Objectives and Endpoints:

STAGE 1

Objectives	Endpoints
Primary	
• To evaluate disease control rate of the abemaciclib treatment arms versus the standard-of-care arm (gemcitabine or capecitabine)	• Disease control rate is the percentage of patients with a best overall response of stable disease, complete response, or partial response according to RECIST 1.1.
Secondary	
• To evaluate objective response rate of the abemaciclib treatment arms versus the standard-of-care arm	• Objective response rate is the percentage of patients with a best overall response of complete response or partial response according to RECIST 1.1.
• Evaluate safety and tolerability of the abemaciclib treatment arms	The safety endpoints evaluated will include but are not limited to the following: • TEAEs and SAEs • Clinical laboratory tests and vital signs
• PK of abemaciclib and its metabolites as well as LY3023414	• Exposure of abemaciclib and LY3023414

Abbreviations: PK = pharmacokinetics; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1; TEAE = treatment-emergent adverse event; SAE = serious adverse event.

Table JPCJ.2.1. Baseline Schedule of Activities

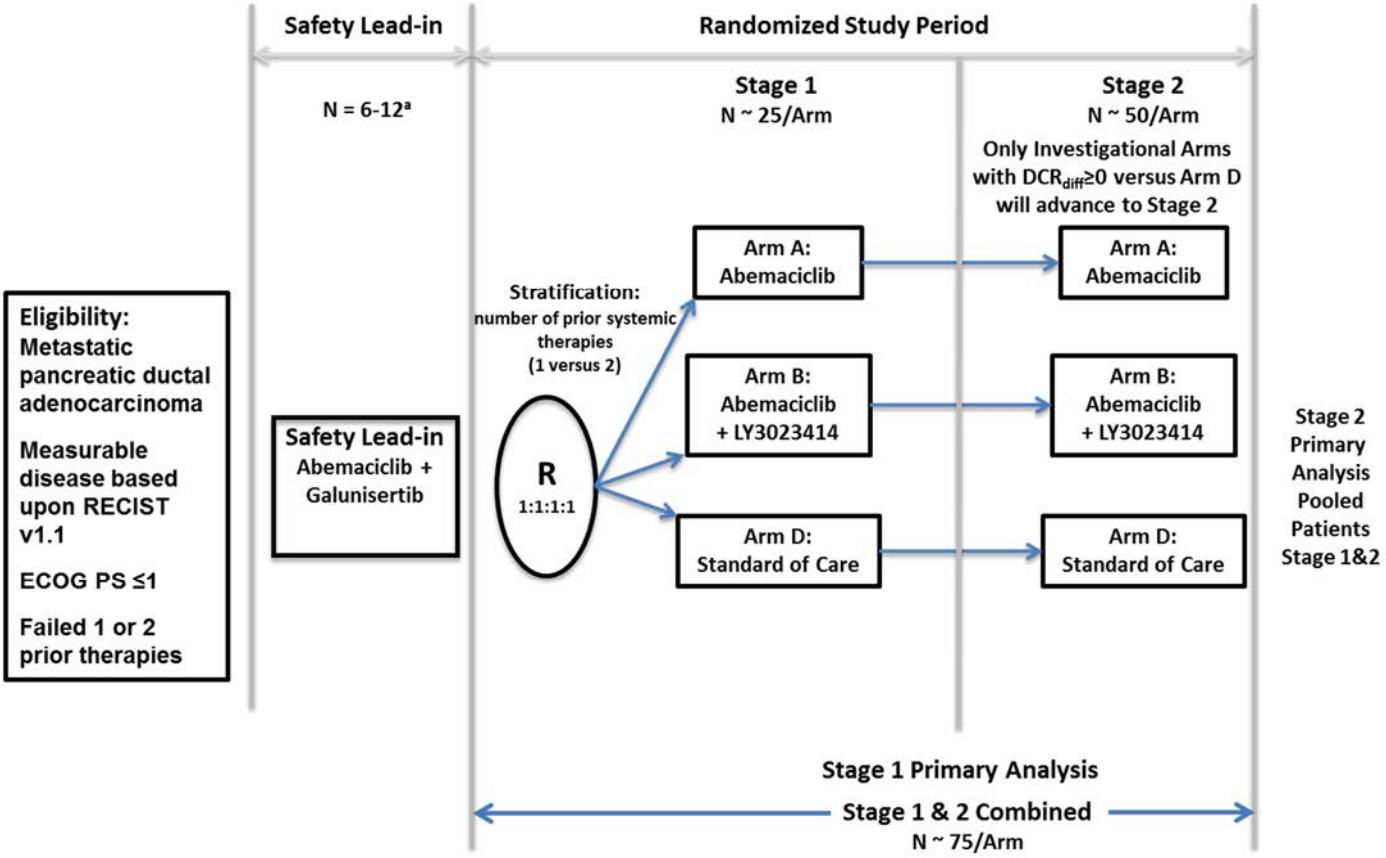
Day Relative to C1D1	≤28	≤14	≤7	
Procedure				**Instructions**
Informed consent	X			ICF must be signed before any protocol-specific procedures are performed.
Inclusion/exclusion criteria	X			
Physical examination		X		
Vital signs		X		Including height and weight temperature, blood pressure, pulse rate, and respiration rate
ECOG performance status		X		
Medical history		X		Including assessment of preexisting conditions and historical illnesses
Substance usage		X		Including tobacco and alcohol use
Prior anticancer therapies and current medications		X		
AE collection		X		CTCAE Version 4.0. To be reported only after study eligibility is confirmed.
Radiologic imaging (Tumor Assessment)	X			RECIST 1.1. Imaging studies (CT or MRI scan of the chest, abdomen, and pelvis) are performed locally (Day -28 to Day -1) at baseline. It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. If this is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and contrast-enhanced MRI of the abdomen/pelvis are encouraged.
Hematology		X		Performed by central laboratory. Local labs may be used for eligibility and treatment decisions, but a duplicate sample must be submitted to the central laboratory.
Clinical chemistry		X		Performed by central laboratory. NOTE: Fasting labs must be drawn for all patients at screening in order to appropriately assess glucose. Local labs may be used for eligibility and treatment decisions, but a duplicate sample must be submitted to the central laboratory.
Coagulation		X		PTT or INR performed locally only for those patients receiving oral coumarin-derivative anticoagulants
Cystatin C		X		Performed by central laboratory to assess renal function
CA 19-9		X		Performed by central laboratory
HbA1c		X		Performed by central laboratory

Table JPCJ.4.2. Objectives and Endpoints Stage 2

Objectives	Endpoints
Primary	
• To evaluate progression-free survival of the abemaciclib treatment arms versus the standard-of-care arm (gemcitabine or capecitabine)	• Progression-free survival is measured from the date of randomization to the date of objective progression or the date of death due to any cause, whichever is earlier.
Secondary	
• To evaluate disease control rate of the abemaciclib treatment arms versus the standard-of-care arm	• Disease control rate is the percentage of patients with a best overall response of stable disease, complete response, or partial response according to RECIST 1.1.
To evaluate clinical benefit rate of the abemaciclib treatment arms versus the standard-of-care arm	Clinical benefit rate is the percentage of patients with a best overall response of complete response, or partial response, or stable disease for ≥6 months according to RECIST 1.1.
• To evaluate objective response rate of the abemaciclib treatment arms versus the standard-of-care arm	• Objective response rate is the percentage of patients with a best overall response of complete response or partial response according to RECIST 1.1
• To evaluate duration of response of the abemaciclib treatment arms versus the standard-of-care arm	• Duration of response is measured from the date of first evidence of complete response or partial response to the date of objective progression or the date of death due to any cause, whichever is earlier.
• To evaluate overall survival of the abemaciclib treatment arms versus the standard-of-care arm	• Overall survival is measured from the date of randomization to the date of death from any cause.
• Evaluate the kinetics of carbohydrate antigen (CA) 19-9	• Change from baseline in CA 19-9
• Evaluate safety and tolerability	The safety endpoints evaluated will include but are not limited to the following: • TEAEs and SAEs • Clinical laboratory tests and vital signs
• To evaluate pain and symptom burden of the abemaciclib treatment arms by best response group (partial response, stable disease, or progressive disease) versus the standard-of-care arm	• modified Brief Pain Inventory short form (mBPI-sf) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
• PK of abemaciclib and its metabolites as well as LY3023414	• Exposure of abemaciclib and LY3023414
• Exposure-response for abemaciclib and LY3023414	• Drug exposure and efficacy outcomes such as objective response rate or progression-free survival and safety outcomes such as neutropenia and diarrhea
Tertiary	
• Assess the relationship between biomarkers and clinical outcome	• Biomarker research may be assessed from tumor, whole blood, and plasma samples, unless precluded by local regulations.

Abbreviations: CA = carbohydrate antigen; PK = pharmacokinetics; RECIST = Response Criteria in Solid Tumors Version 1.1; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Figure JPCJ.5.1 illustrates the study design.



Abbreviations: ECOG = Eastern Cooperative Oncology Group; DCR_{diff} = disease control rate difference; N = number of patients; R = randomize; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; PS = performance status.

a At the time of amendment (c), Lilly determined no additional patients would be enrolled to the safety lead-in.

Figure JPCJ.5.1. Illustration of study design.

5.2. Number of Patients

Prior to initiating Stage 1 of the study, a safety lead-in period with abemaciclib plus galunisertib was to be conducted with up to 12 patients (see Section 7.2); however, as discussed in more detail in Section 5.4.3, Lilly has decided not to continue the assessment of abemaciclib in combination with galunisertib.

For Stage 1, a total of approximately 75 patients (25 patients per arm) will be randomized in a 1:1:1 ratio to 3 treatment arms. Randomization will be stratified by number of prior systemic therapies (1 versus 2). For Stage 2, the treatment arms that meet the decision criteria to advance to Stage 2 (DCR difference ≥0 in abemaciclib containing arms vs. the standard-of-care arm), 50 additional patients will be randomized to each experimental arm, as well as to the

- Modified exclusion criterion [18] to exclude only "symptomatic" CNS metastasis
- Clarified rescreening language
- Clarified text regarding definition of "not tolerated" for safety lead-in and revised DLT definitions
- Clarified text on dosage modifications and included Appendix 10 to provide guidance for specific toxicities for each arm
- Information added for first periodic safety review.

5.4.2. Rationale for Amendment (b)

The rationale for amendment (b) was based on the results of Study JPBJ, a food effect study for LY3023414 (I6A-EW-CBBB [Study CBBB]), and to clarify additional sections of the protocol. Major changes for amendment (b) included the following:

- Reduced the starting dose of LY3023414 to be administered in combination with abemaciclib to reflect the MTD (150 mg BID) as determined in Study JPBJ
- Removed the restriction for taking LY3023414 at least 1 hour before or after a meal. Study CBBB determined that LY3023414 can be administered irrespective of food intake, as the difference in exposure observed with and without food was not considered to be clinically relevant given the inter-subject variability. Further, toxicity was determined to not be a concern based on dietary state.
- Added flexibility to the timing of the C3D1 echocardiogram for patients receiving galunisertib in order to accommodate this procedure which may be performed by a facility at a location other than the investigative site
- Updated most common treatment-related AEs for abemaciclib and LY3023414 in Table JPCJ.7.2 to align with 2016 IB updates.

5.4.3. Rationale for Amendment (c)

Study JPCJ was amended to discontinue enrollment to the safety lead-in for abemaciclib plus galunisertib and remove Arm C (abemaciclib in combination with galunisertib) as well as all galunisertib-related baseline procedures and eligibility requirements.

The combination testing strategy for study JPCJ was reassessed considering other priorities with Lilly molecules in clinical development, and it was decided not to continue the investigation of abemaciclib in combination with galunisertib in this study. This decision was not triggered by safety concerns with the combination.

5.5. Justification for Doses of Investigational Treatments

The dose of abemaciclib monotherapy (200 mg BID) used in this study is the MTD identified in the Phase 1 Study I3Y-MC-JPBA (JPBA) for patients with advanced cancer (either solid tumor or lymphoma). Generally, in Phase 1b combination studies, the dose of abemaciclib selected to be administered with other anticancer therapies is 150 mg BID due to overlapping toxicities and DLTs occurring at higher doses. In Study JPBA, abemaciclib inhibited CDK4 and CDK6 as indicated by inhibition of pRb and topoII alpha, which results in cell cycle inhibition upstream of

9.1.1. Appropriateness of Assessments

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology trials.

9.2. Adverse Events

A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug. The investigator will use CTCAE v4.0 (National Cancer Institute [NCI] 2009) to assign AE terms and severity grades. Any minor version of CTCAE v4.0 (for example, Version 4.0X) may be used for this study. Minor CTCAE v4.0 updates from the NCI will not necessitate a protocol amendment.

Investigators are responsible for:

- monitoring the safety of patients in this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient
- the appropriate medical care of patients during the study
- documenting their review of each laboratory safety report
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via electronic data entry the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study site personnel will record via electronic data entry any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study treatment via electronic data entry.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the study treatment and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via electronic data entry, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment

Although all AEs after signing the ICF are recorded in the electronic data entry, SAE reporting begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Planned hospitalizations or procedures for preexisting conditions that were recorded in the patient's medical history at the time of enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the

associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

9.2.3. Summary of Adverse Event/Serious Adverse Event Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JPCJ.9.1.

Table JPCJ.9.1. Assessment Guide for Adverse Events and Serious Adverse Events

Timing	Types of AEs/SAEs Reported
Baseline Starts at the signing of informed consent and ends at randomization/assignment to study treatment	Preexisting conditions All AEs SAEs related to protocol procedure
On study treatment Starts at first dose of study treatment and ends the day after the patient and the investigator agree that the patient will no longer continue study treatment	All AEs regardless of relatedness All SAEs regardless of relatedness (except SAEs due to progressive disease unless the investigator also deems there to be a possible contribution related to study treatment or protocol procedures)
Short-term follow-up Starts the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days)	All AEs related to study treatment All SAEs regardless of relatedness (except SAEs due to progressive disease unless the investigator also deems there to be a possible relation with study treatment or protocol procedure)
Long-term follow-up, if necessary	Ongoing or new AEs/SAEs possibly related to study treatment or protocol procedures
Continued access treatment period	All AEs/SAEs (same as for patients on study treatment)
Continued access follow-up Starts the day after the patient and the investigator agree that the patient will no longer continue study treatment in the continued access period and lasts approximately 30 days (±7 days).	All AEs/SAEs as above for initial follow-up visit and then as needed for subsequent continued follow-up visits

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

9.2.4. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the respective IBs for abemaciclib, LY3023414, and galunisertib and the product labels for gemcitabine and capecitabine.

9.4. Safety

9.4.1. Cardiac Monitoring

In addition to electrophysiological assessments of the heart for all patients in this study, the most important evaluations are dictated by the galunisertib preclinical findings. Hence, cardiotoxicity monitoring must be performed for patients participating in the Safety Lead-in of this study, based on echocardiographs with Doppler and Chest CT/MRI (see Schedule of Activities [Section 2] and Appendix 6). The chest CT/MRI of the ascending aorta and aortic arch should be performed according to institutional guidelines. The same imaging techniques used at baseline should be used for each patient throughout the evaluation period.

Electrocardiograms (all patients)

For each patient, a 12-lead digital ECG will be collected according to the Schedule of Activities (see Section 2). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, if clinically indicated.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible and ideally while the patient is still present for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, or syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

Chest CT Scan with Contrast or MRI (Safety Lead-in Patients Only)

A chest CT scan with contrast or MRI was required at screening for all patients in the Safety Lead-in and subsequently according to the Schedule of Activities (see Section 2) for these patients. The purpose of this safety assessment is to detect aneurysm formation of the ascending aorta and aortic arch. If a CT scan with contrast or MRI has been done as part of the patient's tumor assessment, this scan may be used for safety screening if the scan has properly assessed the great vessels and the heart. The same method of assessment used at screening should be used for each patient throughout the evaluation period.

Echocardiogram with Doppler (Safety Lead-in Patients Only)

Echocardiography with Doppler (ECHO/Doppler) was locally assessed at screening for all patients in the Safety Lead-in and subsequently according to the Schedule of Activities (see

and central laboratory results that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.

Any clinically significant findings from ECGs, ECHOs, safety CT scans, labs, vital sign measurements, and other study procedures that result in a diagnosis should be reported via electronic data entry as an AE.

9.4.4. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. The first periodic safety review of the randomized portion of the study (Stage 1) will occur after 10 patients have been randomized to each treatment arm and completed 1 cycle (28 days) or have discontinued treatment.

If a patient experiences elevated alanine aminotransferase (ALT) ≥5× upper limit of normal (ULN) and elevated total bilirubin ≥2× ULN in the absence of liver metastases, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT or aspartate aminotransferase (AST) >3× ULN in the presence of liver metastases, monitoring should be triggered if ALT or AST is elevated to >2× baseline.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 5.

9.5. Pharmacokinetics

Pharmacokinetic (PK) samples will be collected as shown in Appendix 4. During the Safety Lead-in, patients receiving the combination of abemaciclib and galunisertib will undergo intense PK sampling. For all patients participating in the study, the PK sample collection should occur on the day that clinical laboratory samples are collected for the purposes of eligibility or health monitoring, corresponding to the originally planned next visit/cycle.

Blood samples will be used to determine the concentrations of abemaciclib and its metabolites, LY3023414, and galunisertib. A patient diary will be used as source to collect the date and time of study treatment doses for the 3 days preceding collection of PK samples.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and Lilly.

Bioanalytical samples collected to measure abemaciclib plus its metabolites, LY3023414, and galunisertib concentrations will be retained for a maximum of 1 year following the last patient visit for the study.

9.6. Pharmacodynamics

Sample collection for pharmacodynamic parameters is covered in Section 9.8.

9.9.2. Health-Related Quality of Life

Broadly used in cancer trials, validated, and available in over 80 different languages, the EORTC QLQ-C30 (Aaronson et al. 1993) is a reliable and validated tool. The EORTC QLQ-C30 self-reported general cancer instrument (Aaronson et al. 1993) consists of 30 items covered by 1 of 3 dimensions:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

The EORTC QLQ-C30 is administered per the Study Schedule (Section 2). The recall period is the past week, completion time is typically 5 to 7 minutes, and the questionnaire will be scored as described by the EORTC scoring manual (Fayers et al. 2001). The EORTC population will include all patients who completed at least 1 baseline followed by at least 1 EORTC postbaseline assessment.

9.9.3. Resource Utilization

Investigators will be asked to report the use of concomitant medications (in particular, analgesics, growth factors, or antidiarrheals), blood product transfusions, and hospitalization days. This information should be collected at baseline, during the study, and at the 30-day follow-up visit.

Time to deterioration in a total score/domain score/item will be summarized descriptively using the Kaplan-Meier method (Kaplan and Meier 1958), and a comparison between treatment arms will be made using the Cox proportional hazards models (Cox 1972).

10.3.3.9. Healthcare Resource Utilization

Hospitalizations, transfusions, and concomitant medication categories (for example, analgesics, growth factors, and antidiarrheals) during study treatment will be summarized descriptively by treatment arm.

10.3.4. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP. The treatment effect within each subgroup will be summarized. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

10.3.5. Stage 1 Analyses

The Stage 1 analysis of efficacy will be conducted under the guidance of an Assessment Committee (AC) after the last planned Stage 1 patient has enrolled and completed at least 16 weeks of treatment or have discontinued (whichever comes earlier). All data accumulated during this period (beyond 16 weeks for some patients, if available), will be included in the analysis. The purpose of this analysis is to evaluate safety and efficacy (DCR) to select which arms will continue to Stage 2. The AC will include an external physician as well as the study statistician, Global Patient Safety physician, and Medical Director.

Day Relative to C1D1	≤28	≤14	≤7	
Procedure				**Instructions**
Serum pregnancy test			X	Performed by local laboratory. Applies only to women of childbearing potential. Must have a negative serum pregnancy test within 7 days of the first dose of study drug (that is, Day -7 to Day -1).
ECG		X		To be performed and read locally.
Administer mBPI-sf and EORTC QLQ-C30 questionnaires		X		Patient should complete mBPI-sf and EORTC prior to extensive interaction with site staff.
Sample Collection				See Appendix 4.
Tissue samples	X			Confirm archival tumor tissue available. For patients without available FFPE tumor tissue at baseline, a core needle biopsy (minimum 3 cores) obtained prior to study treatment initiation is highly encouraged, but not required.

Abbreviations: AE = adverse event; C1D1 = Cycle 1 Day 1; CA = carbohydrate antigen; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FFPE = formalin-fixed, paraffin-embedded; HbA1c = hemoglobin A1c; ICF = informed consent form; INR = international normalized ratio; IV = intravenous; mBPI-sf = modified Brief Pain Inventory short form; MRI = magnetic resonance imaging; PTT = partial prothrombin time; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

	28-Day Cycle		28-Day Cycles		28-Day Cycles	
	Cycle 1		Cycle 2		Cycle 3 - n	
Day within Cycle	**1**	**14**	**1**	**14**	**1**	
Procedure						**Instructions**
Additional tissue sample, if applicable			X		X	If a participant in this study elects to have a surgical procedure at any time during the study that involves removal of tumor, then FFPE tumor from that procedure may also be requested. Patients undergoing surgery during the study should have study treatment suspended for 7 days prior to surgery, as well as 7 days post-operatively.
Urine pregnancy test			X		X	Applies only to women of childbearing potential. Where required by local law or regulation, perform once every 28 days (±7 days) prior to dispensing study treatment.
Administer mBPI-sf and EORTC QLQ-C30 questionnaires	X		X		X	Administer mBPI-sf and EORTC QLQ-C30 prior to administration of study treatment and prior to significant interaction with site staff.
ECG					X (approximately Cycle 7)	To be performed and read locally following 6 months (±15 days) of therapy. Additional ECG assessments should be performed as clinically indicated.
Study Drug						
Dispense abemaciclib	X		X		X	Abemaciclib is taken orally BID, approximately every 12 hours, on Days 1 through 28 of each cycle without regard to food.
Sample collection						For all sample collection, see Appendix 4.
Pharmacokinetics						
Pharmacogenetics						
Biomarkers						

Abbreviations: AE = adverse event; BID = twice daily; CA = carbohydrate antigen; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FFPE = formalin-fixed, paraffin-embedded; INR = international normalized ratio; IV = intravenous; mBPI-sf = modified Brief Pain Inventory short form; MRI = magnetic resonance imaging; PTT = partial prothrombin time; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

	28-Day Cycle		28-Day Cycles		28-Day Cycles	
	Cycle 1		Cycle 2		Cycle 3- n	
Day within Cycle	**1**	**14**	**1**	**14**	**1**	
Procedure						**Instructions**
Additional tissue sample, if applicable			X		X	If a participant in this study elects to have a surgical procedure at any time during the study that involves removal of tumor, then FFPE tumor from that procedure may also be requested. Patients undergoing surgery during the study should have study treatment suspended for 7 days prior to surgery, as well as 7 days post-operatively.
Urine pregnancy test			X		X	Applies only to women of childbearing potential. Where required by local law or regulation, performed once every 28 days (±7 days) prior to dispensing study treatment.
Administer mBPI-sf and EORTC QLQ-C30 questionnaires	X		X		X	BPI-sf and EORTC QLQ-C30 should be administered prior to administration of study treatment and prior to significant interaction with site staff.
ECG					X (approximately Cycle 7)	To be performed and read locally following 6 months (±15 days) of therapy. Additional ECG assessments should be performed as clinically indicated.
Study drug						
Dispense abemaciclib	X		X		X	Abemaciclib is taken orally BID, approximately every 12 hours, on Days 1 through 28 of each cycle without regard to food.
Dispense LY3023414	X		X		X	LY3023414 is taken orally BID, approximately every 12 hours on Days 1 through 28 of each cycle without regard to food.
Sample collection						
Pharmacokinetics						For all sample collection, see Appendix 4.
Pharmacogenetics						
Biomarkers						

Abbreviations: AE = adverse event; BID = twice daily; C = Cycle; CA = carbohydrate antigen; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FFPE = formalin-fixed, paraffin-embedded; HbA1c = hemoglobin A1c; INR = international normalized ratio; IV = intravenous; mBPI-sf = modified Brief Pain Inventory short form; MRI = magnetic resonance imaging; PTT = partial prothrombin time; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

	28-Day Cycle		28-Day Cycles		28-Day Cycles	
	Cycle 1		Cycle 2		Cycle 3 - n	
Day within Cycle	**1**	**14**	**1**	**14**	**1**	
Procedure						**Instructions**
Urine pregnancy test			X		X	Applies only to women of childbearing potential. Where required by local law or regulation, performed once every 28 days (±7 days) prior to dispensing study treatment.
Administer mBPI-sf, EORTC QLQ-C30 questionnaires	X		X		X	mBPI-sf and EORTC QLQ-C30 should be administered prior to administration of study treatment and prior to significant interaction with site staff.
Cardiac Assessments						
ECG					X (approximately Cycle 7)	To be performed and read locally following 6 months (±15 days) of therapy. Additional ECG assessments should be performed as clinically indicated.
Echocardiogram					X	≤7 days prior to Cycle 3 Day 1 and subsequently every 6 months (±15 days). To be performed and read locally. Additional echocardiogram assessments should be performed as clinically indicated (see Appendix 6).
Chest CT-scan with contrast or MRI (safety)					X (approximately Cycle 7)	To be performed and read locally after 6 months (±15 days) of therapy and as clinically indicated for cardiac monitoring. NOTE: At the same time point post baseline, if a MRI or CT scan with contrast has been done for tumor assessment, this same scan may be used for safety assessment, provided the scan has properly assessed the great vessels and the heart.
Study Drug						
Dispense abemaciclib	X		X		X	Abemaciclib is taken orally BID, approximately every 12 hours, on Days 1 through 28 of each cycle without regard to food.
Dispense galunisertib	X		X		X	Galunisertib is taken orally BID, approximately every 12 hours, on Days 1 through 14 of each cycle without regard to food. Galunisertib is not taken on Days 15 through 28 of each cycle.

Day within Cycle	21-Day Cycles Cycle 1 1	21-Day Cycles Cycle 2- n 1	
Procedure			**Instructions**
Additional tissue sample, if applicable		X	If a participant in this study elects to have a surgical procedure at any time during the study that involves removal of tumor, then FFPE tumor from that procedure may also be requested. Patients undergoing surgery during the study should have study treatment suspended for 7 days prior to surgery, as well as 7 days post-operatively.
Urine pregnancy test		X	Applies only to women of childbearing potential Where required by local law or regulation, performed once every 21 days (±7 days) prior to dispensing study treatment.
Administer mBPI-sf and EORTC QLQ-C30 questionnaires	X	X	mBPI-sf and EORTC QLQ-C30 should be administered prior to administration of study treatment and prior to significant interaction with site staff.
ECG		X (approximately Cycle 9)	To be performed and read locally following 6 months (±15 days) of therapy. Additional ECG assessments should be performed as clinically indicated.
Study drug			
Dispense capecitabine	X	X	Capecitabine is taken orally BID, approximately every 12 hours, on Days 1 through 14 of each cycle. Patients should take capecitabine with water within 30 minutes after a meal. Capecitabine is not taken on Days 15 through 21 of each cycle.
Sample collection			For all sample collection, see Appendix 4.
Pharmacokinetics			
Pharmacogenetics			
Biomarkers			

Abbreviations: AE = adverse event; BID = twice daily; CA = carbohydrate antigen; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FFPE = formalin-fixed, paraffin-embedded; INR = international normalized ratio; IV = intravenous; mBPI-sf = modified Brief Pain Inventory short form; MRI = magnetic resonance imaging; PTT = partial prothrombin time; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

	28-Day Cycle				28-Day Cycles			
	Cycle 1				Cycle 2-n			
Day within Cycle	**1**	**8**	**15**	**22**	**1**	**8**	**15**	
Procedure								**Instructions**
CA 19-9	X				X			Performed by central laboratory ≤3 days prior to Day 1 of each cycle
Additional tissue sample, if applicable					X			If a participant in this study elects to have a surgical procedure at any time during the study that involves removal of tumor, then FFPE tumor from that procedure may also be requested. Patients undergoing surgery during the study should have study treatment suspended for 7 days prior to surgery, as well as 7 days post-operatively.
Urine pregnancy test					X			Applies only to women of childbearing potential Where required by local law or regulation, performed once every 28 days (±7 days) prior to dispensing study treatment.
Administer mBPI-sf and EORTC QLQ-C30 questionnaires	X				X			mBPI-sf and EORTC QLQ-C30 should be administered prior to administration of study treatment and prior to significant interaction with site staff.
ECG					X			To be performed and read locally following 6 months (±15 days) of therapy (approximately Cycle 7). Additional ECG assessments should be performed as clinically indicated.
Study drug								
Administer gemcitabine	X	X	X	X	X	X	X	Gemcitabine will be administered intravenously over approximately 30 minutes (and at a maximum of approximately 60 minutes). As a general rule of gemcitabine treatment, it should be administered every 7 (±3) days.
Sample collection								For all sample collection, see Appendix 4.
Pharmacokinetics								
Pharmacogenetics								
Biomarkers								

Abbreviations: AE = adverse event; BID twice daily; CA = carbohydrate antigen; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FFPE = formalin-fixed, paraffin-embedded; INR = international normalized ratio; IV = intravenous; mBPI-sf = modified Brief Pain Inventory short form; MRI = magnetic resonance imaging; PTT = partial prothrombin time; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

Visit	Short-Term Follow-Up[a] 801	Long-Term Follow-Up[b] 802-8XX	
Administer mBPI-sf and EORTC QLQ-C30 questionnaires	X		
ECG	X		
Sample collection			
Pharmacogenetics			For all sample collection, see Appendix 4.
Biomarkers			

Abbreviations: AE = adverse event; CA = carbohydrate antigen; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; INR = international normalized ratio; mBPI-sf = modified Brief Pain Inventory short form; PFS = progression-free survival MRI = magnetic resonance imaging; PTT = partial prothrombin time; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

a Short-term follow-up procedures are to be performed approximately 30 days (±7 days) after the patient and the investigator agree that the patient will no longer continue study treatment. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

b Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or study completion. During long-term follow-up, patients will have a follow-up visit every 60 days (±7 days).

Table JPCJ.2.8. Continued Access Schedule of Activities

Visit	Study Treatment 501-5XX	Follow-Up[a] 901	
Procedure[b]			**Instructions**
AE collection	X	X	CTCAE Version 4.0
Administer/dispense study drug	X		

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

a Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days (±7 days). No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

b Imaging assessments will be done at the investigator's discretion based on the standard of care.

3. Introduction

3.1. Study Rationale

The most common genetic mutations in pancreatic ductal adenocarcinoma (PDAC) include *KRAS* and *CDK2NA*, each of which occurs in approximately 90% of cases (Jones et al. 2008; Biankin et al. 2012; Chiorean and Coveler 2015). Mutation of *KRAS* leads to uncontrolled activation of multiple downstream intracellular signaling pathways, contributing to tumor cell proliferation. However, in clinical trials, KRAS inhibitors have been largely unsuccessful, thus an emphasis has been placed on downstream pathways (Iriana et al. 2016).

Abemaciclib, a cyclin-dependent kinase (CDK) 4 and CDK6 inhibitor, has shown single-agent antiproliferative activity in *KRAS* mutant pancreatic cancer cell lines (Eli Lilly and Company [Lilly] data on file) and has an acceptable safety and tolerability profile in clinical studies. In addition, in preclinical models of pancreatic cancer a synergistic effect of CDK4 and CDK6 inhibitors in combination with phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) or transforming growth factor beta receptor type I (TGF-βRI) inhibitors has been demonstrated (Liu and Korc 2012; Franco et al. 2014). Given the unmet medical need for second- and third-line treatment options, this study aims to explore the safety and efficacy of abemaciclib monotherapy, as well as abemaciclib in combination with other agents (including a PI3K/mTOR dual inhibitor), versus choice of standard of care (gemcitabine or capecitabine) in patients with previously treated metastatic PDAC.

3.2. Background

3.2.1. Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma is considered one of the most lethal solid tumors, likely to become the second-leading cause of cancer deaths in the United States by 2020. Although the survival for most cancers has shown a steady increase, the estimated 5-year survival rate for metastatic PDAC is only 2.4% (Weinberg et al. 2015). Worldwide, the incidence of pancreatic cancer ranges from 1 to 10 cases per 100,000, with adenocarcinoma accounting for 85% of these cases (Ryan et al. 2014). The poor prognosis is attributable to a lack of clinical symptoms and a delay in diagnosis until the cancer has reached an advanced stage. In addition, PDAC is unusually resistant to both cytotoxic and molecularly targeted anticancer agents (Ryan et al 2014; Schober et al. 2015).

Currently, preferred first-line therapy options for patients with metastatic PDAC include the combination of 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), gemcitabine plus nab-paclitaxel, or single-agent gemcitabine. In select patients with good performance status, second-line therapy for patients previously treated with gemcitabine-based therapy includes fluoropyrimidine-based therapy and clinical trial participation; for those patients previously treated with fluoropyrimidine-based therapy, the recommended second-line options are gemcitabine-based therapy, the combination of 5-FU, leucovorin, and liposomal irinotecan (if no prior irinotecan), or clinical trial participation (National Comprehensive Cancer Network

5. Study Design

5.1. Overall Design

Study I3Y-MC-JPCJ (JPCJ) is a multicenter, randomized, open-label, Phase 2 study in patients with metastatic PDAC who have been previously treated with at least one, but no more than 2 prior therapies. At least one of the prior therapies must have been either gemcitabine-based or fluoropyrimidine-based therapy. This study will evaluate the safety and efficacy of abemaciclib as a monotherapy or in combination with other agents versus choice of standard of care (gemcitabine or capecitabine) by implementing a 2-stage design.

No safety data had been generated for the combination of abemaciclib and galunisertib. Therefore, a Safety Lead-in Period was included in the original protocol (see Section 7.2).

The combination of abemaciclib and LY3023414 was assessed in a Phase 1b study (I3Y-MC-JPBJ) in patients with non-small cell lung cancer. Of 5 patients treated with abemaciclib 150 mg twice daily (BID) plus LY3023414 200 mg BID, 2 patients experienced dose-limiting toxicities (DLTs). However, of 3 patients treated with 150 mg abemaciclib BID plus LY3023414 150 mg BID, none experienced a DLT. Therefore, the maximum tolerated dose (MTD) of LY3023414 in combination with abemaciclib was determined to be 150 mg BID.

With amendment (c), Stage 1 of the study will randomize patients 1:1:1 into each of the following arms (25 patients per arm):

- Arm A: Abemaciclib (LY2835219),
- Arm B: Abemaciclib plus LY3023414 (PI3K/mTOR Dual Inhibitor), or
- Arm D: Choice of Standard of Care (gemcitabine or capecitabine).

For Stage 1, the analyses of safety and efficacy will be evaluated approximately 16 weeks after the last planned Stage 1 patient enters treatment. All data accumulated during this period (beyond 16 weeks for some patients, if available), will be included in the analysis. Initial evaluations will compare investigational arms (Arms A and B) with the standard-of-care arm (Arm D), and will include assessment of disease control rate (DCR; complete response [CR]+partial response [PR]+stable disease [SD]). Following the completion of the Stage 1assessment, any treatment arm(s) with a DCR difference ≥ 0 as compared to the standard-of-care arm (Arm D) will be selected to advance to Stage 2. Enrollment in the nonadvancing arm(s) will be discontinued. While the analysis for Stage 1 is ongoing, enrollment for all arms may continue until the assessment is complete. Any patients enrolled during the time that Stage 1 analysis is ongoing will be included in planned enrollment for Stage 2.

For the treatment arms that advance to Stage 2, an additional 50 patients will be randomized equally to each arm for further evaluation of safety and efficacy. The primary analysis of Stage 2 will be conducted when at least 120 total PFS events have occurred for the combination of each individual abemaciclib-containing arm and the standard-of-care arm, or all planned patients have been enrolled in Stage 2, whichever comes later. Data from both Stages 1 and 2 will be pooled for this analysis.

Table JPCJ.7.3. Dose Reductions for Investigational Agents

		Dose Reduction			
		First	Second	Third	Fourth
Abemaciclib (monotherapy)	200 mg BID	150 mg BID	100 mg BID	50 mg BID	discontinue
Abemaciclib (combination)	150 mg BID	100 mg BID	50 mg BID	discontinue	
LY3023414	150 mg BID	100 mg BID	discontinue		
Galunisertib	150 mg BID	80 mg BID	discontinue		

Abbreviation: BID = twice daily.

For patients requiring a dose reduction of investigational agents, any re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP.

Hematologic Toxicities

If a patient experiences Grade 4 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of the study treatment must be reduced by 1 dose level as outlined in Table JPCJ.7.3.

If a patient experiences Grade 3 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of study treatment may be reduced by 1 dose level as outlined in Table JPCJ.7.3 at the discretion of the investigator. If the patient experiences a recurrent episode of Grade 3 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of study treatment must be reduced by 1 dose level.

If a patient requires administration of blood cell growth factors, the dose of study treatment must be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2 then reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

Hematologic toxicities must resolve to either baseline or at least Grade 2 prior to reinitiation of investigational agents.

Nonhematologic Toxicities

If a patient experiences Grade ≥3 nonhematologic toxicity, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of study treatment must be reduced by 1 dose level as outlined in Table JPCJ.7.3. Exceptions are as follows for Grade ≥3 nonhematologic toxicities possibly related to LY3023414:

- Grade 3 fasting hyperglycemia that resolves to ≤Grade 2 within 7 days
- Grade 3 mucositis that resolves to Grade ≤2 within 7 days
- Grade 3 fatigue that resolves to Grade ≤2 within 5 day
- toxicities that can be controlled with adequate treatment, such as nausea, vomiting, skin rash, diarrhea, or asymptomatic electrolyte disturbances

standard-of-care arm. The arms that advance to Stage 2 will enroll a total of 75 patients per arm (including 25 patients from Stage 1).

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure for the last patient.

5.4. Scientific Rationale for Study Design

Study JPCJ is a Phase 2 adaptive design study that will be conducted in 2 stages. Stage 1 will permit decision-making in order to determine if either abemaciclib monotherapy or abemaciclib in combination with other agents provides a level of disease control that is at least comparable to the standard of care. Any arms demonstrating evidence of disease control comparable to or better than the standard of care would merit exploration in a larger population in order to assess PFS, and thus these arms would advance to Stage 2 in the current study.

Although treatment guidelines recommend the use of combination therapies in the second-line setting for metastatic PDAC, there is no consensus on the standard of care in patients who have failed first-line therapy. Further, no standard of care exists in the third-line setting. Based upon historical data, the recommended second-line combination therapies do not provide significant survival benefit over gemcitabine or capecitabine monotherapies. The median OS for patients in a German single-center cohort receiving second-line treatments including XELOX, FOLFOX, gemcitabine (± erlotinib), or FOLFIRI was 5.4 months (Maier-Stocker et al. 2014), which is comparable to the OS observed in prior studies (Section 3.2.1) with gemcitabine (5.7 months) and capecitabine (4.3 months). Another single-institution retrospective study demonstrated a median OS of approximately 5 months in patients treated with gemcitabine/Nab-paclitaxel in the second-line setting (Bertocchi et al. 2015). Given the lack of consensus on standard of care in the disease setting being studied, and the similarity in OS between combination therapies and monotherapies, gemcitabine and capecitabine monotherapies were chosen for the standard-of-care arm.

5.4.1. Rationale for Amendment (a)

The rationale for amendment (a) was based primarily on feedback received from the US Food and Drug Administration. Changes for amendment (a) included the following:

- Incorporated a Day 14 visit during Cycles 1 and 2 for all investigational arms
- Removed pharmacokinetic, pharmacogenetic, and biomarker sample collection from tables in Section 2, reader directed to Appendix 4 for sample timing, Appendix 4 updated
- Added tertiary objective for Stage 1 for biomarkers
- Included statement regarding status of Study JPBJ safety assessment of abemaciclib in combination with LY302414
- Incorporated language to clarify disease control rate analysis
- Added information for the galunisertib dose justification
- Updated inclusion criterion [7] to require specific creatinine clearance (CrCl) in addition to serum creatinine, added Appendix 9 for calculation and updated Appendix 3 for clarification

DNA-PK	DNA-dependent protein kinase
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
effective method of contraception	effective method of contraception means male condom with spermicide, female condom with spermicide, diaphragm with spermicide, cervical sponge, or cervical cap with spermicide. Also see the definition of highly effective method of contraception.
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
enroll	act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board / institutional review board
FFPE	formalin-fixed, paraffin-embedded
FOLFIRINOX	5-fluorouracil, leucovorin, irinotecan, and oxaliplatin
GCP	good clinical practice
HbA1c	hemoglobin A1c
highly effective method of contraception	combined oral contraceptive pill and mini-pill, NuvaRing®, implantable contraceptives, injectable contraceptives (such as Depo-Provera®), intrauterine device (such as Mirena® and ParaGard®), contraceptive patch for women <90 Kg (<198 pounds), bilateral tubal occlusion, total abstinence, or vasectomy. Also see the definition of effective method of contraception.
HR	hazard ratio
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
INR	international normalized ratio
interim analysis	analysis of clinical trial data conducted before the final reporting database is created/locked.

Sampling Schedule for Pharmacokinetics—Abemaciclib Monotherapy (Arm A)

PK Sample Number	Cycle(C) and Day(D)	PK Sampling Time[a]
1	C1D1	2 h after abemaciclib dosed in clinic
2	C2D1[b]	Predose (0 h)
3	C3D1[b]	Predose (0 h)
4	C4D1[b]	Predose (0 h)

Abbreviations: h = hours; PK = pharmacokinetic.

a Samples of approximately 2 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites.

b Samples should be drawn prior to any study treatment on these days. In the event of a delay to a cycle due to toxicity, these predose samples should be drawn on the day when the cycle would have normally begun, to be close in time to the labs upon which the decision whether or not to begin a cycle is made.

Sampling Schedule for Pharmacokinetics—Abemaciclib + LY3023414 (Arm B)

PK Sample Number	Cycle and Day	PK Sampling Time[a]
1	C1D1	2 h after combination
2	C2D1[b]	Predose (0 h)
3	C3D1[b]	Predose (0 h)
4	C4D1[b]	Predose (0 h)

Abbreviations: C = cycle; D = day; h = hour; PK = pharmacokinetics.

a Samples of approximately 2 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites concentrations. Separate samples of approximately 2 mL of whole blood will be drawn for measurement of LY3023414 concentrations. Abemaciclib and LY3023414 will be administered together, approximately at the same time.

b Samples should be drawn prior to any study treatment on these days. In the event of a delay to a cycle due to toxicity, these pre-dose samples should be drawn on the day when the cycle would have normally begun, to be close in time to the labs upon which the decision whether or not to begin a cycle is made.

STAGE 2

Objectives	Endpoints
Primary	
• To evaluate progression-free survival of the abemaciclib treatment arms versus the standard-of-care arm (gemcitabine or capecitabine)	• Progression-free survival is measured from the date of randomization to the date of objective progression or the date of death due to any cause, whichever is earlier.
Secondary	
• To evaluate disease control rate of the abemaciclib treatment arms versus the standard-of-care arm	• Disease control rate is the percentage of patients with a best overall response of stable disease, complete response, or partial response according to RECIST 1.1.
• To evaluate clinical benefit rate of the abemaciclib treatment arms versus the standard-of-care arm	• Clinical benefit rate is the percentage of patients with a best overall response of complete response, or partial response, or stable disease for ≥6 months according to RECIST 1.1.
• To evaluate objective response rate of the abemaciclib treatment arms versus the standard-of-care arm	• Objective response rate is the percentage of patients with a best overall response of complete response or partial response according to RECIST 1.1.
• To evaluate duration of response of the abemaciclib treatment arms versus the standard-of-care arm	• Duration of response is measured from the date of first evidence of complete response or partial response to the date of objective progression or the date of death due to any cause, whichever is earlier.
• To evaluate overall survival of the abemaciclib treatment arms versus the standard-of-care arm	• Overall survival is measured from the date of randomization to the date of death from any cause.
• Evaluate the kinetics of carbohydrate antigen (CA) 19-9	• Change from baseline in CA 19-9
• Evaluate safety and tolerability	The safety endpoints evaluated will include but are not limited to the following: • TEAEs and SAEs • Clinical laboratory tests and vital signs
• To evaluate pain and symptom burden of the abemaciclib treatment arms by best response group (partial response, stable disease, progressive disease) versus the standard-of-care arm	• modified Brief Pain Inventory short form (mBPI-sf) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
• PK of abemaciclib and its metabolites as well as LY3023414	• Exposure of abemaciclib and LY3023414
• Exposure-response for abemaciclib and LY3023414	• Drug exposure and efficacy outcomes such as objective response rate or progression-free survival and safety outcomes such as neutropenia and diarrhea

Abbreviations: CA = carbohydrate antigen; PK = pharmacokinetics; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

the G1 restriction point at concentrations achieved by doses of 50 mg to 200 mg BID. This inhibition was associated with clinical benefit.

The dose of LY3023414 (150 mg BID) used in this study was the MTD identified in combination with abemaciclib 150 mg BID in the Phase 1b Study JPBJ.

The dose of galunisertib (150 mg BID) used in the safety lead-in period has demonstrated a favorable risk/benefit profile across multiple studies, when administered as a single agent or in combination with various chemotherapies. The galunisertib dose was identified based on results from preclinical pharmacodynamic biomarkers and non-clinical toxicology models, which allowed for a prospective definition of a therapeutic window. Simulations suggested that target-related inhibition of p-SMAD (a downstream target of TGF-β activation) by more than 50% for at least 8 hours, should provide sufficient activity, while minimizing the potential for cardiovascular toxicity. Plasma exposures observed in clinical trials following administration of 150 mg BID are within this predicted therapeutic window (Gueorguieva et al. 2014). Furthermore, clinical trials utilizing 150 mg BID have demonstrated activity in hepatocellular and pancreatic cancer patients (Faivre et al. 2014; Melisi et al. 2016), without significant toxicity.

The current study will assess the safety and pharmacokinetics (PK) of abemaciclib 150 mg BID plus galunisertib 150 mg BID for the 7 patients enrolled in a safety lead-in period at the time of amendment (c), but will not assess this combination in the randomized period of the study.

Section 2) for these patients, and safety decisions made by physicians or a team of people who are qualified by experience or training. Individuals so qualified must be identified at each Safety Lead-in site. The same person should be responsible for reading the ECHO on any individual study patient.

For patients who develop clinically significant changes, ECHO should continue to be performed at 2-month intervals until clinically stable for 6 months, then every 6 months thereafter. If the patient has clinically significant cardiac findings at the 30-day follow-up visit, ECHO will be repeated every 2 months for 6 months. If there are no clinically significant cardiac findings at the 30-day follow-up visit, a repeat ECHO will be performed within 6 months of the last ECHO. If there were no clinically significant cardiac findings at the last cardiac assessment conducted within the last 30 days and the patient has started another treatment, the 30-day follow-up visit ECHO will not be performed.

9.4.2. Guidance for Monitoring of Renal Function in Patients on Abemaciclib

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C calculated glomerular filtration rate (see Section 3.2.4 of the abemaciclib IB for additional background). Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function. Based on this information, it is suggested that for those patients with an increased serum creatinine test result while receiving abemaciclib, a serum cystatin-C test can be performed to confirm renal function. Cystatin-C blood concentration depends almost entirely on the glomerular filtration rate and is not affected by diet, nutrition, inflammation, or malignant disease. Dose alterations (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function.

9.4.3. Other Safety Measures

For each patient, vital signs, laboratory tests, or other tests should be collected as shown in the Schedule of Activities (Section 2).

Blood samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Local laboratory tests performed for eligibility purposes must include analytes with associated eligibility criteria (absolute neutrophil count, platelet count, hemoglobin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, serum creatinine, and HbA1c), as well as fasting glucose, at a minimum. Subsequent to enrollment, local laboratory tests may include the institution's standard chemistry and hematology panels, but must be performed under fasting conditions to assess glucose for all patients participating in Arm B; Arm B must also include HbA1c. Discrepancies between local

9.7. Pharmacogenomics

9.7.1. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Appendix 4, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in PDAC. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/institutional review boards (IRBs) impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of abemaciclib or LY3023414 or after these study treatments become commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies include whole genome and exome sequencing, genome-wide association studies, multiplex assays, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to abemaciclib, galunisertib, LY3023414, gemcitabine, capecitabine, immune function, cell cycle, and/or PDAC, and/or for related research methods or validation of diagnostic tools or assays.

Samples for biomarker research will be collected as specified in Appendix 4, where local regulations allow. It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 9.8.1 and 9.8.2.

10. Statistical Considerations

10.1. Sample Size Determination

According to the original study protocol, prior to randomization for Stage 1, approximately 6 to 12 patients were to be enrolled in the safety lead-in part of the study. However, with amendment (c), no additional patients will be enrolled to the safety lead-in and Arm C (abemaciclib plus galunisertib) will be removed.

During Stage 1, 25 patients will be treated per arm to provide a preliminary assessment of tumor response and assessment of safety. The null hypothesis is based on the assumption that the DCR is no greater than 50%; Table JPCJ.10.1 shows the probability of stopping at the end of Stage 1 (ranges from 11% to 72%) for DCR differences ranging from -10% (experimental arm DCR worse than standard of care) to 15% (experimental arm DCR better than standard of care).

At the end of Stage 1, an additional 50 patients will be enrolled in each of the advancing treatment arms from Stage 1, giving a total of approximately 75 patients in each treatment arm (combined Stage 1 and 2). This will allow the detection of PFS HR of 0.65 (median PFS of 2.3 months in abemaciclib containing arms vs. 1.5 months in the standard-of-care arm) with a two-tailed log-rank test at 0.10 significance level and a power of 76%. Analysis for Stage 2 will be performed when approximately 120 total events have occurred for the combination of each individual abemaciclib-containing arm and the standard-of-care arm, or all planned patients have been enrolled in Stage 2, whichever comes later.

Table JPCJ.10.1. Probability of Stopping at Stage 1

Null DCR	Alternative DCR	DCR Difference	Sample Size	Probability of abemaciclib containing treatment arm to stop at Stage 1 (that is, not advancing to Stage 2)
0.5	0.40	-0.10	25	0.72
0.5	0.50	0	25	0.44
0.5	0.65	0.15	25	0.11

Abbreviation: DCR = disease control rate.

10.2. Populations for Analyses

The following populations will be defined for this study:

Intention-to-Treat (ITT) population: will include all randomized patients. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This population will be used for all baseline, efficacy, and health economics analyses.

Safety population: will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a patient actually received, regardless of the arm to

11. References

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Table JPCJ.2.2. On-Study-Treatment Schedule of Activities—Abemaciclib Monotherapy (Arm A)

Note: Screening procedures performed within 72 hours prior to Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

	28-Day Cycle		28-Day Cycles		28-Day Cycles	
	Cycle 1		Cycle 2		Cycle 3 - n	
Day within Cycle	**1**	**14**	**1**	**14**	**1**	
Procedure						**Instructions**
Physical examination	X	X	X	X	X	
Vital signs	X	X	X	X	X	Includes weight, temperature, blood pressure, pulse rate, and respiration rate
Concomitant medication	X	X	X	X	X	
AE collection	X	X	X	X	X	CTCAE Version 4.0
ECOG performance status	X	X	X	X	X	
Radiologic imaging (Tumor Assessment)			X (every 8 weeks)			• Performed locally according to RECIST 1.1, by the same method used at baseline, every 8 weeks (±3 days) following randomization until radiographic disease progression, death, or study completion, whichever occurs first. • Performed as scheduled, even if study treatment is delayed or omitted. • If patient has known metastases to chest, chest CT is also to be conducted on the same schedule. If no known chest metastases at screening, then chest CT should be repeated every 24 weeks (±3 days). It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. • If IV contrast is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred.
Hematology	X	X	X	X	X	Performed by central laboratory ≤3 days prior to each visit (more frequent assessments may be performed if clinically indicated). Local labs may be used for eligibility and treatment decisions, but a duplicate sample must be submitted to the central laboratory.
Clinical chemistry	X	X	X	X	X	Performed by central laboratory ≤3 days prior to each visit (more frequent assessments may be performed if clinically indicated). Local labs may be used for eligibility and treatment decisions, but a duplicate sample must be submitted to the central laboratory.
Coagulation	X		X		X	≤3 days prior to Day 1 of each cycle, PTT or INR performed locally only for those patients receiving oral coumarin-derivative anticoagulants.
CA 19-9	X		X		X	Performed by central laboratory ≤3 days prior to Day 1 of each cycle.

Table JPCJ.2.3. On-Study-Treatment Schedule of Activities—Abemaciclib Plus LY3023414 (Arm B)

Note: Screening procedures performed within 72 hours prior to Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

	28-Day Cycle		28-Day Cycles		28-Day Cycles	
	Cycle 1		Cycle 2		Cycle 3- n	
Day within Cycle	**1**	**14**	**1**	**14**	**1**	
Procedure						**Instructions**
Physical examination	X	X	X	X	X	
Vital signs	X	X	X	X	X	Includes weight, temperature, blood pressure, pulse rate, and respiration rate.
Concomitant medication	X	X	X	X	X	
AE collection	X	X	X	X	X	CTCAE Version 4.0.
ECOG performance status	X	X	X	X	X	
Radiologic imaging (Tumor Assessment)			X (every 8 weeks)			• Performed locally according to RECIST 1.1, by the same method used at baseline, every 8 weeks (±3 days) following randomization until radiographic disease progression, death, or study completion, whichever occurs first. • Performed as scheduled, even if study treatment is delayed or omitted. • If patient has known metastases to chest, chest CT is also to be conducted on the same schedule. If no known chest metastases at screening, then chest CT should be repeated every 24 weeks (±3 days). It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. • If IV contrast is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred.
Hematology	X	X	X	X	X	Performed by central laboratory ≤3 days prior to each visit (more frequent assessments may be performed if clinically indicated). Local labs may be used for eligibility and treatment decisions, but a duplicate sample must be submitted to the central laboratory.
Clinical chemistry	X	X	X	X	X	Performed by central laboratory. NOTE: Fasting labs must be drawn for patients in Arm B in order to appropriately assess glucose. Samples may be obtained ≤3 days prior to each visit (more frequent assessments may be performed if clinically indicated). Local labs may be used for eligibility and treatment decisions, but a duplicate sample must be submitted to the central laboratory.
Coagulation	X		X		X	≤3 days prior to Day 1 of each cycle, PTT or INR performed locally only for those patients receiving oral coumarin-derivative anticoagulants.
CA 19-9	X		X		X	Performed by central laboratory ≤3 days prior to Day 1 of each cycle.
HbA1c					X	To be performed ≤3 days prior to Cycle 3 Day 1 and every other cycle thereafter (C3D1, C5D1, C7D1, etc).

Table JPCJ.2.4. On-Study-Treatment Schedule of Activities—Abemaciclib Plus Galunisertib (Safety Lead-In)

Notes: Screening procedures performed within 72 hours prior to Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

	28-Day Cycle		28-Day Cycles		28-Day Cycles	
	Cycle 1		Cycle 2		Cycle 3 - n	
Day within Cycle	**1**	**14**	**1**	**14**	**1**	
Procedure						**Instructions**
Physical examination	X	X	X	X	X	
Vital signs	X	X	X	X	X	Includes weight, temperature, blood pressure, pulse rate, and respiration rate.
Concomitant medication	X	X	X	X	X	
AE collection	X	X	X	X	X	CTCAE Version 4.0.
ECOG performance status	X	X	X	X	X	
Radiologic imaging (Tumor Assessment)			X (every 8 weeks)			• Performed locally according to RECIST 1.1, by the same method used at baseline, every 8 weeks (±3 days) following randomization until radiographic disease progression, death, or study completion, whichever occurs first. • Performed as scheduled, even if study treatment is delayed or omitted. • If patient has known metastases to chest, chest CT is also to be conducted on the same schedule. If no known chest metastases at screening, then chest CT should be repeated every 24 weeks (±3 days). It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. • If IV contrast is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred.
Hematology	X	X	X	X	X	Performed by central laboratory ≤3 days prior to each visit (more frequent assessments may be performed if clinically indicated). Local labs may be used for eligibility and treatment decisions, but a duplicate sample must be submitted to the central laboratory.
Clinical chemistry	X	X	X	X	X	Performed by central laboratory ≤3 days prior to each visit (more frequent assessments may be performed if clinically indicated). Local labs may be used for eligibility and treatment decisions, but a duplicate sample must be submitted to the central laboratory.
Coagulation	X		X		X	≤3 days prior to Day 1 of each cycle, PTT or INR performed locally for only those patients receiving oral coumarin-derivative anticoagulants.
CA 19-9	X		X		X	Performed by central laboratory ≤3 days prior to Day 1 of each cycle.
Additional Tissue Sample, if applicable			X		X	If a participant in this study elects to have a surgical procedure at any time during the study that involves removal of tumor, then FFPE tumor from that procedure may also be requested. Patients undergoing surgery during the study should have study treatment suspended for 7 days prior to surgery, as well as 7 days post-operatively.

	28-Day Cycle		28-Day Cycles		28-Day Cycles	
	Cycle 1		Cycle 2		Cycle 3 - n	
Day within Cycle	**1**	**14**	**1**	**14**	**1**	
Sample Collection						
Pharmacokinetics						For all sample collection, see Appendix 4.
Pharmacogenetics						
Biomarkers						

Abbreviations: AE = adverse event; BID = twice daily; CA = carbohydrate antigen; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life.

Questionnaire-Core 30; FFPE = formalin-fixed, paraffin-embedded; INR = international normalized ratio; IV = intravenous; mBPI-sf = modified Brief Pain Inventory short form; MRI = magnetic resonance imaging; PTT = partial prothrombin time; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

Table JPCJ.2.6. On-Study-Treatment Schedule of Activities—Standard of Care Gemcitabine (Arm D)

Note: Screening procedures performed within 72 hours prior to Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

	28-Day Cycle				28-Day Cycles			
	Cycle 1				Cycle 2-n			
Day within Cycle	**1**	**8**	**15**	**22**	**1**	**8**	**15**	
Procedure								**Instructions**
Physical examination	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	Includes weight, temperature, blood pressure, pulse rate, and respiration rate. NOTE: Weight is required only on Day 1 of each cycle.
Concomitant medication	X	X	X	X	X	X	X	
AE collection	X	X	X	X	X	X	X	CTCAE Version 4.0.
ECOG performance status	X				X			
Radiologic imaging (Tumor Assessment)					X			• Perform according to RECIST 1.1, by the same method used at baseline, performed locally, every 8 weeks (±3 days; approximately Cycle 3, Day 1 and every other cycle thereafter) until radiographic disease progression, death, or study completion, whichever occurs first. • Performed as scheduled, even if study treatment is delayed or omitted. • If patient has known metastases to chest, chest CT is also to be conducted on the same schedule. If no known chest metastases at screening, then chest CT should be repeated every 24 weeks (±3 days). It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. • If IV contrast is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred.
Hematology	X	X	X	X	X	X	X	Performed by central laboratory ≤3 days prior to Day 1 of each cycle. Local labs may be used for eligibility and treatment decisions prior to Day 1 of each cycle, but a duplicate sample must be submitted to the central laboratory. Local labs to be done per institutional guidelines prior to infusions on subsequent days of each cycle (central labs not required for each subsequent infusion within a cycle).
Clinical chemistry	X	X	X	X	X	X	X	Performed by central laboratory ≤3 days prior to Day 1 of each cycle. Local labs may be used for eligibility and treatment decisions prior to Day 1 of each cycle, but a duplicate sample must be submitted to the central laboratory. Local labs to be done per institutional guidelines prior to infusions on subsequent days of each cycle (central labs not required for each subsequent infusion within a cycle).

Table JPCJ.2.7. Post-Treatment Follow-Up Schedule of Activities

Visit	Short-Term Follow-Up[a] 801	Long-Term Follow-Up[b] 802-8XX	
Procedure			**Instructions**
Physical examination	X		
Vital signs	X		Includes weight, temperature, blood pressure, pulse rate, and respiration rate.
Concomitant medication	X		
AE collection	X	X	CTCAE Version 4.0. During the Long-Term Follow-up, only AEs that are related to study treatment or protocol procedures will be collected. The frequency of evaluation is based upon the judgment of the investigator.
ECOG performance status	X		
Radiologic imaging	X	X	For patients that discontinued study treatment prior to disease progression, perform every 8 weeks (± 3 days) according to RECIST 1.1, by the same method used at baseline and throughout the study, until: • the patient has objective disease progression, or • the study's primary analysis of PFS. After the patient has objective disease progression, radiologic tests are no longer required, and the patient will have follow up approximately every 60 days (±7 days) until death or study completion.
Collection of survival information	X	X	Following Short-term follow-up, perform every 60 days (±7 days) until death or study completion. If an in-person visit is not possible, confirm survival by contacting the patient directly via phone.
Collection of post-study-treatment anticancer therapy information	X	X	Following Short-term follow-up, perform every 60 days (±7 days) until death or study completion.
Hematology	X		Performed by central laboratory.
Clinical chemistry	X		Performed by central laboratory.
Coagulation	X		PTT or INR to be performed locally for only those patients receiving capecitabine during the study treatment period.
CA 19-9	X		Performed by central laboratory.

[NCCN] Guidelines Version 1.2017). Additional second-line options include gemcitabine or fluorouracil monotherapies if patients have either an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or a comorbidity profile that precludes more aggressive regimens (Sohal et al. 2016). In the third-line setting, no standard of care exists; recommendations are to provide palliative and best supportive care or enroll patients in a clinical trial.

Recently, a Phase 3 study in patients previously treated with gemcitabine-based therapy has shown that nanoliposomal irinotecan (Onivyde™ [Merrimack Pharmaceuticals, Cambridge, MA, USA]) in combination with 5-FU and leucovorin compared to 5-FU and leucovorin alone resulted in improvement in progression-free survival (PFS) of 3.1 months versus 1.5 months and in overall survival (OS) of 6.1 months compared to 4.2 months (Wang-Gillam et al. 2016). In a retrospective review of patients treated in the second-line setting with gemcitabine monotherapy, PFS was 2.0 months and OS was 5.7 months (da Rocha Lino et al. 2015). A Phase 2 study of second-line ruxolitinib and capecitabine versus capecitabine alone in patients previously treated with a gemcitabine-based therapy resulted in a PFS rate of 13% at 3 months and median OS of 4.3 months for patients receiving capecitabine monotherapy (Hurwitz et al. 2015).

Despite advances in both first- and second-line therapies for PDAC, OS remains poor, and treatment of PDAC remains an unmet medical need. Current second- and third-line treatments for metastatic disease have limited efficacy and novel therapies are urgently needed. Given these data, the current study will use gemcitabine alone or capecitabine alone as the standard-of-care treatment for the control arm.

3.2.2. Cyclin-Dependent Kinases 4 and 6 and Role in Pancreatic Ductal Adenocarcinoma

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for proper regulation of cell proliferation (Sherr 1996; Ortega et al. 2002). Cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) participate in a complex with the D-type cyclins to initiate progression through the G1 restriction point. The CDK4 and CDK6 – Cyclin D1 complex regulates the G1 restriction point through phosphorylation and inactivation of the retinoblastoma (Rb) tumor suppressor protein, thereby promoting S phase entry. Alterations in this pathway occur frequently in human cancers, including PDAC, and involve 1) loss of functional CDK inhibitors, such as $p16^{INK4A}$, through deletion or epigenetic silencing, 2) activating mutations and/or overexpression of CDK4 and CDK6 or the D-type cyclins, and 3) loss of functional Rb through mutation or deletion. Except for tumors with functional loss of Rb, which functions downstream of the CDK4 and CDK6 – Cyclin D1 complex, most cancers are potentially sensitive to pharmacologic inhibition of CDK4 and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a small molecule is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

A key regulator of cell cycle progression in the CDK4 and CDK6/Cyclin D/Rb pathway is the CDK inhibitor, $p16^{INK4A}$. The catalytic activity leading to reduced phosphorylation of Rb, and thus G_1 cell cycle arrest, is inhibited when $p16^{INK4A}$ binds to CDK4 and 6. In more than 90% of

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea; see below) that does not resolve with maximal supportive measures within 7 days to either baseline or at least Grade 1, then dosing may be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of study treatment may be reduced by 1 dose level as outlined in Table JPCJ.7.3 at the discretion of the investigator.

If a patient experiences persistent or recurrent Grade 2 diarrhea that does not resolve with maximal supportive measures (see Section 7.7.2) within 24 hours to at least Grade 1, then study treatment should be suspended (until the toxicity resolves to at least Grade 1) and the dose of study treatment may be reduced by 1 dose level as outlined in Table JPCJ.7.3 at the discretion of the investigator. If the same dose level was resumed and diarrhea recurs despite maximal supportive measures, the dose of study treatment must be reduced by 1 dose level as outlined in Table JPCJ.7.3.

Before the start of each cycle, nonhematologic toxicity (except alopecia and fatigue) must resolve to either baseline or at least Grade 1. Patients receiving galunisertib must receive a minimum of 10 days of dosing in a 28-day cycle. If a patient does not recover from the toxicity within 14 days from the time of last treatment, the patient should be considered for permanent discontinuation from study treatment. In exceptional circumstances, a delay >14 days is permitted upon agreement between the investigator and the Lilly CRP.

7.4.2. Dosage Modifications for Gemcitabine

The safety profile of gemcitabine as a single agent is well characterized in studies of a variety of malignancies (Gemzar® gemcitabine HCl [for injection] prescribing instructions page [WWW]), in which patients received gemcitabine 800 mg/m^2 to 1250 mg/m^2. For these patients, the hematologic toxicity was mild with only 1% to 4% of patients having Grade 3/4 thrombocytopenia, 1% to 7% having Grade 3/4 anemia, and 6% to 19% of patients having Grade 3/4 neutropenia. The most common (≥5%) Grade 3 /4 nonhematologic toxicities of this regimen were nausea/vomiting, increased ALT, increased alkaline phosphatase, and increased AST. All of these toxicities are monitorable, manageable, and reversible. Therefore, Lilly recommends to reduce gemcitabine only to manage hematologic toxicities of neutropenia and thrombocytopenia or if nonhematologic toxicity arises.

The gemcitabine dose can be adjusted following Table JPCJ.7.4 in the event of a hematologic toxicity, as this presents the in-label recommendations for dose reductions for gemcitabine when used as monotherapy.

Table JPCJ.7.4. Gemcitabine Dose Modifications for Hematological Toxicity

ANC Preinfusion ($\times 10^9$/L)		Platelet Preinfusion ($\times 10^9$/L)	% Full Dose
≥1.0	and	≥100	100
≥0.5 to <1.0	or	≥50 to <100	75
<0.5	or	<50	Hold

Abbreviation: ANC = absolute neutrophil count.

investigational product	pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
IV	intravenous
KRAS	Kirsten rat sarcoma
LLT	lower level term
LVEF	left ventricular ejection fraction
MATE	multidrug and toxin extrusion protein
mBPI-sf	modified Brief Pain Inventory short form
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NONMEM	nonlinear mixed effect modelling
OS	overall survival
PD	pharmacodynamics
PDAC	pancreatic ductal adenocarcinoma
PET	positron emission tomography
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase

Intense Sampling Schedule for Pharmacokinetics of Abemaciclib + Galunisertib (Safety Lead-in)

PK Sample Number	Cycle and Day	Dosing of Study Drugs		PK Sampling Time for Abemaciclib and Galunisertib
1	C1D1	Abemaciclib	Galunisertib	Predose (0 h)[b]
2	C1D1			30 min after combination (0.5 h)
3	C1D1			1 hour after combination (1 h)
4	C1D1			2 hours after combination (2 h)
5	C1D1			4 hours after combination (4 h)
6	C1D1			6 hours after combination (6 h)
7	C1D1			8 hours after combination (8 h) (±1.5 hour to accommodate clinic hours)
8	C1D14	Abemaciclib	Galunisertib	Predose (0 h)[b]
9	C1D14			30 min after combination (0.5 h)
10	C1D14			1 hour after combination (1 h)
11	C1D14			2 hours after combination (2 h)
12	C1D14			4 hours after combination (4 h)
13	C1D14			6 hours after combination (6 h)
14	C1D14			8 hours after combination (8 h) (± 1.5 hour to accommodate clinic hours)
15	C2D1	Abemaciclib	Galunisertib	Predose (0 h)[c]
16	C3D1	Abemaciclib	Galunisertib	Predose (0 h)[c]
17	C4D1	Abemaciclib	Galunisertib	Predose (0 h)[c]

Abbreviations: C = cycle; D = day; h = hour; min = minute; PK = pharmacokinetic(s).

[a] Samples of approximately 2 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites concentrations. Separate samples of approximately 2 mL of whole blood will be drawn for measurement of galunisertib concentrations. Abemaciclib and galunisertib will be administered together, approximately at the same time.

[b] If a patient will have galunisertib dosing suspended prior to D14, that the patient should be brought in for PK on the morning of the last day of dosing, if possible.

[c] Samples should be drawn prior to any study treatment on these days. In the event of a delay to a cycle due to toxicity, these predose samples should be drawn on the day when the cycle would have normally begun, to be close in time to the labs upon which the decision whether or not to begin a cycle is made.