and technically unresectable, as determined by the multidisciplinary group following the NCCN definition v1 2020 (see Appendix 5)

b. Potentially resectable, but subject is judged not a candidate for surgery, after multidisciplinary review at the investigative site
c. Potentially resectable, but the subject 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

3. Completed at least 6 weeks of chemotherapy consisting of FOLFIRINOX, mFOLFIRINOX, and/or a gemcitabine-based doublet regimen prior to start of SBRT. Other variations such as FOLFOX or FOLFIRI are also acceptable; any other variations must be discussed with the Medical Monitor prior to randomization.
4. Remain non-metastatic as confirmed by a CT scan at screening.
5. Female or male subjects ≥ 18 years of age.
6. ECOG performance status of 0-2.
7. Adequate end-organ function, based on routine clinical and laboratory workup:
   a. Absolute Neutrophil Count > 1,000 µL, platelets ≥ 75,000 µL, hemoglobin ≥ 7.0 g/dl
   b. Calculated creatinine clearance ≥ 30 ml/min
   c. Total bilirubin ≤ 2.5 × ULN , AST and ALT ≤ 3 x ULN
   d. International normalized ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless participant is receiving anticoagulant therapy,
8. Males and females of childbearing potential must agree to use highly effective contraception (Appendix 8)starting prior to the first day of treatment and continuing for 30 days (females) and 90 days (males) after the last dose of GC4711 or placebo.
9. Ability to understand and the willingness to sign a written informed consent form (ICF).

Exclusion Criteria

1. Subjects with documented metastatic disease using standard work-up (per investigator) at diagnosis or at screening response evaluation
2. First-line chemotherapy other than FOLFIRINOX, mFOLFIRINOX, and/or a gemcitabine-based doublet regimen. Subjects receiving either regimen after initial gemcitabine monotherapy are eligible.

3. Prior abdominal RT with substantial overlap in radiation fields as determined by the treating radiation oncologist.
4. Subjects not recovered/controlled from treatment-related toxicities judged by the local investigator.
5. Uncontrolled malignancy other than PC that requires active treatment.
6. History of allergic reactions attributed to compounds of similar chemical or biologic composition to GC4711.
7. Uncontrolled gastric or duodenal ulcer disease within 30 days of dosing.
8. Visible invasion of bulky tumor into the lumen of the bowel or stomach on endoscopy (Note: Radiological or superficial bowel infiltration is allowed, unless deemed clinically unsafe).
9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring delay of therapy, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements.
10. Subjects with Gilbert syndrome who are known to be homozygous for the UGT1A polymorphism.
11. Subjects with hypokalemia whose QT/QTc interval > 470 ms (for women) and > 450 ms (for men) on the screening ECG at visit
12. Treatment with any investigational drug outside this protocol since diagnosis until disease progression given for the disease in study. Prior to the randomization of subjects on other investigational agents, Sponsor's written approval must be obtained.
13. 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.
14. Female subjects who are pregnant or breastfeeding.
15. Any other conditions that, in the investigator's opinion, might indicate the subject to be unsuitable for the study.
16. Subjects who have already undergone resection of their pancreatic tumors.

Duration of Treatment:

SBRT will be administered in 5 sequential fractions of 10 Gy with each fraction preceded by 1 dose of GC4711 or placebo (total of 5 doses). All doses should be given within 10 calendar days.

Reference Therapy, Dosage, and Mode of Administration:

Study will include two treatment arms:

- **Arm A:** GC4711 100 mg 15 min (+ 5 minute), 100 mL IV infusion to be completed within 180 minutes of the start of SBRT) administered before each SBRT from the first fraction of SBRT to the last fraction of SBRT.

- **Arm B:** Placebo 15 min (+ 5 minute), 100 mL normal saline IV infusion to be completed within 180 minutes of the start of SBRT) administered before each SBRT as described for Arm A. Normal saline will be provided by the site's unblinded pharmacists.

Criteria for Evaluation:

For OS evaluation:

- OS is defined as the time from randomization to the date of death from any cause. Survival data will be collected every 3 months in the first 2 years and then every 6 months after until 3 years following protocol therapy. Subjects not known to have died will be censored at the last known date the subject was known to be alive.

For PFS, local control, locoregional control, time to distant metastases, and best tumor response (overall and within-field):

- CT (chest/abdomen) using RECIST 1.1*,

*Local progression on imaging 4 weeks after SBRT requires confirmation at the next scheduled imaging, to rule out early pseudo-progression after SBRT (Eisenhauer 2009; Appendix 2)

For resection rates:

- Multi-disciplinary review of resectability judgements and in explored subjects, margin (e.g., R0/R1) and pathological response (pCR, pNR, pPR, no response) status will be recorded.

For toxicity/safety:

- Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, to monitor adverse events (AEs/SAEs); all through 90 days post-SBRT and late toxicity until distant disease progression (Section 6.4, Table 3) or until 1 year post-SBRT. (CTCAE vs 5, 2017)

Exploratory:

- PRO-CTCAE pancreas to evaluate patient-reported symptoms (Basch 2014, Kluetz 2016,Appendix 6)
- CA19.9 values will be recorded from diagnosis, at screening, and during the first year of follow-up after SBRT or until documented distant or local progression. Normalization is defined as $\leq$ 37 U/ml. Significant decrease is estimated as >30%.
- Plasma concentrations of GC4711 and major metabolites during SBRT+GC4711/placebo treatment.

Safety Monitoring and Toxicity Management:

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

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

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

Patients who experience a toxicity noted above during or shortly after the infusion of GC4711/placebo should have their infusion times increased to 30 minutes (+5 minutes).

If the toxicity recurs, the infusion time should be increased to 45 minutes (+5 minutes), and may be increased to 60 minutes (+5 minutes) if hypotension occurs with a 45-minute infusion.

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

Concomitant Medications/Treatments:

Investigators may prescribe concomitant medication or supportive care as deemed necessary. All such medications taken, including anti-emetics, steroids, and anti-tumor treatments, as well as any (surgical) interventions will be recorded from 30-days prior to dosing of GC4711/placebo through 90 days after completion of SBRT. After the 3 Month follow up

visit, only medications used to treat late radiation toxicities should be recorded in the subject's eCRF through 1 year (or distant disease progression, whichever comes first), including inhalers, steroids, oxygen supply, etc. Additionally, any new anti-cancer therapy given at any time during follow-up should be recorded in the CRF through 36 months post-SBRT, including during the survival follow-up.

Supportive care may include antiemetic prophylaxis, hematopoietic growth factor therapy as used per ASCO guidelines, systemic antibiotics, hydration to prevent renal damage, or other medications or treatments, consistent with the local standard of practice with the following exceptions:

Prohibited medications/treatments:

- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildenafil, tadalafil, or similar agents) or other drugs that in the judgment of the treating investigator could create a risk of a precipitous decrease in blood pressure are prohibited from 1 day prior to dosing until at least 24 hours after the last dose of GC4711 or placebo.
- Treatment with any investigational drug outside this protocol since diagnosis until disease progression given for the disease in study (e.g., chemotherapy, immunotherapy, targeted therapy, hormone therapy, and biologic therapy). Prior to the randomization of subjects on other investigational agents, Sponsor's written approval must be obtained.

Statistical Considerations:

An independent Data Monitoring Committee (DMC) will be empaneled.

Efficacy evaluations will be done on the intent-to-treat population of all randomized subjects.

The primary efficacy analysis will be the comparison of OS between the two treatment groups using a stratified log-rank test at an overall two-sided 5% level of significance. Stratification will be performed at randomization based on borderline resectable versus unresectable disease, as documented by the site's institutional multidisciplinary treatment team. Medically inoperable subjects and subjects refusing surgery will be grouped under unresectable. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians, and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for OS will be estimated along with its 95% confidence interval using a stratified Cox model using the same stratification values as for the log-rank test (Cox 1972).

Median OS in the control arm is expected to be 11 months from randomization, with 120 deaths needed to provide 90% power to detect a reduction in the OS hazard ratio to 0.55 (i.e., median OS of 20 months in the experimental arm) using a two-sided Type I error rate of 0.05 and accounting for an interim analysis after 84 events.

Approximately 220 subjects will be randomized at a 1:1 ratio.

Safety evaluations will be done on all randomized subjects who receive at least one dose of GC4711 or placebo. Acute and late adverse events (CTCAE v5) will be summarized by treatment arm. A Data Monitoring Committee (DMC) will perform an analysis after approximately 20 subjects are enrolled and have reached the 4-week post-SBRT timepoint and will periodically review safety data and related delays in SBRT administration throughout the whole study as outlined in the DMC Charter.

In addition to an interim test of superiority planned at N=84 deaths (70% information) as detailed below, a preliminary assessment will be performed at approximately N=36 events (30% information) to assess treatment effect and potentially result in decision to stop the trial early.

An interim analysis of the OS primary endpoint is planned after approximately 84 events (deaths) have occurred with controlled disclosure of the results to maintain blinding for the full study. Additional details will be provided in the Statistical Analysis Plan (SAP).

Secondary efficacy end points (time-to-event endpoints PFS, LCR, and TDM; and overall and in-field best response rates) will be measured on CT imaging following RECIST 1.1 and centrally reviewed. Kaplan-Meier estimates of time-to event endpoints will be made.

Because surgical resection has been reported as associated with improved OS and PFS for this patient population (Mellon 2015, Jaoude 2020), the rate of surgical resection will be

documented and compared between treatment arms. Surgical exploration rates, margin status (R0, R1) and pathologic response will be summarized and compared descriptively.

Exploratory endpoints will be summarized and analyzed descriptively and include CA19-9 normalization (≤ 37 U/ml) and a decrease of ≥ 30% (van Veldhuisen 2018), BRCA mutation impact, and changes in patient reported symptoms (PRO-CTCAE),

Figure 1: Study Design

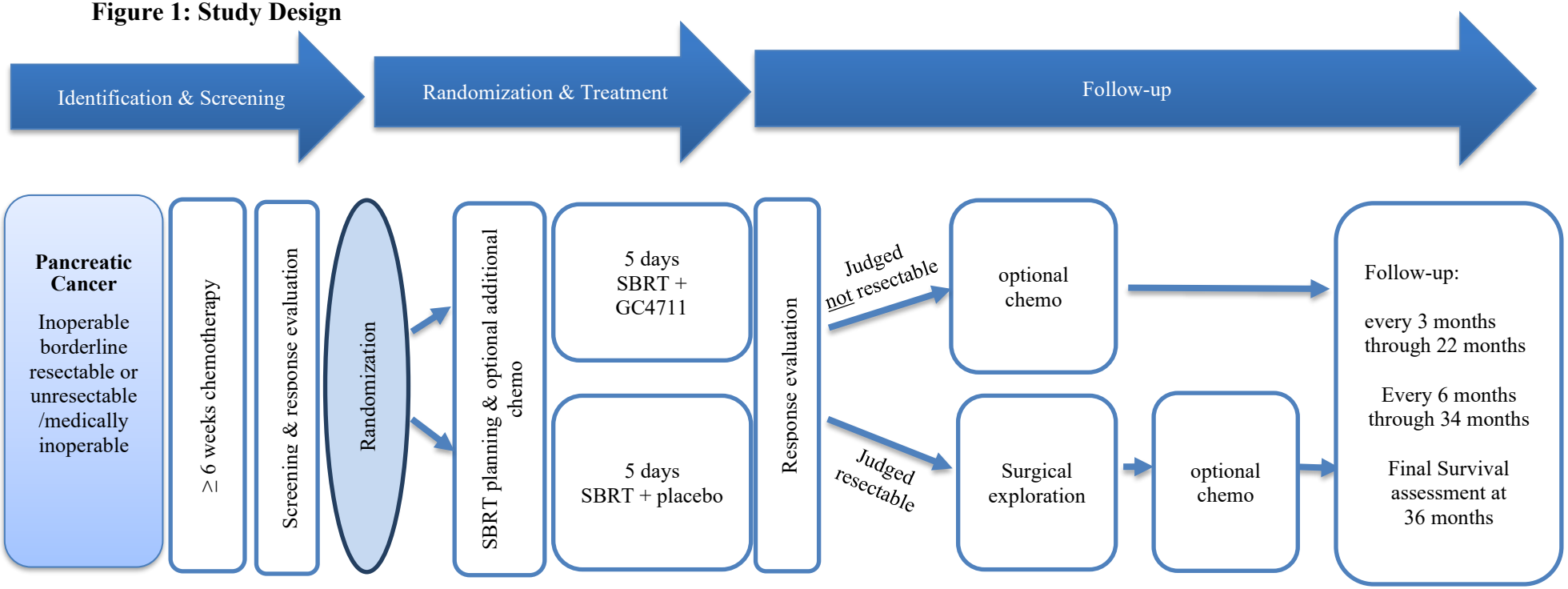


Table 1: Schedule of Assessments

SCREENING[a]		**RANDOMIZATION**[b]	**OPTIONAL CHEMOTHERAPY**[p]	**ACTIVE TREATMENT PERIOD**									
				SBRT Visits (5-10 days)					M1(4 weeks post-SBRT)	M3[r]	M4, 7, 10, 13, 16, 19, 22	M28, 34	M36
	(day -28 to 1)			1	2	3	4	5	± 15 days	+ 7 days	+14days	+14 days	
Informed consent	X												
Inclusion and exclusion criteria[b]	X												
Medical history[c]	X												
Demography	X												
Complete physical examination including weight	X								X		X[s]		
ECOG Performance Status	X								X	X	X[s]		
Vital signs[d]	X			X (*before and after study infusion)* [d]					X				
12-lead ECG[e]	X			X	X		X	X					
AE/SAE review[f]				X					X	X	X		
Concomitant medication, treatment, and supportive care review [g]	X			X					X	X	X	X	X
Survival status[h]									X	X	X	X	X
Serum pregnancy test (WOCBP)	X [n]			X[n]									
Serum chemistry panel	X								X				
Complete blood count with differential	X								X				
CT chest/abdomen	X								X[q]		X	X	
MRI (abdomen)	X [o]								X				
PRO-CTCAE questionnaire	X							X	X		X (M7,13)		
GC4711 or placebo IV infusion				X	X	X	X	X					
SBRT administration[i]				X	X	X	X	X					
Blood samples for PK analysis[j]				X	X		X	X					
Endoscopy + biopsy[k]	X												
CA19.9 [l]	X								X	X	X[l]		
Multi-disciplinary review summary sheet[m]	X								X				

AE = adverse event, BP = blood pressure, CT = computed tomography, CTCAE = Common Terminology Criteria for Adverse Events, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EOS=End of Study, FU = Follow-up, IV = intravenous, M = month, MRI = magnetic resonance imaging, PE = physical examination, PK = pharmacokinetics, SAE = serious adverse event, WOCBP= women of childbearing potential

[a] A previously performed CT scan, MRI scan, safety blood work (serum chemistry and complete blood work) or other study assessments done per standard of care may be utilized for screening if done within 28 days prior to randomization.

[b] Randomization should occur after all screening assessments are performed, eligibility is confirmed, and within 5 weeks before the first dose of SBRT. Confirmation of eligibility should include confirmation of diagnosis and histology and exclusion of distant disease by standard practice. Reason for inclusion of resectable subjects who refuse surgery will be clearly documented (performance, co-morbidity, decline, other).

[c] If BRCA mutation is tested/known, it should be documented in source and CRF.

[d] Blood pressure and heart rate should be taken prior to each infusion, monitoring possible hypotensive symptoms, and repeated at the end of infusion.

[e] Triplicate ECGs should be collected pre- and post-infusion as close to blood draws for PK analysis as possible. The end of infusion PK blood sample should be drawn within 10 minutes after the end of the infusion, and the ECG should be performed within 10 minutes of the blood draw for PK analysis. Only a single ECG is required at screening and at the 24-hour post dose assessment.

[f] All AEs/SAEs will be collected for all randomized subjects who receive at least one dose of study drug starting from the Day 1 dosing through 90 days post-SBRT, regardless of disease status. Ongoing SAEs at 90 Days post-SBRT will be followed through resolution. After 90 days post-SBRT, AEs/SAEs associated with late toxicities will be followed through 1-year post-SBRT or until distant disease progression, whichever comes first.

[g] Medications taken from 30 days prior to dosing through 3 Months post SBRT should be documented in source records and CRF. After the 3 Month follow up visit, only medications used to treat late radiation toxicities should be recorded through 1 year (or distant disease progression, whichever comes first), including inhalers, steroids, oxygen supply, etc. Additionally, any new anti-cancer therapy given at any point during follow-up (including survival follow-up) should be recorded in the CRF through 36 months post-SBRT.

[h] If a subject experiences distant disease progression, survival status will be followed every 3 months through 2 years post-SBRT and then every 6 months until 3 years. Telephone contacts are acceptable for survival follow up. No additional study assessments or AE/SAE recordings will be required after documented distant disease progression, following 90 days post SBRT completion.

[i] SBRT will start from 7 to 42 days after the last pre-SBRT chemotherapy cycle (the 7 – 42-day window will begin at the end of the treatment cycle, not on the last day of actual treatment time) and will start within 5 weeks from randomization. SBRT will be administered in 5 daily doses (minimum of 18 and maximum of 72 hours between fractions. Additionally, an occasional 96-hour window is acceptable (i.e. in case of a holiday or machine breakdown). GC4711 or placebo will be administered prior to each dose of SBRT starting on the first day of SBRT through the last day of SBRT. GC4711 or placebo will be administered within 180 minutes prior to the start of SBRT.

[j] Blood samples for PK analyses should be taken at Day 1 of GC4711 or placebo infusion (before, immediately after, and 24 hours after the Day 1 infusion but before next study drug infusion and on Day 4 of GC4711 or placebo infusion (before, immediately after, and 24 hours after the Day 4 infusion but before infusion on Day 5).

[k] A previous endoscopy and biopsy performed prior to screening may be utilized for confirmation of diagnosis. If BRCA mutation was tested, this should be documented. In case of suspicion of macroscopic tumor in the bowel lumen, a repeat endoscopy evaluation prior to SBRT is recommended and can be combined with fiducial positioning if used for CT-guided patient set-up. A repetition of the biopsy is not needed, if a repeat endoscopy is done.

[l] Local lab values and normal range of CA19.9 should be collected at screening as close to randomization as feasible and at each follow-up visit for the first year or until documented local or distant progression. CA19.9 value at time of diagnosis and disease progression should be documented, if available.

[m] Multi-disciplinary judgement on technically and medically resectability, as well as SBRT feasibility are documented.

[n] A serum pregnancy test must be performed within the screening period. A urine pregnancy test must be performed on Day 1 prior to dosing and prior to chemotherapy restart following SBRT.

[o] An MRI of the abdomen is required to be done prior to SBRT for adequate planning and may be completed following randomization and as close to SBRT as feasible. When MRI is contraindicated, a CT is acceptable if fiducials have been placed.

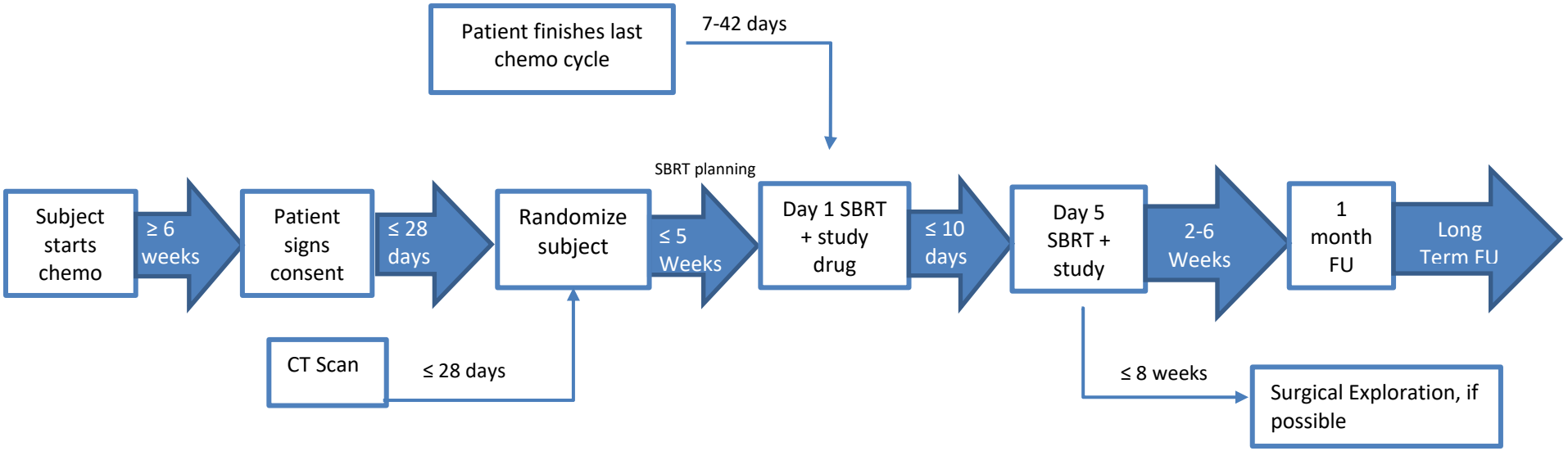
[p] Subject may be given additional chemotherapy following randomization prior to SBRT start but it is not required. SBRT must start from 7 to 42 days after the last pre-SBRT chemotherapy cycle (the 7 – 42 day window will begin at the end of the treatment cycle, not on the last day of actual treatment time).

[q] CT-based observed local disease progression at 4-weeks post SBRT requires confirmation at the next scheduled imaging timepoint. Subjects with local (regional) progression without distant disease will be continued in follow-up (visits, CT scans) as by Schedule of Assessments (SOA). After documented distant disease progression, no further protocol assessments are required and follow up will change to survival only with the collection of additional anti-cancer therapy given.

[r] The month 3 visit may be done by telephone if subject is unable to visit the site. CA19.9 can be collected locally.

[s] Physical Exam and ECOG should be completed every 3 months through 13 months.

Figure 2: Subject Flow



2 INTRODUCTION

2.1 Radiotherapy for Unresectable or Borderline Resectable Pancreatic Cancer

Pancreatic cancer (PC) is a one of the most lethal cancer diagnoses today. Incidence is rising, and the estimated 5-year survival rate is only 9% (Rawlaa 2019, Ryan 2014). At the time of diagnosis, approximately half of patients present with metastatic disease (stage IV), and less than 10% present with resectable disease. All other patients are classified unresectable or borderline resectable (NCCN v.1.2020, Appendix 5) as determined by the extent of tumor contact with the vascular system, limiting resection as well as radiotherapy (RT) because of proximity to the bowel structures (Murphy 2018, Palta 2019).

The American Society of Clinical Oncology and NCCN v1.2020 (Appendix 5) defined more exact criteria for borderline resectable and unresectable PC using computed tomography (CT) and magnetic resonance imaging (MRI) and recommended induction chemotherapy followed by local therapies such as (chemo) radiotherapy (RT) and/or surgery (Palta 2019, Khorana 2019, Balaban 2016) for patients responding to 3 or more cycles of induction chemotherapy. Selecting responding patients is important for avoiding toxicities and the costs associated with local treatment in patients with fast progressing distant disease. In borderline and unresectable patients judged 'technically resectable' (Al-Hawary 2014, NCCN v1.2020, Appendix 5), surgical exploration is recommended within 8 weeks after RT, where possible, yielding an important impact on survival (Mellon 2015, Jaoude 2020).

While systemic treatment of PC has improved, patients with borderline or unresectable PC nevertheless still have low resection rates and poor outcomes overall. Both toxicity and disease progression during induction chemotherapy limit the number of potential candidates for surgery (Maggino 2019, Lambert 2019). NCCN guidelines state (m)FOLFIRINOX (Von Hoff 2013, Suker 2016) or Gemcitabine-doublet (Conroy 2011) as first choice of neoadjuvant treatment, extrapolating from series in adjuvant and metastatic settings. Both regimens have proven benefit over gemcitabine-only, however, differ in toxicity profile (Perri 2020, Chiorean 2019, Pusceddu 2019, Cho 2020). Alterations in germline BRCA and PALB2 are detected in approximately 5–9% of patients with PC and can lead to homologous repair deficiency (HRD). PC with HRD is more susceptible to cytotoxic agents, such as platinum salts and topoisomerase inhibitors, favoring first-line gemcitabine-cisplatin chemotherapy (Wong 2020). BRCA carriers are often prescribed gemcitabine-cisplatin, however, increased rate of pathological response after neoadjuvant FOLFIRINOX (Golan 2020) is reported. Systematic testing of mutations is, however, not in current standard of care guidelines (NCCN.org).

In the protocol, FOLFIRINOX, (m)FOLFIRINOX or gemcitabine-doublet are inclusion criteria, while allowing simplification and dose-reduction for toxicity (expected in up to half of subjects over 6 months, Suker 2016). Switching of the treatment regimen is permissible per institutional practice/SOC/NCCN guidelines.

Optimal use of local treatment, including stereotactic body radiation therapy (SBRT), is evolving (Balaban 2016, Palta 2019). Neoadjuvant radiation at moderate dose has been reported to improve

local control but not overall survival (OS) (Krishnan 2016, Hammel 2013, Polistina 2010, Chin 2018); thus, RT has been shifting to higher dose delivery (Schellenberg 2011, Colbert 2018, Petrelli 2017) with the goal of improving surgical intervention rates and overall outcomes (Mellon 2015, Jung 2019). Use of SBRT regimens that employ 3-5 fractions have been reported to show acceptable toxicity profiles (Sutera 2017, Shaib 2016, Reyngold 2019, Palta 2019, Suker 2019, Boldrini 2019, Mellon 2015, Herman 2015) and superiority to conventionally fractionated RT (Zhong 2017, Petrelli 2017). Online imaging has made SBRT even more precise and a 5 ×10 Gy regimen is regarded as safe (Hassanzadeh 2020, Henke 2018). Tumor control with SBRT still offers ample opportunity for improvement, however, and normal tissue constraints limit tumor coverage and present a toxicity risk (Elhammali 2015, Reyngold 2019, Jung 2019).

2.2 Investigational Medicinal Product

GC4711 is a novel, water-soluble, low-molecular weight, manganese pentaaza-macrocyclic ligand complex (MnPAM) whose catalytic activity for the dismutation of superoxide to hydrogen peroxide mimics that of naturally occurring superoxide dismutase (SOD) enzymes. GC4711 and other MnPAMs are a new pharmacologic class of drugs, which are termed selective dismutase mimetics, that are being developed for administration by intravenous (IV) infusion.

SOD enzymes are expressed in the cytoplasm (SOD1 Cu/Zn-based), mitochondria (SOD2, Mn-based), and extracellular spaces (SOD3, Cu/Zn-based) of mammalian cells (Fridovich 1997). These enzymes eliminate superoxide (O2•-) by converting it to hydrogen peroxide (H_2O_2), which is then further detoxified by peroxidase enzymes producing molecular oxygen (O_2) and water (H_2O) (Fukai 2011, Miller 2012). In certain inflammatory disease states and during RT and chemotherapy for cancer, native SOD enzyme activity can be overwhelmed due to excessive superoxide production, resulting in normal tissue damage (Mapuskar 2019). Thus, the removal of excess superoxide with supraphysiological levels of SOD activity can protect normal tissues from therapeutic radiation damage, as has been demonstrated by multiple lines of evidence (Thompson 2010, Greenberger 2007, Murphy 2008, Anderson 2018, 2019).

GC4711 and its MnPAM analogues are highly selective and specific dismutase mimetics. Studies with the GC4711 analogue, GC4419, employed electron paramagnetic resonance to demonstrate that it quenched the increased levels of $O_2^{\bullet-}$ formed in cancer and normal cells but did not alter the hydroxyl radical (OH) generation by radiation that is believed primarily responsible for cancer cell DNA damage and killing (El-Mahdy 2020). Consistent with this, combining GC4419 with radiation augmented the cytotoxic effects of radiation on cancer cells while protecting normal cells.

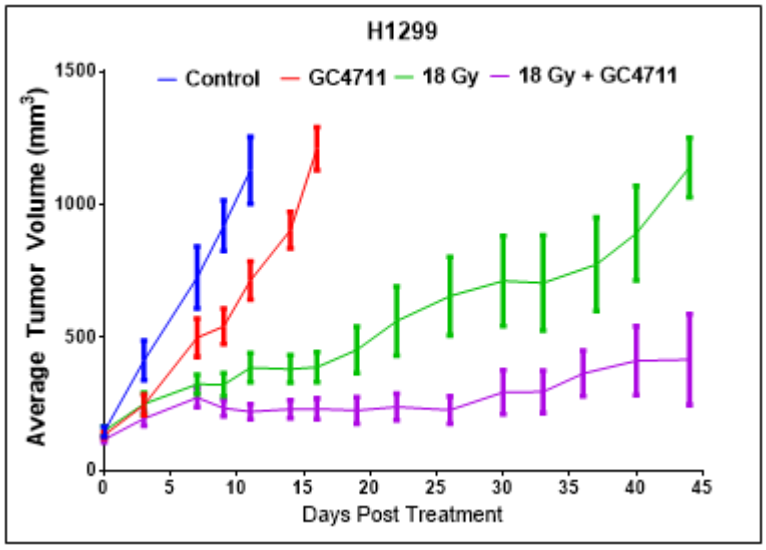
In vivo, mouse tumor model studies with GC4711 and analogues in combination with high dose per fraction radiation have shown anti-cancer synergy (Sishc 2018). In other animal models, GC4419 has shown reduction of normal tissue radiation toxicity (El-Mahdy 2020, Sishc 2019), and another analogue, GC4403, demonstrated radioprotection of the small intestine (Thompson 2010) and oral epithelium (Murphy 2008). Similarly, in a randomized, double-blind, placebo-controlled Phase 2b trial, GC4419 demonstrated a reduction in the incidence and severity of oral mucositis due to RT for head and neck malignancies (Anderson 2018, 2019).

MnPAM dismutase mimetics demonstrate mechanism-related anti-tumor synergy with high dose per fraction radiation.

SBRT greatly increases cellular superoxide concentrations, which selective dismutase mimetics exploit to generate high levels of hydrogen peroxide, creating a highly toxic environment for tumor cells, as hydrogen peroxide is more toxic to tumor cells than to normal cells. This cancer cell sensitivity may reflect lower levels of catalase, glutathione peroxidase, and other enzymes that degrade hydrogen peroxide in the cancer cell (Oberley 1997), a translocation of catalase (Bohm 2015), or susceptibility of cancer metabolism. As superoxide levels and thus the amount of hydrogen peroxide produced by the selective dismutase mimetic increase with fraction dose size, hydrogen peroxide levels can reach levels that have significant anti-tumor effects (Greenberger 2007, Sishc 2021, Sishc 2019). In a model in which the H1299 tumor was engineered to express catalase inducible with a doxycycline promoter, these synergistic anti-tumor effects were demonstrated to be related to the mechanism of the dismutase mimetic GC4419 (Sishc 2021).

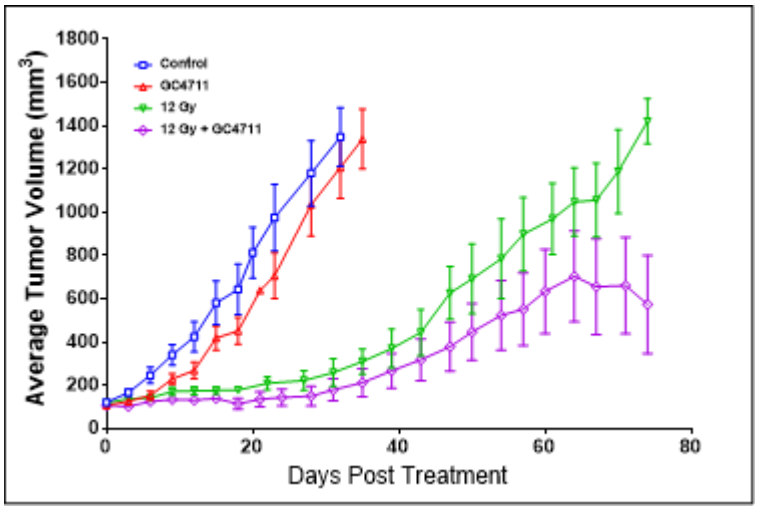
GC4711 alone, administered once daily at 24 mg/kg for 5 consecutive days, significantly delayed growth of H1299 NSCLC lung or Panc 02.03 pancreatic tumors in xenografted mice compared with vehicle control animals (
 NSCLC and **Error! Reference source not found.** for PC). The combination treatment of 24 mg/kg GC4711 administered on Days 1 to 5 and 18 Gy in lung and 12Gy in PC SBRT on Day 1 demonstrated an additive effect on tumor growth, resulting in smaller average tumor volumes compared with GC4711 or SBRT alone.

Figure 3: GC4711 Potentiated the Antitumor Effects of SBRT in a Human NSCLC Model



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

Figure 4: GC4711 Potentiated the Antitumor Effects of SBRT in a Human Pancreatic Adenocarcinoma Model



SBRT = stereotactic body radiotherapy.
The human pancreatic adenocarcinoma cell line, Panc 02.03 (ATCC® CRL-2553™), was implanted by subcutaneous (SC) injection into the flank of 6-week-old female nu/nu mice. When the average tumor size per group reached 100 mm^3, a single 12 Gy dose of SBRT was administered (Day 1). Control and GC4711 groups (n = 9-12 animals per group) received the vehicle (10 mM sodium bicarbonate in saline) or 24 mg/kg GC4711 by IP injection approximately 30 minutes before SBRT and on Days 2 through 5 (consecutive days). Tumor dimensions were measured 2 times per week by caliper and tumor volumes calculated. Tumor volumes expressed as the group mean +/- standard error of the mean.

2.3 Pilot clinical data with GC4711 analogue GC4419

A pilot, randomized, double-blinded, placebo-controlled multicenter adaptive dose-finding trial of SBRT with the GC4711 analogue GC4419 (GTI-4419-101) was conducted in patients with locally advanced PC. After completing first-line chemotherapy, 42 patients with unresectable (32 subjects) or borderline resectable (10 subjects) PC were randomized in a double-blind fashion to receive either 90 mg GC4419 or placebo (PBO) via IV infusion prior to each of 5 daily SBRT fractions (planned 5 ×10, 11, or 12 Gy). Median duration of chemotherapy prior to randomization was 22 weeks (range, 12-36) for placebo and 18 weeks (range, 9-67) for GC4419. SBRT dose assignment started at 10 Gy per fraction and proceeded separately in each arm based on dual endpoints (Gr 3-4 GI toxicity/death through 90 days post SBRT, and local stable disease/improvement at 90 days post SBRT) using a Late Onset Efficacy/Toxicity tradeoff (LO-ET) Bayesian adaptive design in which acceptable posterior probabilities of 90-day safety and efficacy were set at 0.15 and 0.75, respectively. The primary endpoint was recommended SBRT dose for further study in each arm, based on the LO-ET model. Other endpoints included acute (90 day) and late (12 month) radiation toxicity, OS, progression-free survival (PFS), locoregional control (LRC), and time to distant metastases (TDM).

All subjects completed the assigned SBRT: 5 × 10 Gy (n=24) or 5 × 11 Gy (n=18). The design called for 24 subjects per arm in a 1:1 randomization, but the placebo arm was terminated early, prior to the maximum sample size of 24 patients, at 18 patients, due to unacceptably low probability of efficacy at any dose, compared to the fixed lower limit of 0.75.

An SBRT dose regimen of 10 Gy x 5 was selected for further study in the present trial.

Final analysis of safety and efficacy is available after completion of 12-month follow up for all surviving patients (data on file, Galera Therapeutics, Inc). The adverse event profiles for GC4419 and placebo were similar (Table 2a2a and Table 2b). Hazard ratios of <0.5 for OS, PFS, local control, and time to distant metastases (Table 33) suggested an efficacy benefit for the dismutase mimetic, supporting further study with GC4711 in the present trial.

Table 2a: Safety summary from pilot randomized trial GTI-4419-101

AEs Considered related by Investigator to SBRT		**SBRT + PBO**	**SBRT + GC**
≤90 days after SBRT	Any AE	67%	46%
	GI AE	44%	42%
	Severe AE	0%	0%
>90 days after SBRT	Any AE	22%	25%
	GI AE	17%	21%
	Severe AE	11%	8%

Table 2b: Safety summary from pilot randomized trial GTI-4419-101

AEs Considered related by Investigator to GC/PBO		**SBRT + PBO**	**SBRT + GC**
≤90 days after SBRT	Any AE	67%	46%
	GI AE	44%	42%
	Severe AE	0%	0%
>90 days after SBRT	Any AE	17%	21%
	GI AE	17%	17%
	Severe AE	11%	4%

Table 3: Comparison of tumor outcomes after SBRT with GC4419 or placebo in the pilot trial GTI-4419-101

Arm	**Median (Months)**			
	OS	**PFS**	**LRC**	**TDM**
GC4419 (n=24)	17.0	11.2	24.2	13.9

PBO (n=18)	13.3	7.1	9.6	7.0
Hazard Ratio	0.48	0.46	0.30	0.39
P (log-rank)	0.09	0.04	0.06	0.03

Abbreviations: NR = not reached
Source: Galera Therapeutics, Inc, data on file

2.4 GC4711 Nonclinical Safety Data

Four GLP 14-day repeat-dose studies with 14-day non-treatment recovery periods were conducted in Sprague-Dawley rats and beagle dogs using either 15- or 60-minute GC4711 IV infusions.

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

- GC4711 was overall well tolerated in rats and beagle dogs in all repeat-dose studies with no adverse effects on central nervous system or respiratory parameters in rats (15-minute infusion) and no adverse cardiovascular effects in dogs (15-minute infusion).
- Mortality was observed in 2 rats in the 15-minute infusion study at the high dose level of 16 mg/kg/day, and these deaths were of unknown relationship to GC4711.
- Adverse effects included weight loss, which was observed in rats at doses of 16 mg/kg/day (15-minute infusion) and 18 and 24 mg/kg/day (60-minute infusion). The rat AEs were reversible during the 14-day recovery period.
- The no observed adverse effect level (NOAEL) was 8 mg/kg/day for rats and 9 mg/kg/day for dogs in the 15-minute GC4711 infusion studies. The NOAEL was 12 mg/kg/day for rats and 12.5 mg/kg/day for dogs in the 60-minute GC4711 infusion studies.
- There were no indications of clastogenicity or genotoxicity associated with administration of GC4711.

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

2.5 GC4711 Clinical Development

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

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

A Phase 1 Study (Study GTI-4711-002) involving serial cohorts of healthy volunteers who received GC4711 or placebo via 15-minute IV infusion at a single dose up to 120 mg of GC4711 (Cohorts 1-6: 30, 60, 75, 90, 105, or 120 mg) and then via once daily 90 mg infusions for 14 days (Cohort 7) has been completed. A total of 10 subjects in each cohort were randomized at a 6:4 ratio to receive GC4711 or placebo treatment. All cohorts included a sentinel cohort consisting of 2 subjects (1 GC4711, 1 placebo) who were observed for at least 24 hours following infusion and the safety data were reviewed by the treating investigator before dosing the rest of the subjects in the cohort.

In this study, the pharmacokinetics (PK) profile of GC4711 following 15-minute IV infusion at doses from 30 mg to 120 mg as a single dose and 90 mg/day for 14 days revealed the following results:

- Quantifiable plasma concentrations for up to 6 to 12 hours after infusion were observed across all dose cohorts.
- Greater than dose proportional behavior for the concentration maximum (Cmax) and area under the curve (AUC) of GC4711 across single dose administration cohorts. For GC4711, this behavior may be attributed to the fact that the first dose (30 mg) was not measurable for a long period of time, resulting in a much lower AUC.
- The half-life ($t_{1/2}$) for GC4711 was approximately 2 hours.
- Low levels of exposure to the GC4711 metabolites GC4764 and GC4765, with metabolite to parent ratios of < 6% and 1.2%, respectively, across all dose cohorts. Based on the combination of low prevalence and biological activity in nonclinical studies, these metabolites do not appear to be of clinical significance in human patients.
- No marked accumulation of GC4711 was observed by Day 8 following daily administration of 90 mg/day.

The safety profile of GC4711 was comparable following single 15-minute IV infusion doses up to 120 mg and multiple 15-minute IV infusion doses of 90 mg/day for 14 days. Consistent with the mechanism of action of GC4711 (specifically, potentiation of nitric oxide (Kasten 1994)), transient orthostatic symptoms (e.g., headache, dizziness, and light-headedness), hypotension, and facial tingling or paresthesia were expected and consistently observed. Reports of paresthesia appeared to be dose-related; however, it was mild to moderate in intensity and was not treatment-limiting. All treatment-emergent adverse events (TEAEs) were Grade 1 or Grade 2 in intensity. None of the TEAEs were graded serious, and there were no deaths. No clinically significant abnormalities in any laboratory evaluations were noted. Please see the IB for further details.

Assessment of ECG data from the single ascending dose cohort of the Phase 1 study (Study GTI-4711-002) demonstrated no clear dose-related trends, nor changes in ECG measures or shifts from normal to abnormal that were clinically significant. Overall, there were 3 subjects (1 [16.7%] at 30 mg and 2 [33.3%] at 120 mg) who reported ECG changes that were judged to be not clinically significant. This addressed shifts in QT interval 2 hours after the infusion relative to baseline (5.3 msec for the subject in the 30 mg group and +5.0 and +16.7 msec for the subjects in the 120 mg group) and QTcF interval (5.3 msec for the subject in the 30 mg group and +9.0 and +7.7 msec for the subjects in the 120 mg group). Although these ECG shifts were rated as not clinically significant, ECG and QT intervals are to be closely followed when patients are first exposed to GC4711 (Section 8.3).

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

2.6 Rationale for Present Trial

Mechanism and nonclinical data with the MnPAM dismutase mimetics strongly suggest anti-tumor synergy with high dose per fraction radiation (SBRT) and protection of normal tissue from radiation-related injury. With respect to the proposed indication here, GC4711 has demonstrated anti-tumor synergy in combination with SBRT (12 Gy x 1) in a pre-clinical xenograft model of pancreatic cancer (Sishc 2020, Thompson 2010, **Error! Reference source not found.**). Interim results of the pilot clinical trial (GTI-4419-101) of GC4419 (an analogue of GC4711) plus SBRT in locally advanced PC further support this class anti-tumor synergy and the safety of a 5 × 10 Gy SBRT regimen in this population.

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

Therefore, based on nonclinical pharmacology studies and previously collected clinical data, GC4711 is an appropriate experimental drug candidate to study its potential to safely provide significant benefit to PC patients by improving tumor response to SBRT without increasing the risk of GI toxicities. By the virtue of being a short one-week regimen, SBRT can be given earlier in the clinical pathway before chemotherapy resistance (including early metastasis) or unacceptable toxicity may develop (Suker 2016, Lambert 2019).

3 OBJECTIVES AND ENDPOINTS

3.1 Rationale for Primary Endpoint

OS is a critical endpoint for analysis of treatment efficacy in non-metastatic PC. In literature (Mellon 2015, Jaoued 2018) both OS and PFS are largely dependent on local response enabling resection of the primary tumor, being the driver in survival outcome. Chemotherapy can control distant disease, but local disease control requires this surgical intervention. The potential for surgical intervention is improved with each effective treatment modality, including SBRT, which is known to increase surgical candidates and positively impact daily life, leading to survival benefit in PC patients (Herman 2015, Bonnetain 2014, Kovic 2018, Hamada 2016).

OBJECTIVES	ENDPOINTS
Primary	
To determine the effect on OS of adding GC4711 to SBRT compared to placebo in subjects with unresectable or borderline resectable, nonmetastatic PC	Overall Survival Status followed for 3 years post SBRT
Secondary	
• To evaluate the effects of adding GC4711 to SBRT on progression-free survival (PFS) locoregional control (LRC), and time to distant metastases (TDM) • To evaluate the overall and in-field response following GC4711 + SBRT • To evaluate surgical resection outcomes: proportion of subjects in whom R0 or R1 resection is achieved; pathological response in resected specimens • To evaluate the acute and late toxicity observed after SBRT	For PFS, LRC, TDM, Best Overall and in-field response: • CT (chest/abdomen) using RECIST 1.1 (Appendix 2) For resection rates: • Multi-disciplinary review of resectability judgements and in explored subjects, margin (e.g., R0/R1) and pathological response (pCR, pNR, pPR, no response) status will be recorded. • For toxicity/safety: Reporting all observed AEs/SAEs in first 90 days by NCI-CTCAE, version 5.0 (See Section 8.4 and Appendix 4) and specific late toxicities until distant disease progression or 1 year (See Section 6.4, Table 3, including bowel stenosis, obstruction or perforation, abdominal bleeding, vascular events, kidney or liver failure, and spinal cord injuries).
Exploratory	
• To evaluate the effect of GC4711 + SBRT on patient-reported symptoms • To evaluate changes in CA19-9 with GC4711 + SBRT • To assess pharmacokinetics of GC4711 in the study population	• PRO-CTCAE pancreas to evaluate patient-reported symptoms (Basch 2014, Kluetz 2016,Appendix 6) • CA19.9 values will be documented at diagnosis, screening and after SBRT at all visits during the first year or until distant or local disease progression. • Plasma concentrations of GC4711 and major metabolites

4 STUDY DESIGN

4.1 Overall Design

GTI-4711-201 is designed to determine the effect on OS of adding GC4711 to SBRT after chemotherapy in subjects with unresectable or borderline resectable, nonmetastatic PC. This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled study, wherein approximately 220 subjects will be randomized.

Patients will be randomly assigned, in 1:1 ratio, to study either GC4711 or placebo for an estimated 110 patients per arm. Patients will be randomized at approximately 25 centers in the US, and 15 additional centers outside the US (Canada, EU, or UK). See Section 9.1 for Sample Size Determination.

Subjects must be diagnosed with nonmetastatic unresectable or borderline resectable PC or be medically unfit for surgery for PC. Subjects who remain metastasis-free after response evaluation following chemotherapy will be considered for participation. Eligible subjects will be randomized in a 1:1 ratio to receive either GC4711 100 mg (Arm A) or placebo (Arm B) via IV infusion over 15 minutes (+5 min) before each of 5 fractions of SBRT, beginning the day of the first fraction of SBRT and ending the last day of SBRT (Figure 1: Study Design).

All newly diagnosed subjects will receive at least 6 weeks of chemotherapy consisting of EITHER a) FOLFIRINOX, modified FOLFIRINOX (without bolus administration 5FU, q14) OR b) a gemcitabine-doublet regimen (e.g., gemcitabine combined with nab-paclitaxel, cisplatin, capecitabine, q30) prior to SBRT. There is no upper limit on the number of pre-SBRT chemotherapy cycles that a subject may receive as long as there is no evidence of metastatic spread during treatment with the initial chemotherapy regimen. Subjects may change chemotherapy regimens prior to SBRT (but still limited to FOLFIRINOX, mFOLFIRINOX or a gemcitabine-doublet regimen) for issues of toxicity or intolerance, per institutional practice/SOC/NCCN guidelines. Subjects with local progression are not excluded as long as they remain non-metastatic at screening Subjects who commence chemotherapy with single-agent gemcitabine but who are then able to tolerate either a gemcitabine doublet, FOLFIRINOX or mFOLFIRINOX may also be included in the trial as long as they fulfill the requirements for at least 6 weeks of pre-SBRT combination chemotherapy with these regimens as outlined above. Other variations such as FOLFOX or FOLFIRI are also acceptable; any other variations must be discussed with the Medical Monitor prior to randomization. After at least 6 weeks of combination chemotherapy subjects will be evaluated by CT and MRI scan for SBRT feasibility and for disease progression; those without metastases will be considered for enrollment.

Eligible subjects will be stratified at randomization based on disease status at diagnosis: borderline resectable vs unresectable (radiographically or medically inoperable, as determined by the multidisciplinary group following the NCCN definition v1.2020, see Appendix 5).

Due to the risk of a radio-sensitizing effect of fluorouracil and gemcitabine, SBRT should not be started until at least one week following the end of the last chemotherapy cycle. Following SBRT (and surgery, if possible), patients may receive additional adjuvant chemotherapy at the discretion

of the investigator per institutional practice/SOC/NCCN guidelines. All anti-cancer therapy will be collected and documented through study duration.

SBRT will be delivered in 5 fractions of 10 Gy to the confirmed residual GTV (macroscopic tumor) and at least 30Gy to the CTV, while respecting normal tissue constraints; no nodal elective fields will begiven, only macroscopic tumor areas will be targeted (Palta 2019). SBRT fractions should be given with MR or CT-image guidance, matching both target and avoidance structures, confirming respect of constraints. Fractions will be given within 180 minutes from the end of the GC4711 or placebo infusion. Between fractions, a minimum of 18 and a maximum of 72 hours is permitted. Additionally, an occasional 96-hour window is acceptable (i.e. in case of a holiday or machine breakdown). All 5 fractions must be given within a maximum of 10 calendar days. If a subject is unable to receive their treatment within 10 days, the Medical Monitor and Galera study team should be notified. Each participating center will provide SBRT certification, and all radiation treatment plans will be centrally reviewed.

Detailed information on the Radiation Therapy Quality Assurance (RTQA), CT/MRI imaging (at randomization, RT planning/treatment, and 4 weeks after SBRT) is outlined in the RTQA Manual. Blood sampling for PK analysis and cardiac monitoring will be performed on each subject following two separate doses of GC4711 or placebo, and samples will be collected pre-infusion, immediately after infusion, and 24 hours after infusion for each of the two doses.

After SBRT, subjects judged by the site's institutional multidisciplinary group to be technically unresectable or medically inoperable or refusing surgery may receive additional chemotherapy at the discretion of the investigator, and according to standard of care, institutional practice, and NCCN guidelines, as applicable.

The subjects judged by the multidisciplinary group to be 'technically and medically resectable' on CT/MRI (Appendix 5) after SBRT will be surgically explored within 8 weeks following SBRT, and outcomes of margins and pathology remission will be scored from the local pathology reports. Following surgery, additional chemotherapy may be administered at the discretion of the investigator and according to standard of care, institutional practice, and NCCN guidelines, as applicable. All anti-cancer therapy will be collected and documented through study duration.

An independent Data Monitoring Committee (DMC) will be established. Refer to Section 9.7.

All imaging for efficacy assessment will undergo retrospective, independent central review (following RECIST 1:1). Local imaging assessments will be used for study eligibility and treatment decisions.

4.2 Study Duration for Participants

The study duration for participants is expected to be up to approximately 40 months. This includes a 28-day screening period, chemotherapy, a treatment period with SBRT, surgical exploration where possible, additional chemotherapy and follow up for survival, progression and long-term safety.

In case of distant disease progression, following the 90-day AE follow up period, subjects will be followed every 3 months through 2 years post-SBRT and then at 28, 34 and 36 months post-SBRT to monitor survival status and new anti-cancer therapy; no additional study assessments will be required after this point.

4.3 Replacement of Participants

All subjects randomized will be included in the intent-to-treat (ITT) population. The reasons why subjects did not receive SBRT and/or drug will be recorded. Screen-failures (see section 5.2) can be replaced if randomization did not take place.

4.4 End of Study Definitions

End of Study (Individual Participant): A participant is considered to have completed the study if he/she has been followed for survival through death or for at least 3 years following SBRT.

Primary Completion: The primary completion date is defined as the date when the last participant is assessed or receives an intervention for the final collection of data for the primary endpoint for the purposes of conducting the primary analysis.

End of Study (End of Trial): The end of the study is defined as the date of the last visit of the last participant in the study. Both the sponsor and the investigator reserve the right to terminate the study at any time. In terminating the study, Galera Therapeutics, Inc., and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (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.

4.5 Rationale for SBRT Regimen

In non-clinical development, GC4711 has shown the potential of increasing efficacy of high-dose RT as well as limiting the associated inflammatory and fibrotic reactions in normal tissues. SBRT is increasingly used in PC, facilitating dose-escalation; however, dose coverage is still hindered by normal tissue constraints. Several reports on multicenter 5-fraction SBRT regimens have confirmed

feasibility and potential survival benefits (Suker 2019, Mellon 2015, Herman 2015) as well as superiority to conventionally fractionated RT (Zhong 2017). With online imaging tools and adaptive planning (CT-on-rails, MR-linac), total dose of 5 × 8 Gy on tumor with 3-mm margins (Boldrini 2019, Suker 2019) or 5 ×10 Gy prescribed on tumors with reduced margins towards bowel structures (Hassanzadeh 2020, Henke 2018) have been reported safe and are currently being used in an on-going clinical trial (NCT03621644). Dose escalation (> 55 Gy) is directly related to survival improvement when RT is given after induction chemotherapy, although these doses are limited by normal tissue constrains (Jung 2019, Elhammali 2015).

By adding GC4711 to a 5-fraction SBRT regimen performed with daily image guidance (Reyngold 2019, Rudra 2019, Palta 2019), we aim to enhance both tolerance and disease control in locally advanced or borderline resectable PC. SBRT will be delivered with BED of 100 Gy in 5 fractions (Hoyer 2005, Colbert 2018, Petrelli 2017, Jaoude 2020) as used in the GC4419-101 trial and the SMART trial (https://clinicaltrials.gov/ct2/show/NCT03621644).

4.6 Rationale for GC4711 Dose and Schedule

A GC4711 dose of 100 mg administered via IV over 15 minutes on 5 days concurrent with SBRT administered in 5 fractions over the same period is proposed for this trial. In the healthy human volunteer study (GTI-4711-002), IV administration of GC4711 was found to be well-tolerated with a single administration at dose levels up to 120 mg and with repeated dosing of 90 mg/day for 14 days or a total weekly dose of 630 mg. Therefore, GC4711 at a dose of 100 mg given daily over 5 days is expected to be tolerated by cancer patients.

5 STUDY POPULATION

Before any study-specific activities/procedures can be performed, the appropriate written informed consent must be obtained.

5.1 Eligibility Criteria

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

Inclusion Criteria:

1. Histological or biopsy proven adenocarcinoma of the pancreas. Cytology is acceptable if histology cannot be obtained
2. Newly diagnosed non-metastatic PC judged by site's institutional multi-disciplinary group to be feasible for SBRT, as well as having measurable disease as defined by RECIST 1.1 and classified following NCCN guidelines v1.2020 (see Appendix 5):
   a. Locally advanced and technically unresectable determined by multidisciplinary review at the investigative site
   b. Potentially resectable, but subject is judged not a candidate for surgery, determined by multidisciplinary review at the investigative site

c. Potentially resectable, but the subject refuses surgery and is considered an acceptable candidate for SBRT determined by multidisciplinary review at the investigative site (reason for b and c are documented at randomization)
d. "Borderline" resectable, as determined by multidisciplinary review, including absence of distant lymphadenopathy

3. Completed at least 6 weeks of chemotherapy consisting of FOLFIRINOX, mFOLFIRINOX, and/or a gemcitabine-based doublet regimen prior to start of SBRT. Other variations such as FOLFOX or FOLFIRI are also acceptable; any other variations must be discussed with the Medical Monitor prior to randomization.
4. Remain non-metastatic as confirmed by a CT scan at screening
5. Female or male subjects ≥ 18 years of age
6. ECOG performance status of 0-2
7. Adequate end-organ function, based on routine clinical and laboratory workup:
   a. ANC > 1,000 cells/µl, platelets ≥ 75,000 cells/µl, hemoglobin ≥ 7.0 g/dl
   b. Calculated creatinine clearance ≥ 30 ml/min
   c. Total bilirubin ≤ 2.5 × ULN, AST and ALT ≤ 3 x ULN
   d. International normalized ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless participant is receiving anticoagulant therapy
8. Males and females of childbearing potential must agree to use highly effective contraception starting prior to the first day of treatment and continuing for 30 days (females) and 90 days (males) after the last dose of GC4711 or placebo (Appendix 8))
9. Ability to understand and the willingness to sign a written informed consent form (ICF)

Exclusion Criteria

1. Subjects with documented metastatic disease using standard work-up (per investigator) at diagnosis and/or at the screening response evaluation
2. First-line chemotherapy other than FOLFIRINOX, mFOLFIRINOX, and/or a gemcitabine-based doublet regimen. Subjects receiving either regimen after initial gemcitabine monotherapy are eligible.
3. Prior abdominal RT with substantial overlap in radiation fields as determined by the treating radiation oncologist
4. Subjects not recovered/controlled from treatment-related toxicities judged by the local investigator
5. Uncontrolled malignancy other than PC that requires active treatment
6. History of allergic reactions attributed to compounds of similar chemical or biologic composition to GC4711
7. Uncontrolled gastric or duodenal ulcer disease within 30 days of dosing
8. Visible invasion of bulky tumor into the lumen of the bowel or stomach on endoscopy (Note: Radiological or superficial bowel infiltration is allowed, unless deemed clinically unsafe).

9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring an inpatient stay or delay of therapy, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements
10. Subjects Gilbert syndrome who are homozygous for the UGT1A polymorphism.
11. Subjects with hypokalemia whose QT/QTc interval > 470 ms (for women) and > 450 ms (for men) on the screening ECG at visit
12. Treatment with any investigational drug outside this protocol since diagnosis until disease progression given for the disease in study. Prior to the randomization of subjects on other investigational agents, Sponsor's written approval must be obtained.
13. 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
14. Female subjects who are pregnant or breastfeeding
15. Any other conditions that, in the investigator's opinion, might indicate the subject to be unsuitable for the study
16. Subjects who have already undergone resection of their pancreatic tumors.

5.2 Screen Failures

Initial eligibility determination will be at the discretion of the treating investigator and discussion in the site's institutional multidisciplinary group, following NCCN v1.2020 guidelines (Appendix 5) for diagnostic criteria of unresectable or borderline resectable PC and standard work-up for documentation of distant disease. The Medical Monitor will be available for discussion regarding eligibility criteria.

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

5.3 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Subject Study Withdrawal: In accordance with the Declaration of Helsinki, a subject has the right to withdraw from the study at any time for any reason. Subjects who withdrawal consent early should be encouraged to continue with survival and late toxicity follow-up, if feasible.

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

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

- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, etc.)
- The subject was "lost to follow-up"
- Unacceptable adverse event necessitating treatment cessation (Grade 4 or recurrent Grade 3 adverse event related to GC4711/placebo).
- More than three infusion modifications of GC4711/placebo
- Subject requests to withdrawal from the study treatment
- Subject becomes pregnant
- Other reasons (reason must be specified, for example: the subject moved, investigator decision, Sponsor decision to terminate trial, etc.)

If a subject discontinues from the study treatment early (did not complete all 5 fractions of SBRT), they will continue to be followed for progression, toxicities and survival as outlined in the SOA.

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

6 STUDY INTERVENTION

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

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

6.1 Investigational Product: GC4711

6.1.1 Dosage Formulation and Preparation

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

6.1.2 GC4711 Dosage, Administration, and Schedule

Arm A: 100 mg/day of GC4711 will be given via IV infusion over 15 minutes (+5 minutes), prior to each SBRT dose, from the first to the last SBRT treatment (5 doses). On days of SBRT,

GC4711 will be administered with a maximum of 180 minutes between the end of infusion and the start of SBRT.

Arm B: Placebo (normal saline) will be administered via IV infusion over 15 minutes (+5 minutes) to be completed with a maximum of 180 minutes prior to SBRT as for Arm A.

A total of 100 mL of GC4711 or Placebo (normal saline) will be infused IV over a 15-minute period using a programmable pump, when feasible. Each infusion should be given before each of the 5 SBRT treatments, and all treatments should occur within a 10-day window. (See Table 1: Schedule of Assessments)

6.1.3 GC4711 Handling/Storage/Accountability

Study drug will be administered under the supervision of study site personnel. The infusion volume and timing of each dose will be recorded. A separate study Pharmacy Manual will provide additional details for preparation/handling/storage and accountability.

6.1.4 GC4711 Drug Packaging and Labeling

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

Normal saline will be provided and prepared by the local site pharmacy for subjects assigned to placebo.

6.1.5 Maintenance of the Blind

All staff at the site should be designated as either blinded or unblinded.

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

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

6.1.6 Investigational Product Storage

GC4711 should be stored in the pharmacy at or below -15°C. The sodium bicarbonate aqueous buffer diluent will also be stored in the pharmacy. The diluent must be stored under refrigerated conditions (2 to 8ºC) and must not be frozen. The storage temperature should be monitored and recorded daily as per site SOPs to ensure temperatures are maintained as per above. Copies of temperature monitoring logs will be made available to the CRA upon request. The Sponsor must be notified of any deviation from the specified storage conditions.

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

6.1.7 Study Intervention Compliance

Study drug will be administered under the supervision of study site personnel. The infusion volume and timing of each dose will be recorded. Accidental overdoses should be reported to the Sponsor/designee promptly (see Section 8.4.7).

6.2 Concomitant Medications

Investigators may prescribe concomitant medication or supportive care as deemed necessary. All such current medications taken, including anti-emetics, steroids, and anti-tumor treatments, as well as any (surgical) interventions will be recorded from 30-days prior to dosing of GC4711/placebo through 3 months after completion of SBRT. After the 3 Month follow up visit, only medications used to treat late radiation toxicities should be recorded through 1 year (or distant disease progression, whichever comes first), including inhalers, steroids, oxygen supply, etc. Additionally, any new anti-cancer therapy given at any point during follow-up (including survival follow-up) should be recorded in the CRF through 36 months post-SBRT.

6.3 Drug Interactions

6.3.1 CYP2D6 Substrates

The clinical potential of GC4711 to increase the concentration of drugs that are CYP2D6 substrates has not yet been studied. However, a GC4711 analogue also in clinical development, GC4419, has demonstrated preclinically and clinically to be a strong inhibitor of CYP2D6. It is recommended to avoid concomitant use of GC4711 with CYP2D6 substrates where minimal increases in concentration of the CYP2D6 substrate may lead to serious or life-threatening toxicities (substrates with a narrow therapeutic range or are strong inhibitors of CYP2D6).

The following medications are classified as strong inhibitors of CYP2D6 (drugs that cause a ≥ 5-fold increase in the plasma AUC values or more than a 80% decrease in clearance): bupropion, fluoxetine, paroxetine, and quinidine. (https://drug-interactions.medicine.iu.edu/MainTable.aspx)

The following medications are classified as CYP2D6 substrates with a narrow therapeutic index: dosulepin, flecainide, sotalol, pimozide, procainamide, theophylline, trabectedin, enasidenib, erlotinib, idarubicin, ixazomib, tamoxifen, rucaparib, dacomitinib, clonidine, desipramine, clomipramine, amitriptyline, imipramine, notriptyline, trimipramine, bortezomib, amoxapine, dronedarone, astemizole, ponatinib, phenytoin, doxorubicin.
https://go.drugbank.com/categories/DBCAT004031.

In addition, inducers or strong inhibitors of CYP2D6 should be avoided in conjunction with administration of GC4711. A list of such inducers and inhibitors may be found at: https://drug-interactions.medicine.iu.edu/MainTable.aspx

6.3.2 **OCT2, MATE1 and MATE2-K Transporters**

GC4711 was tested *in vitro* for its potential as an inhibitor or substrate for the human transporters organic cationtransporter (OCT) 2, multidrug and toxin extrusion transporter (MATE) 1, and MATE2K. GC4711 demonstrated inhibition against 3 of the transporters, OCT2, MATE1, and MATE2K, all involvedin the transport of organic cations (e.g., creatinine, metformin, and cimetidine). The Cmax of GC4711 demonstrated potential to inhibit renal OCT2, MATE1 and MATE2-K transporters which could affect the clearance of other organic cation drugs.

Based on this information caution should be used when administering the following OCT2, MATE1 and MATE2K subtrates with a narrow therapeutic index concomitantly with GC4711: topotecan, procainamide, baricitinib, niraparib, abemaciclib, tipiracil, flecainide, niraparib, cisplatin, oxaliplatin, dalfampridine, dofetilide, clofarabine and gentamicin.
(https://go.drugbank.com/categories/DBCAT004582,
https://go.drugbank.com/categories/DBCAT004525,
https://go.drugbank.com/categories/DBCAT004526)

In addition, caution should be used when concomitantly administering the following MATE2K inhibitors with GC4711: tazemetostat, avapritinib, trilaciclib, capmatinib, fexinidazole, and olaparib. (https://go.drugbank.com/categories/DBCAT005491)

6.4 Prohibited Medications

Investigators may prescribe any concomitant medication or supportive care. All medications and new treatments will be reported in the follow-up visits through 3 months following SBRT completion, and medications associated with late toxicities will be reported until documented progressive disease. Supportive care includes anti-emetic prophylaxis, hematopoietic growth factors used according to ASCO guidelines, systemic antibiotics, hydration to prevent renal damage, or other treatments, consistent with local standard of practice. GC4711 may cause mechanism-related, transient hypotension, or lightheadedness.

Because of the potential for such mechanism-related toxicities, the following drugs that could precipitate drops in blood pressure, should not be taken by patients while receiving GC4711:

- Nitrates (sublingual, oral or transdermal nitroglycerin; oral isosorbide mono- or dintitrate)

- Phosphodiesterase type 5 (PDE 5) inhibitors (sildenafil, tadalafil, vardenafil, avanafil).

- Alpha adrenergic blocking agents prescribed for hypertension, benign prostatic hypertrophy, prostate cancer treatment effects, and peripheral artery disease (doxazosin, prazosin, terazosin, tamsulosin, alfuzosin, silodosin, phenoxybenzamine, phentolamine).

- Other drugs that in the judgment of the treating investigator could create a risk of a precipitous decrease in blood pressure are prohibited until at least 24 hours after the last dose of GC4711 or placebo.

- Treatment with any investigational drug outside this protocol since diagnosis until disease progression given for the disease in study (e.g., chemotherapy, immunotherapy, targeted therapy, hormone therapy, and biologic therapy). Prior to the randomization of subjects on other investigational agents, Sponsor's written approval must be obtained.

If nitrate-based medication was replaced by alternative treatment or stopped by the local investigator before study entry, subjects can restart their regular medications 24 hours after completion of GC4711 or placebo treatment.

Patients on antihypertensives should take their hypertensive medications separated by several hours from GC4711. As an example, if GC4711 is to be administered early in the day, any antihypertensive medication should be administered later in the day. Drugs that have the capacity to cause precipitous drops in blood pressure should be avoided.

In addition to the above, a single patient with a history of myasthenia gravis and carotid sinus sensitivity developed severe symptomatic bradycardia associated with nausea and hypotension after receiving GC4419. Given that GC4711 is an analog of GC4419, GC4711 should be used with caution for patients with a clinical history or with medication requirements that may place them at risk for being unable to mount a physiologic tachycardia to decreases in blood pressure.

6.5 Anticipated toxicities

6.5.1 Anticipated Toxicities of GC4711

Per the IB, the following individual AEs observed in healthy volunteer studies are listed and considered "expected" after GC4711 infusions:

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

- fatigue

6.5.2 Toxicity Management/Infusion Modifications

Any subject who receives treatment with GC4711/Placebo on this protocol will be evaluable for toxicity. Each subject will be assessed for the development of toxicity according to the SOA (Table 1). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

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

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

Patients who experience a toxicity noted above during or shortly after the infusion of GC4711/placebo should have their infusion times increased to 30 minutes (+5 minutes).

If the toxicity recurs, the infusion time should be increased to 45 minutes (+5 minutes), and may be increased to 60 minutes (+5 minutes) if hypotension occurs with a 45-minute infusion.

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

6.5.3 Anticipated Toxicities of SBRT

PC by itself can also induce many symptoms (e.g., abdominal pain, bleeding, and obstruction), stressing the fact that disease progression needs to be excluded before relating these symptoms to treatment. All subjects are exposed to multi-modality treatment and therefore are at risk to accumulate different toxicities from chemotherapy, SBRT, and surgery as well (Jaoude 2020, Reyngold 2019). Explaining the risk of local high dose RT delivery is important for each individual subject. The following adverse events are used in the protocol and informed consent form based on Common Toxicity Criteria (CTCAE) version 5 (Table 3).

Very likely (80-90%):

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

Less likely (30%):

- Temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms

- Vomiting (during therapy)
- Diarrhea
- Ulcers
- Skin irritation, redness, itchiness, discomfort
- Pain
- Breathing discomfort, hick-ups

Nausea and vomiting may be managed with standard anti-emetic regimens (5-HT3-receptor antagonists, NK1 receptor antagonists); diarrhea may be managed with standard anti-diarrheal agents (loperamide); pain/abdominal pain may be managed with routine analgesics. Changes in blood counts should be carefully followed and patients transfused with blood products as clinically indicated or treated with prophylactic antibiotics in the event of neutropenia. Skin irritation may be managed with dermatologic lubricants (e.g., aloe).

Less likely, but serious (<20%):

- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction, or changes in motility following therapy (may require medications or surgery, < 10% permanent changes)

- Radiation-induced liver disease (RILD, <5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver

- Non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in subjects with large tumors and/ pre-existing liver disease.

- Permanent thrombocytopenia (<1%); this may lead to bleeding

- Kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.

- Spinal cord injury

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

Table 3: Expected acute and late SBRT toxicities summarized

Acute:	**Late:**
• Abdominal pain • Nausea, vomiting	• Liver failure • Kidney failure

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

6.5.4 Anticipated Complications of Surgery

Overall, 50% of the borderline resectable and 30% of the unresectable subjects are expected to be surgically explored. Surgery can be performed within 8 weeks after SBRT or in a later stage if awaiting greater mass reduction or need for a palliative intent (e.g., bypass for obstruction).

Pancreatic surgery is known for 30-day mortality rates of 5%, which are lower in high-volume medical centers (Bradley 2002). The most common causes of mortality are gastric ischemia, post-pancreatectomy hemorrhage, pneumonia, liver ischemia, abdominal infection, and sepsis with multi-organ failure. The additional 90-day major morbidity rate is around 25%, most often featuring delayed gastric emptying, post-pancreatectomy hemorrhage, and pancreatic fistulas or postoperative organ space infections (Klompmaker 2019).

6.5.5 Anticipated Complications of Chemotherapy

Most common Grade 3-4 AEs following FOLFIRINOX are (febrile) neutropenia, thrombocytopenia, anemia, fatigue, nausea, diarrhea, vomiting, neuropathy, and increased ALT (Suker 2016). In this protocol, modified FOLFIRINOX is proposed because it offers comparable survival benefits with fewer AEs compared to the conventional dosage (Tong 2018).

In subjects treated with gemcitabine-doublets (e.g., combinations with cisplatin or 5FU- or targeted therapies) Grade 3–4 toxicities, neutropenia, febrile neutropenia, and nausea were reported lower, while neurotoxicity and anemia were lower with FOLFIRINOX (Pusceddu 2019, Chiorean 2019).

6.5.6 Chemotherapy dosing adjustments

Subjects will receive at least 6 weeks of chemotherapy prior to evaluation for SBRT consisting of FOLFIRINOX, mFOLFIRINOX, or a gemcitabine-based doublet regimen (e.g., gemcitabine combined with nab-paclitaxel, cisplatin, capecitabine). Many subjects will need dose reduction and/or simplification of their chemotherapy regimen throughout the period of chemotherapy administration; all such changes will be made at the discretion of the investigator and based on the full-prescribing information for each individual agent and accepted standards of medical practice/NCCN guidelines for the administration of FOLFIRINOX/mFOLFIRINOX or gemcitabine-doublet regimens.

7 STEREOTACTIC BODY RADIATION THERAPY (SBRT)

7.1 SBRT Principles

All subjects will be evaluated by the treating radiation oncologist at the local site. Based on location and size of the tumor, dose planning will be determined by clinical appropriateness that balances ablation of the lesion(s) and corresponding macroscopic tumor areas (GTV), while respecting normal tissue constraints. Details of the radiotherapy treatment can be found in the RTQA manual.

7.2 Treatment schedule

The start of SBRT must be at least 7 days but maximum 42 days after last chemotherapy cycle is given (the 7 – 42 day window will begin at the end of the treatment cycle, not on the last day of actual treatment). Treatments may start on any day, given sequentially within a 10-day window. Fractions should be given sequentially daily within 180 minutes of the end of the infusion of GC4711 or placebo. Between fractions, a minimum of 18 hours and a maximum of 72 hours is permitted. Additionally, an occasional 96-hour window is acceptable (i.e. in case of a holiday or machine breakdown). All 5 fractions should be given within a maximum of 10 calendar days. If a subject is unable to receive their treatment within 10 days, the Medical Monitor and Galera study team should be notified.

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

Prescription of proton inhibitors for each subject is strongly recommended. Anti-emetic and anti-diarrheal prophylaxis and hematopoietic growth factor use should be administered per ASCO guidelines.

7.3 Quality Review

Each participating center will provide SBRT certification, and all radiation treatment plans will be centrally reviewed.

Radiation plans for all subjects will be reviewed per site by the local investigator prior to treatment start. Signing off can be done by another radiation oncologist in the same institution but is preferred to be done by both the treating physician and the local investigator.

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

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.

After internal validation, the RTQA group will perform a quality check on the first 2 subjects' treatment plans before start of treatment and all other plans in a retrospective manner per the RTQA Manual.

The RTQA group will work with all sites at site initiation to ensure consistency in RT among participating centers, including discussion of standard cases, SBRT experience, motion management approach and planning rules.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SOA (Table 1).

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention. Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. A previously performed CT scan, MRI scan, safety blood work (serum chemistry and complete blood work) or other study assessments done per standard of care may be utilized for screening if done within 28 days prior to randomization.

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

8.1 Imaging protocols

8.1.1 CT imaging

Staging and disease response evaluation will be performed by CT scan according to the SOA. Both local and central review reading will be based on RECIST 1:1 (Eisenhauer 2009), see Appendix 2). CT scans are reported following the outline of the Imaging Manual and will drive trial inclusion and treatment decisions. Images should be performed with IV contrast, if possible (i.e., no allergies and appropriate kidney function), and with a slice thickness of 5 mm or less. All CT-imaging will be interpreted locally by the investigational site radiologist and retrospectively centrally reviewed. In case of allergies to IV contrast, MRI or PET/CT are allowed for response evaluation measurements. The same method of imaging used at baseline should be used at each follow-up evaluation for evaluation of treatment response, if possible (see Imaging Manual).

In case the CT-scan at 4 weeks after SBRT shows local progression, confirmation will be needed at the next scheduled imaging timepoint at Month 4 to exclude the risk of pseudo-progression after SBRT (Ma 2019), based on post-RT inflammatory reactions.

8.1.2 MRI imaging

MRI imaging (at 1.5 or 3.0 Tesla) is used in the protocol for the local judgement in the multidisciplinary group upon:

1) definition of unresectable versus borderline resectable disease (see Imaging Manual),

2) SBRT feasibility and planning, and

3) evaluation of technical resectability 4 weeks after completion of SBRT (confirming a tissue plane between the tumor and normal structures excluded from Whipple resection (e.g., large vessels).

The MRI images will be collected and centrally reviewed retrospectively.

For RT planning, the T1 sequences are important for the GTV delineation, while the T2 can show tumor invasion in vascular and bowel structures to be included in the CTV. Aside of the target volumes, the OARs are contoured on CT images (4D acquired), see RTQA Manual for more information.

When MRI is contraindicated, a CT scan is acceptable if fiducials have been placed.

8.2 Efficacy Assessments

8.2.1 Definitions for Response Evaluation

8.2.1.1 Overall Survival

The OS is defined as the time from randomization to death due to any cause. Survival status will be collected as defined by the SOA. Subjects will be followed for survival status every 3 months until 2 years then every 6 months through 3 years post-SBRT completion. All subjects who are in the Survival Follow-up and not known to have died prior to Sponsor requests for additional survival status timepoints may be contacted at that time to confirm survival status.

8.2.1.2 Progression-Free Survival

The PFS is defined as the time from the date of randomization to first occurrence of local and/or regional progression, distant metastases (=PD), or death due to any cause, whichever occurs first.

8.2.1.3 Local and Regional Control

Local and regional control is defined as the time from randomization to any local and regional recurrence or progression (in RECIST 1.1 reported as target lesions). Local enlargement, marginal

failures, involved nodal failure, or local failure (see below) will be considered failure events for local and regional control. Regional failure (see below) will be a failure event for local and regional control. Distant metastases are not considered local progression. Patients who die without progression of PC will be considered non-failures for local and distant progression and will be censored as of the data of their last imaging assessment which demonstrated progression free.

8.2.1.4 Time to Distant Metastatic Disease

TDM rate refers to the time from randomization to cancer that has spread from the original (primary) tumor to distant organs (in RECIST 1.1 addressed as any new lesion).

8.2.1.5 Best Overall and In-Field Response

The best overall response is determined once all the data for each subject is known. The best overall response is the best response recorded from randomization until disease progression/recurrence across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). Best overall response rates will take both target (pancreas lesion and up till 5 nodal lesions taken together) and development of new non-target lesions (distant lesions) into account, taking as reference for progressive disease the smallest measurements recorded since the treatment started. Best in-field response is defined as the best response from randomization across all time points and considers the defined target lesions only.

8.2.1.6 Resection rates

Surgical resection is known as the main prognostic driver for survival (Mellon 2015, Jaoude 2020). In both arms, the number of subjects judged by each institution's multidisciplinary group after SBRT as "technically resectable" will be counted. Margin status will be documented as R0 (negative) or R1 (positive). Not all subjects, who are surgically explored, will be resected, and the reasons for this will be documented.

The proportion of all randomized subjects in whom R0 or R1 resection is achieved will be compared among arms. Response is classified as unresectable (no resection performed), pNC (no response as observing more than 30% residual tumor cells in the specimen), pPR (partial response as ≥ 5% to 30% residual tumor cells) pNR (near complete response as 1 to < 5% residual tumor cells) and pCR (complete response as 0% residual tumor cells).

8.2.1.7 CA19.9 normalization

Normalization is defined as reaching the value of ≤37 U/ml from screening across all follow-up time points. Three categories are defined: normalization throughout 6 months, decrease of >30% but no normalization and increase over 90 U/ml before 6 months or no significant decrease (<30%). Distribution into these categories will be compared across the two arms and related to resection rates and survival.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SOA (See Appendix 4 for definitions and Table 1 for timing).

8.3.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Weight will also be measured and recorded. Height should only be recorded at screening. The physical examination should be performed by a physician or health professional and licensed to perform physical examinations.

8.3.2 Vital Signs

Vital sign measurements prior to each infusion will include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature. Pulse and blood pressure readings will be taken within 15-minutes prior to and after each infusion. The subject should be at rest (seated or supine) for 2-5 minutes prior to taking the vital signs.

8.3.3 Electrocardiograms

A 12-lead ECG recording will be conducted using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The recordings should be as close as possible to corresponding PK sampling (see the SOA, Table 1) ± 10 minutes from the PK blood draw. The pre-dose and post-dose ECG should be done in triplicate with a single ECG at the 24-hour timepoint prior to the next dosing.

8.4 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

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

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

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

All AEs/SAEs will be collected for all subjects from the Day 1 dosing through 90 days post-SBRT. Ongoing SAEs at 90 Days post-SBRT will be followed through resolution. After 90 days post-SBRT, AEs/SAEs associated with late toxicities will be followed through 1 year post-SBRT or until distant disease progression (see Table 3, Section 8.4.6).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. Specific SAE reporting instructions are provided in a separate manual.

8.4.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

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

8.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is given in Appendix 4.

8.4.4 Regulatory Reporting Requirements for Serious Adverse Events

1. Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
2. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
3. Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators, as necessary.
4. An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

The risks of treatment with GC4711 during pregnancy have not been evaluated. Male subjects and female subjects of childbearing potential who engage in sexual intercourse should use a highly effective method of contraception throughout the study and for 30 days (females) or 90 days (males) following the last dose of GC4711 or placebo. If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 8.

8.4.6 Late Toxicities

Late toxicities will be collected as per the SOA. Late toxicities (See Section 6.4) are collected from 90 days through 1 year after SBRT completion (see Table 3 for distinction acute versus late and most common AEs). Collection will be stopped after documented distant disease progression, because of accumulation of symptoms generated by disease and/or sequential treatments. Late toxicities scored are restricted after 90 days of follow-up to and defined as below using CTCAE (version 5.0):

1. Grade 2-5 GI events, including bowel stenosis, obstruction, or perforation
2. Grade 3-5 spinal cord/brachial plexopathy and vascular events
3. Grade 3-5 persisting hematological disorders
4. Grade 3-5 general disorders as fatigue, anorexia
5. Grade 3-5 liver or kidney injury or failure

8.4.7 Treatment of Overdose

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated per protocol for a given subject. Any study drug overdose during the study should be noted on the study medication eCRF.

All AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in 4. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Galera Therapeutics Clinical Trial Report Form for SAEs and in an expedited manner but should be noted as non-serious on the form and the Adverse Event eCRF.

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

8.4.8 Misuse/Abuse

Any AEs associated with misuse or abuse will be appropriately reported as AEs or SAEs and monitored per Section 8.4.3 and 4.

8.5 Pharmacokinetics

PK sampling for GC4711 and its two metabolites GC4752 and GC4757 will be performed on all subjects. Blood sampling will be performed along with the ECGs on the days and times indicated in the SOA (Table 1) and outlined Table 4 below.

Table 4: PK Draw and ECG Windows

PK blood draw	PK draw window	ECG
Pre-dose	- 1 hour from start of infusion	±10 minutes of PK draw (triplicate)
EOI	+ 10 minutes from EOI	±10 minutes of PK draw (triplicate)

24-hours After Dose	± 1 hour from EOI or prior to dosing if delivered on next sequential day	±10 minutes of PK draw (single)

Abbreviations: EOI=end of infusion; PK=pharmacokinetics.

Refer to PK Manual for additional details on PK sample collection.

9 STATISTICAL CONSIDERATIONS

This section provides a high-level overview of the planned statistical analyses of the trial. A separate statistical analysis plan finalized before the database lock will include the full analytic details. In cases where the statistical analysis plan and this statistical section of the protocol differ, the details in the statistical analysis plan will guide the final analysis of the data.

9.1 Sample Size Calculation

The intended enrollment for the study is 220 patients. The sample size calculation is based on the primary endpoint of OS. Median OS in the control arm (placebo + SBRT) is estimated to be approximately 11 months from randomization (Mellon 2015, Krishnan 2016, Hammel 2013). Treatment with GC4711 + SBRT is expected to result in a 45% reduction in the OS hazard rate, which corresponds to an increase in median OS to 20 months assuming exponential survival.

To ensure 90% power to test the null hypothesis: OS hazard ratio = 1, versus the specific alternative hypothesis: OS hazard ratio = 0.55, 120 deaths need to be observed, assuming a two-sided Type I error rate of 5% and randomization at a 1:1 allocation ratio. To allow an interim analysis for benefit after 84 deaths (i.e., at roughly 70% information time) 120 deaths must be observed to maintain 90% power.

9.2 Randomization/Blinding

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, Sponsor, medical monitoring, the study monitor, contract research organization (CRO) personnel, and blinded statisticians, will be blinded to treatment assignment. The dispensing site study personnel will be unblinded. An unblinded Study Monitor will be assigned to the study for confirming drug accountability and monitoring at the site's pharmacy. The statistician who prepares the master randomization schedule will be unblinded as will the statistical reporting group that prepares safety and efficacy reports for the Data Monitoring Committee. Additional unblinding may include drug supply/RTSM staff, pharmacovigilance, and regulatory affairs as needed to comply with reporting requirements. The master randomization schedule will be saved in an access-controlled location to maintain the study blind.

Section Treatment assignment should remain blinded until analyses of the primary efficacy results of the study have been performed on the final, locked data through the end of post-SBRT follow-up for all subjects. Only in the case of an emergency, when knowledge of the investigational product is essential for the clinical management or welfare of the subject, may the investigator unblind an individual subject's treatment assignment prior to the completion of the primary and secondary

safety and efficacy analyses. The investigator will, whenever possible, discuss options with the Medical Monitor or appropriate Sponsor/CRO study personnel before unblinding. If the blind is broken for any reason and the investigator is unable to contact the Sponsor prior to unblinding, the investigator must notify the Sponsor/CRO as soon as possible following the unblinding incident without revealing the subject's study treatment assignment, unless the information is important to the safety of subjects remaining in the study.

If an SAE is reported to the Sponsor/CRO, the Sponsor/CRO staff may unblind the treatment assignment for the individual subject. If an expedited regulatory report to one or more regulatory agencies is required, the report will identify the subject's treatment assignment, consistent with applicable regulations for the territory in which the report is made. When applicable, a copy of the regulatory report may be sent to investigators in accordance with relevant regulations, the Sponsor policy, or both.

Randomization codes are generated and assigned using a Randomization and Trial Supply Management System, and electronic access to the randomization codes will be granted for unblinded team members or in cases where the treatment assignment is needed by the Pharmacovigilance/Safety team, risk management, or drug supply oversight by unblinded team members.

9.3 Analysis Populations

The primary efficacy population will include the intent to treat (ITT) population of all randomized subjects; the primary efficacy analysis will be performed on the primary efficacy population. The safety population will include all randomized subjects who receive any study drug (i.e., GC4711 or placebo). A "per protocol" efficacy analysis, limited to the safety population, may also be performed. Subjects will be analyzed according to the treatment (GC4711/placebo) and strata used at randomization. Stratification for borderline resectable versus unresectable will be based on the primary diagnosis as judged by the multidisciplinary group using NCCN v1.2020 guidelines (Appendix 5) before start of chemotherapy. Medically inoperable subjects and subjects refusing surgery will be included in the unresectable stratum. Survival is reported to be similar for (m)FOLFIRINOX or gemcitabine-doublet used in first line, therefore no stratification will be used for choice of first-line chemotherapy regimen（Chiorean 2019, Pusceddu 2019).

9.4 Analysis of the Primary Endpoint

The primary objective is to determine whether treatment with GC4711 combined with SBRT prolongs OS compared to placebo combined with SBRT.

9.4.1 Definition of Primary Endpoint

OS is defined as the time from randomization to the date of death due to any cause without consideration for whether subjects undergo resection following randomization. Subjects will be analyzed according to the treatment (GC4711/placebo) and strata used at randomization. Stratification for borderline resectable versus unresectable will be based on the primary diagnosis as judged by the multidisciplinary group using NCCN v1.2020 guidelines (Appendix 5) before start of

chemotherapy. Medically inoperable subjects and subjects refusing surgery will be included in the unresectable stratum.

9.4.2 Method of Analysis

The primary efficacy analysis will be the comparison of OS between the two treatment groups using a stratified log-rank test at an overall two-sided 5% level of significance. The stratification will be based on the stratification factors as entered at randomization. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians, and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for OS will be estimated along with its 95% confidence interval using a stratified Cox model using the same stratification values as for the log-rank test (Cox 1972).

9.4.3 Handling of Intercurrent Events

The primary analysis will account for different intercurrent events as follows:

1. **Discontinuation of study treatment**: survival data collected after treatment discontinuation will be used for the primary analysis regardless of the study treatment discontinuation reason.

2. **Surgical resection**: because study treatment could affect the probability of undergoing surgical resection, data on vital status after surgical resection of the primary tumor will be collected and included in the primary analysis.

3. **Other anti-cancer therapy:** survival data collected after initiation of other anti-cancer therapy will be included in the primary analysis.

9.4.4 Handling of Missing Values/Censoring/Discontinuations

In the primary analysis, subjects who do not die will be censored at the date last known to be alive before withdrawal of consent, loss to follow-up, or study closure.

9.4.5 Sensitivity and Supportive Analyses

In addition to the primary analysis, the OS hazard ratio and 95% confidence interval will also be assessed from analyses:

1. that censor subjects following resection of their primary tumor
2. that censor subjects after initiation of any other anti-neoplastic therapy
3. of each level of randomization stratification factor. If the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics may also be performed. Important subgroups will be specified in the statistical analysis plan.

9.5 Analysis of Key Secondary Endpoint

PFS, the key secondary endpoint, is defined as the time from randomization to the date of first documented progression or death due to any cause. Progression will be measured by local and/or distant progression confirmed by centrally reviewed CT based RECIST 1.1.

Assuming that the OS is significant, PFS may be formally tested at a two-sided 5% significance level. Other secondary endpoints will be analyzed descriptively.

9.5.1 Method of analysis of PFS

PFS will be analyzed in a similar manner as the primary OS endpoint.

9.5.2 Handling of intercurrent events for PFS

The analysis of PFS will account for different intercurrent events as follows:

1. **Discontinuation of study treatment**: tumor assessment data collected after treatment discontinuation will be used for the primary analysis regardless of the study treatment discontinuation reason.

2. **Surgical resection**: tumor assessment data and vital status after surgical resection of the primary tumor will be considered in the analysis of PFS. A sensitivity analysis may also be performed censoring subjects at last adequate tumor response assessment prior to resection.

3. **Start of other new anti-neoplastic therapies prior to disease progression**: PFS events documented after the initiation of new anti-neoplastic therapy (aside from resection) will not be used for the primary analysis. A sensitivity analysis may be performed that considers such assessments after initiation of new therapy.

9.5.3 Handling of Missing Values/Censoring/Discontinuations for PFS

In the main analysis of the endpoint, PFS will be censored on the date of the last adequate tumor assessment if no PFS event is observed. Because study treatment could affect the probability of undergoing surgical resection, PFS events documented after surgical resection of the primary tumor will be considered for the primary analysis provided tumor assessments continue. For subjects receiving a new anti-neoplastic therapy without prior progression, PFS will be censored on the date of the last adequate tumor assessment before the therapy. For subjects with PFS events observed after one or more missing or inadequate tumor assessments, PFS will be censored on the date of the last adequate assessment before the missing assessment(s).

The statistical analysis plan will include a complete set of censoring rules.

9.5.4 Sensitivity and Supportive Analyses

In addition to the main analysis of the endpoint, the PFS hazard ratio and 95% confidence interval will also be assessed from an analysis:

1. using the local investigators' determination of progression
2. censoring subjects after surgical resection
3. that considers tumor assessment and vital status information collected after initiation of anti-neoplastic therapies
4. of each level of randomization stratification factor. If the overall analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics may also be performed. Important subgroups will be specified in the statistical analysis plan.

9.6 Other endpoints

Other secondary efficacy endpoints are local tumor control and distant metastasis-free survival, which will be summarized descriptively using time-to-event methods; overall and in-field tumor response over time, will be descriptively compared using a Cochran-Mantel-Haenszel test stratified by the strata used at randomization.

Because surgical resection has been reported as associated with improved OS and PFS for this patient population (Mellon 2015, Jaoude 2020), the proportion of subjects with surgical resection will be documented and descriptively compared using a Cochran-Mantel-Haenszel test stratified by the strata used at randomization. Surgical exploration rates, margin status (R0, R1) and pathologic response will be summarized and compared descriptively.

Safety including both acute (for 90 days) and late (until distant progression or 1 year) toxicities, which will be summarized descriptively.

Exploratory endpoints consist of changes in patient-reported symptoms (PRO-CTCAE; Basch 2014, Kluetz 2016, Appendix 6) as well as collection of CA19.9 values and normalization patterns, BRCA mutations, and pharmacokinetics will be summarized descriptively.

9.7 Data Monitoring Committee (DMC)

This trial will be monitored for safety and efficacy by an independent Data Monitoring Committee (DMC). Based on its review, the DMC will make recommendations regarding the conduct of the study, i.e., to continue enrollment, to hold enrollment until further review, to amend the protocol, or to stop the study early. Details will be included in a separate DMC Charter.

9.7.1 DMC Interim Safety Analysis

After 20 subjects have been randomized, the DMC will be convened to review safety data through the 4 week visit after SBRT. At this analysis, the DMC will review all unblinded safety data available and will consider a recommendation to continue the trial, to make modifications or to temporarily suspend enrollment and treatment, and consider study revisions for safety if more than 4 subjects encounter a significant toxicity (section 10.8) in the experimental arm than in the control per arm. The DMC will review as part of its safety review the frequency of unacceptable delays in SBRT administration in the two study arms. For the purposes of this review, unacceptable delay

will be defined as EITHER a gap of 5 or more days between SBRT fractions OR a total SBRT delivery time (first to fifth fraction, inclusive) of more than 15 days. The expected frequency of such delays in the control arm is 10%. If the DMC judges the frequency of such delays due to potential toxicity and not to other factors (e.g., disease progression, missed visits due to COVID-19) in the GC4711 arm to exceed twice that of the control arm, it will consider recommending modification of the trial. The DMC Charter will include details of the safety analysis.

9.7.2 DMC Interim Efficacy Analysis

In addition to an interim test of superiority planned at N=84 deaths (70% information) as detailed below, a preliminary assessment will be performed at approximately N=36 events (30% information) to assess treatment effect and potentially result in decision to stop the trial early. Specifically, an observed hazard ratio exceeding 0.65 will support a decision to stop. Under exponential survival, an HR of 0.65 corresponds to a conditional power of 67% when the observed effect is assumed for the remainder of the trial. No alpha adjustment to the 2 look O'Brien-Fleming boundaries to assess superiority will be made.

After approximately 84 deaths have occurred, the DMC will be convened to review efficacy data. The goal of the interim efficacy analysis is to allow early stopping of the trial for overwhelming superiority. Unblinded results from the interim analysis will not be communicated to the Sponsor unless the DMC recommends that 1) OS has crossed the pre-specified boundary of efficacy and the trial should be stopped for benefit. or 2) the study needs to be terminated for safety or risk-benefit ratio considerations.

The pre-specified boundary will be calculated using a 2-look O'Brien-Fleming boundary as implemented using a Lan-DeMets alpha-spending function.

9.8 Significant Toxicities

Significant toxicities are defined (using the NCI-CTCAE grading scale) as Grade 3-5 AEs occurring from Day 1 through the 4 weeks' visit post SBRT, and *excluding* the following:

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

- Grade 4 neutropenia lasting >7 days.
- Grade 3 thrombocytopenia with clinically significant bleeding.
- Grade 4 anemia and grade 4 thrombocytopenia

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., participant recruitment advertisements) will be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

The investigator will be responsible for the following:

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

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with enough, accurate financial information, as requested, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the study and for one year after completion of the study.

10.1.3 Informed Consent Process

An initial Master-ICF-template sample ICF will be provided for the investigator to prepare the ICF to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Galera Trial Manager to the investigator. The written ICF is to be prepared in the language(s) of the potential subject population.

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If the ICF is amended, participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4 Data Protection

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

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

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

10.1.5 Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. The Sponsor or designee is responsible for the data management of this study including quality checking of the data. The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.6 Source Documents

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

10.1.7 Start and Closure of Study and/or Sites

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

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

The investigator may initiate study-site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended termination. Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

- Discontinuation of further study intervention development

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

10.1.8 **Publication Policy**

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

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

APPENDIX 1: Clinical Laboratory Tests

The tests detailed in Table 5 will be performed by the local laboratory at Baseline. Abnormal clinically significant local laboratory results including any collected outside of the protocol should be captured as Adverse Events.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5: Protocol-Required Safety Laboratory Assessments

Hematology	Biochemistry	Other
ANC Hemoglobin Hematocrit Red blood cell (RBC) Count White blood cell (WBC+diff) count Platelet count	Blood urea nitrogen (BUN) Creatinine Creatinine clearance Glucose Potassium Sodium Calcium Chloride CO_2 Inorganic phosphate Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transferase (GGT) Total bilirubin (direct bilirubin reflex if elevated) Albumin Alkaline phosphatase (ALP) Uric acid	INR/PTT* CA19.9**
Blood counts and chemistry labs collected at screening and the 4 week post-SBRT visit *INR/PTT only at screening **CA19.9 collected at follow-up visits through 1 year post-SBRT or until local or distant disease progression		

APPENDIX 2: RECIST 1.1 Tumor Response Evaluation

RECIST 1.1 Tumor Response Evaluation Definitions of the criteria used to determine objective tumor response for target lesions (Eisenhauer, 2009)	
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

APPENDIX 3: Reporting Guideline for Pancreas Imaging by CT and MRI

The below information should be included in each CT and MRI report

Morphologic Evaluation

Appearance (in the pancreatic parenchymal phase): hypo-, iso-, or hyperattenuating
Size (maximal axial dimension in centimeters): measurable or non-measurable (iso-attenuating tumors)
Location (head right of SMV, body left of SMV): head/uncinate or body/tail
Pancreatic duct narrowing/abrupt cutoff with or without upstream dilatation: present or absent
Biliary tree abrupt cutoff with or without upstream dilatation: present or absent

Arterial evaluation

SMA: Present or absent
Degree of solid soft tissue contact: ≤180° or >180°
Degree of increased hazy attenuation/stranding contact: ≤180° or >180°
Focal vessel narrowing or contour irregularity: present or absent
Extension to first SMA branch: present or absent
Celiac Axis: Present or absent
Degree of solid soft tissue contact: ≤180° or >180°
Degree of increased hazy attenuation/stranding contact: ≤180° or >180°
Focal vessel narrowing or contour irregularity: present or absent
CHA: Present or absent
Degree of solid soft tissue contact: ≤180° or >180°
Degree of increased hazy attenuation/stranding contact: ≤180° or >180°
Focal vessel narrowing or contour irregularity: present or absent
Extension to celiac axis: present or absent
Extension to bifurcation of right/left hepatic artery: present or absent
Arterial Variant: Present or absent
Variant anatomy: Accessory right hepatic artery, replaced right hepatic artery, replaced common hepatic artery, others (origin of replaced or accessory artery)
Variant vessel contact: present or absent
Degree of solid soft tissue contact: ≤180° or >180°
Degree of increased hazy attenuation/stranding contact: ≤180° or >180°
Focal vessel narrowing or contour irregularity: present or absent

Venous evaluation

MPV: Present, absent, or complete occlusion
Degree of solid soft tissue contact: ≤180° or >180°
Degree of increased hazy attenuation/stranding contact: ≤180° or >180°
Focal vessel narrowing or contour irregularity (tethering or tear drop): present or absent
SMV: Present, absent, or complete occlusion
Degree of solid soft- tissue contact: ≤180° or >180°
Degree of increased hazy attenuation/stranding contact: ≤180° or >180°

Focal vessel narrowing or contour irregularity (tethering or tear drop): present or absent
Extension to first draining vein: present or absent
Thrombus within vein: present or absent (MPV, SMV, or splenic vein) (tumor, bland)
Venous collaterals: present or absent (around pancreatic head, porta hepatis, root of the mesentery, or left upper quadrant)

Extra-pancreatic evaluation

Liver lesions: present or absent; suspicious/indeterminate or likely benign
Peritoneal or omental nodules: present or absent
Ascites: present or absent
Suspicious lymph nodes: present or absent (porta hepatis, celiac, splenic hilum, paraaortic, aortocaval)
Other extra-pancreatic disease (invasion of adjacent structures): present or absent
Impression: Tumor: size and location
Vascular contact: absent or present (vessel involved and extent)
Metastasis: absent or present (location)

(Fonseca 2018)

APPENDIX 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Event

AE Definition
An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention.
NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

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

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

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

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

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- All SAEs should be reported within 24 hours of research staff awareness of the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Galera Therapeutics in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Galera Therapeutics. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Galera Therapeutics.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- The investigator must assign the following AE attributes:
  - AE diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Intensity (or toxicity defined below);
  - Assessment of relatedness to GC4711, SBRT; and
  - Action taken.

Assessment of Intensity/Grade

The investigator will assess intensity for each AE and SAE reported during the study and assign a grade per NCI CTCAE vs. 5.0. For those AEs not directly referenced in CTCAE, the investigator should use clinical judgment in assessing the intensity of such events using the categories below as a guide

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- Life Threatening: an event that in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death

- Fatal: an event resulting in death

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. The greatest intensity during a continuous episode should be recorded.

Assessment of Causality

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

Follow-up of AEs and SAEs

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

Reporting of SAEs

SAE Reporting to Galera Therapeutics
The SAE/AESI reporting period begins from the Day 1 dosing of study drug. SAEs will be reported until 90 days post-SBRT. Within 24 hours of knowledge of a new SAE, the Investigator must report the event on a Safety Event Report Form to Propharma Safety Management or risk a major protocol deviation. The SAE report may be faxed, phoned or emailed to Propharma Safety Management. A phoned SAE report must be followed by a written report as soon as possible. Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

APPENDIX 5: NCCN Guidelines v1.2020- Criteria Defining Locally advanced Versus Borderline Resectable PC

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Pancreatic Adenocarcinoma
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

CRITERIA DEFINING RESECTABILITY STATUS AT DIAGNOSIS[a]

- Decisions about resectability status should be made in consensus at multidisciplinary meetings/discussions.

Resectability Status	Arterial	Venous
Resectable	• No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	• No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure (some panel members prefer these criteria to be in the locally advanced category).	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Locally Advanced[b,c]	Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° Pancreatic body/tail: • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

[a] Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014 Jan; 270:248-260.
[b] Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans.
[c] Distant metastasis (including non-regional lymph node metastasis), regardless of anatomic resectability, implies disease that should not be treated with upfront resection.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PANC-C
1 OF 2

APPENDIX 6: PRO-CTCAE

See Basch 2014, Kluetz 2016.

NCI- PRO-CTCAE™ ITEMS

Item Library Version 1.0

English

Form Created on 24 September 2020

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days...

1a. In the last 7 days, what was the SEVERITY of your DECREASED APETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did DECREASED APETITE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
2b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, how OFTEN did you have HEARTBURN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
4b. In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5.a In the last 7 days, did you have any INCREASED PASSING OF GAS (FLATULENCE)?	
O Yes	O No

6a. In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
6b. In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

7a. In the last 7 days, how OFTEN did you have HICCUPS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
7b. In the last 7 days, what was the SEVERITY of your HICCUPS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

8a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

9a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

10a. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
10b. In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
10c. In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

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

12a. In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
12b. In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

13a. In the last 7 days, how OFTEN did you have PAIN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
13b. In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
13c. In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

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

15a. In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
15b. In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

16a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
16b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

17a. In the last 7 days, how OFTEN did you feel ANXIETY?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
17b. In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
17c. In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

18a. In the last 7 days, how OFTEN did you FEEL THAT NOTHING COULD CHEER YOU UP?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
18b. In the last 7 days, what was the SEVERITY of your FEELINGS THAT NOTHING COULD CHEER YOU UP at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
18c. In the last 7 days, how much did FEELING THAT NOTHING COULD CHEER YOU UP INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

19a. In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
19b. In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
19c. In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

OTHER SYMPTOMS					
Do you have any other symptoms that you wish to report?					
O Yes		O No			
Please list any other symptoms:					
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe

APPENDIX 7: Multidisciplinary Review Worksheets

Galera Study GTI-4711-201: Screening Multidisciplinary Review Worksheet

Site Number:	Subject ID Number:
NOTE: This worksheet should be completed for the tumor board conducted during screening/prior to randomization	

Date of Tumor Board	____ / _____ / _____ DD MMM YYYY
Was diagnosis non-metastatic pancreatic cancer confirmed?	☐ Yes ☐ No
Was diagnosis specified as:	☐ Resectable, but medically inoperable ☐ Resectable, but refusal of surgery ☐ Borderline resectable ☐ Unresectable
If Resectable, but medically inoperable, Specify Reason:	☐ N/A ☐ Performance ☐ Cardiovascular co-morbidity ☐ Hematological Disorder ☐ Former extensive Abdominal ☐ Surgery ☐ Obesity ☐ Other, specify:
Was SBRT judged feasible	☐ Yes ☐ No
Specify Tumor Size:	☐ Less than 3 cm ☐ 3 to 5 cm ☐ More than 5 cm
Loco-regional nodal disease?	☐ Yes ☐ No
Distant Disease:	☐ Yes ☐ No

Documented Solid Soft Tissue Contact of:	
Superior Mesenteric Artery (SMA):	☐ None ☐ <= 180 degrees ☐ More than 180 degrees
Superior Mesenteric Vein (SMV):	☐ None ☐ <= 180 degrees ☐ More than 180 degrees

Galera Study GTI-4711-201: Screening Multidisciplinary Review Worksheet

Celiac Axis (CA):	☐ None ☐ <= 180 degrees ☐ More than 180 degrees
Aorta (AO):	☐ None ☐ <= 180 degrees ☐ More than 180 degrees
Common Hepatic Artery (CHA):	☐ None ☐ <= 180 degrees ☐ More than 180 degrees

Last Response Evaluation:	____ / ____ / _____ DD MMM YYYY
Outcome:	☐ Local stable disease, no distant progression ☐ Local partial response, no distant progression ☐ Local limited progressive disease (SBRT still feasible), no distant progression ☐ Local stable disease, but distant progression ☐ Local progressive disease and distant progression
Was GRECO-2 trial inclusion discussed?	☐ Yes ☐ No

Principal Investigator Name	Principal Investigator Signature	Date

Galera Study GTI-4711-201: Post-SBRT Multidisciplinary Review Worksheet

Site Number:	Subject ID Number:
NOTE: This worksheet should be completed for the tumor board conducted following completion of SBRT.	

Date of Tumor Board:	____ / _____ / _____ DD MMM YYYY
Date of Response Evaluation:	____ / _____ / _____ DD MMM YYYY
Outcome:	☐ Local stable disease, no distant progression ☐ Local partial response, no distant progression ☐ Local limited progressive disease, no distant progression ☐ Local stable disease, but distant progression ☐ Local progressive disease and distant progression

Judgement of Tumor Board		
"Technically resectable" (based on CT/MRI and/or PET)	☐ Yes	☐ No
"Medically resectable" (based on age, performance, co-morbidity, obesities)	☐ Yes	☐ No

Final Judgement	
To plan resection:	☐ Yes ☐ No
If No Resection; Adjuvant Chemotherapy:	☐ Yes ☐ No
If No, Specify Alternative:	☐ Observation ☐ Supportive Care ☐ Other Local Intervention

Date of Last CA 19-9 Collection	____ / _____ / _____ DD MMM YYYY
Result of CA19-9:	
CA19.9 Response Judged Sufficient for Surgical Exploration:	☐ Yes ☐ No
Important Inflammatory Reaction in Target Area/Pancreatitis Observed On Post-SBRT Imaging:	☐ Yes ☐ No

Principal Investigator Name	Principal Investigator Signature	Date

APPENDIX 8: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP

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

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

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

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

Effective Methods of Contraception

- A highly effective method of contraceptive is defined as any methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.
- Such methods include:
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:

- oral
- injectable
- implantable

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

Male participants with partners who become pregnant

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

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

Female Participants who become pregnant/breastfeed

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

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

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

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

APPENDIX 9: Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	Activated partial thrombin time
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	Area under the curve
BED	biologically equivalent dose
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulation
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTV	Clinical target volume
DFS	disease free survival
DMC	Data Monitoring Committee
DRE	disease related event
E/D	early discontinuation
ECG	electrocardiogram
ECOG PS	eastern cooperative oncology group performance status
eCRF	electronic Case Report Form
5FU	F – fluorouracil
FDA	Food and Drug Administration

FOLFIRINOX	Chemotherapy combination of cancer drugs that includes: FOL – folinic acid (also called leucovorin, calcium folinate or FA) F – fluorouracil (also called 5FU) Irin – irinotecanand Ox – oxaliplatin.
(m)FOLFIRINOX	modified FOLFIRINOX, no bolus given
FOLFOX	Chemotherapy combination of cancer drugs that includes: FOL – folinic acid (also called leucovorin, calcium folinate or FA) F – fluorouracil (also called 5FU) and Ox – oxaliplatin
FOLFIRI	Chemotherapy combination of cancer drugs that includes: FOL – folinic acid (also called leucovorin, calcium folinate or FA) F – fluorouracil (also called 5FU) and Iri – irinotecan
FSH	follicle stimulating hormone
FU	follow-up
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GTV	Gross tumor volume
Gy	Gray
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IEC	Independent Ethics Committees
IMRT	Intensity modulated radiation therapy
INR	International normalized ratio
IRB	Institutional Review Boards
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
IXRS	interactive voice or web-based randomization system
LC-MS	liquid chromatography – mass spectrometry

LD	largest tumor diameter
LE	local enlargement
LRC	Local regional control
MDSCs	myeloid-derived suppressor cells
MRI	Magnetic resonance imaging
MS	mass spectrometry
MTD	maximum tolerated dose
NCCN	National comprehensive cancer network
NSCLC	Non-small lung cancer
NK cells	natural killer cells
NMR	nuclear magnetic resonance
NOAEL	no observed adverse effect level
OAR	Organs at risk
OS	overall survival
PC	Pancreatic cancer
PDE 5	phosphodiesterase type 5
PE	physical examination
PET	FDG-positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetic(s)
PT	Prothrombin time
PTV	planning target volume
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
RT	radiation therapy
RTOG	radiation therapy oncology group
RTQA	radiation therapy quality assurance
RT-qPCR	reverse transcriptase polymerase chain reaction
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event

SABR	stereotactic ablative body radiation therapy
SBRT	stereotactic body radiation therapy
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOA	schedule of assessments
SOD	superoxide dismutase
SRC	safety review committee
SUSAR	suspected unexpected serious adverse reactions
TCD	tumor cure dose
TDM	Time to distant metastases
TEAEs	Treatment emergent adverse events
Tregs	T regulatory cells
ULN	upper normal limit
WBC	white blood cell
WOCBP	woman of childbearing potential

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12 SUMMARY OF CHANGES

Revisions made in Amendment 6 dated 08 October 2023 are summarized below:

Summary of Change	**Rationale**	**Affected Protocol Sections**
Added an interim test of superiority at approximately 36 deaths	The addition of an interim efficacy analysis by the DMC at approximately 36 events (i.e., deaths) has been added to the protocol to determine if the clinical trial is on track to meet its objective of demonstrating an improvement in overall survival. With the current standard of care for the treatment of locally advanced pancreatic cancer, subjects are living longer and therefore the number of events required to perform the previously defined interim analysis for superiority is taking longer to meet than anticipated. This additional analysis, blinded to Sponsor unless the DMC recommends stopping the trial for futility, will assess the likelihood of demonstrating statistical superiority of study drug if the trial continues to full enrollment and follow up, and allow a decision to be made regarding further patient enrollment.	· Synopsis · Section 9
Administrative, Clerical and Formatting updates	Revised to permit better readability.	· Overall Protocol